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Increased Left Ventricular Mass and Hypertrophy Are Associated With Increased Risk for Sudden Death

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Objectives. **This study examined the relations of echocardiographically determined left ventricular (LV) mass and hypertrophy to the risk of sudden death.**

Background. **Echocardiographic LV hypertrophy is associated with increased risk for all-cause mortality and cardiovascular disease morbidity and mortality. However, little is known about the association of echocardiographic LV hypertrophy with sudden death.**

Methods. **We examined the relations of LV mass and hypertrophy to the incidence of sudden death in 3,661 subjects enrolled in the Framingham Heart Study who were ≥40 years of age. The baseline examination was performed from 1979 to 1983 and LV hypertrophy was defined as LV mass (adjusted for height) >143 g/m in men and >102 g/m in women. During up to 14 years of follow-up there were 60 sudden deaths. Cox models examined the relations of LV mass and LV hypertrophy to sudden death risk after adjusting for known risk factors.**

Results. **The prevalence of LV hypertrophy was 21.5%. The risk factor–adjusted hazard ratio (HR) for sudden death was 1.45 (95% confidence interval [CI] 1.10 to 1.92, p = 0.008) for each 50-g/m increment in LV mass. For LV hypertrophy, the risk factor–adjusted HR for sudden death was 2.16 (95% CI 1.22 to 3.81, p = 0.008). After excluding the first 4 years of follow-up, both increased LV mass and LV hypertrophy conferred long-term risk of sudden death (HR 1.53, 95% CI 1.01 to 2.28, p = 0.047 and HR 3.28, 95% CI 1.58 to 6.83, p = 0.002, respectively).**

Conclusions. **Increased LV mass and hypertrophy are associated with increased risk for sudden death after accounting for known risk factors.**

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Sudden death is a leading public health problem and, despite a continuing decline in cardiovascular disease mortality, there are 300,000 sudden deaths annually (1). Although there have been many advances in sudden death research, there has been limited impact on the incidence of sudden death (2). Prevention of sudden death may require a better understanding of its pathophysiologic mechanisms and predisposing factors.

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Previous studies have documented high rates of adverse cardiovascular events in subjects with left ventricular (LV) hypertrophy (3–11). It has been consistently shown that LV hypertrophy on the electrocardiogram is strongly associated with increased risk for multiple manifestations of coronary heart disease, including sudden death (5–7,9,12–14). Echocardiographic LV hypertrophy also has been reported to be associated with increased risk for cardiovascular disease and all-cause mortality in hospital- and clinic-based studies (8,10,11,15–17) and in population-based investigations (3,4).

The association of echocardiographic LV mass and hypertrophy with risk for sudden death has not been thoroughly examined in a free-living population. This study was undertaken to extend a previous study that suggested an increased risk for sudden death in subjects with LV hypertrophy on the echocardiogram (3).

Methods

Study population and outcome events. Since 1948 the Framingham Heart Study has followed participants at regular intervals as part of a prospective population-based investigation of cardiovascular disease. Study design and recruitment procedures have been published previously (18); 5,209 men and women aged 28 to 62 years were enrolled. Every 2 years a follow-up visit included a medical history, physical examination, blood pressure measurements, 12-lead electrocardiogram and laboratory tests. Beginning in 1971 the Framingham Offspring Study enrolled 5,124 men and women who were

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Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
LV = left ventricular

offspring or spouses of offspring of original Framingham Heart Study subjects (19). The second through fifth Framingham Offspring Study examinations were conducted 8, 12, 16 and 20 years, respectively, after the initial examination cycle.

Methodology for assessing risk factors has been published previously (18,19). Age, gender, height, weight, blood pressure, antihypertensive medication use, total and high density lipoprotein cholesterol, diabetes mellitus, and cigarette smoking were routinely obtained for each participant. Body mass index (kilograms/square meter) was used as a measure of obesity. Sitting systolic and diastolic blood pressures were measured twice by a physician using a mercury column sphygmomanometer and averaged. Serum cholesterol was measured by the Abell–Kendal method. Diabetes was diagnosed if subjects were under treatment for diabetes, if they had a record of an abnormal glucose tolerance test or if they had a random blood glucose level of 150 mg/100 ml or more on at least two examinations (20). Participants were categorized as smokers if they currently smoked cigarettes or if they had quit within 1 year before the clinic examination. Coronary heart disease and congestive heart failure were routinely assessed at each examination, and suspected events were reviewed by a panel of three physicians. Criteria for congestive heart failure and coronary heart disease have been described previously (20). A diagnosis of congestive heart failure was made if at least two major criteria or one major and two minor criteria were met (20). Coronary heart disease was diagnosed if subjects had a history of myocardial infarction, coronary insufficiency or angina pectoris (20). Electrocardiographic LV hypertrophy was present when increased voltage was associated with major ST-T repolarization changes (strain pattern) (6,20).

Because of the low incidence of sudden death in young subjects, this study was restricted to those study participants who were ≥40 years of age at the baseline examination conducted from 1979 to 1983. All deaths were reviewed and probable cause was established by a committee of three physicians after a review of hospital records, autopsy findings, death certificates and interviews with family members. If a subject, apparently well, died within 1 h of onset of symptoms, and if the cause of death could not reasonably be attributed, on the basis of the full clinical information and the information concerning death, to some potentially lethal disease other than coronary heart disease, this was called sudden death and was attributed to coronary heart disease (20).

Echocardiographic methods. Subjects were studied with M-mode echocardiography as described previously (21). Measurements of the internal diameter and wall thickness of the left ventricle were made at end diastole according to the methods of Devereux and Reichek (22). Left ventricular mass was calculated with the following formula: LV mass (in grams) $= 1.04\,[(\mathrm{LVID} + \mathrm{VST} - \mathrm{PWT})^3] - 13.6$, where LVID denotes the LV internal diameter, VST the ventricular septal thickness and PWT the posterior wall thickness. To correct for differences in heart size in subjects of different body size, LV mass (in grams) was divided by height (in meters) because of the association observed between LV mass and height in a healthy reference group (21). Left ventricular hypertrophy was defined as an LV mass two or more standard deviations above the mean for the healthy reference group. The cutoff values for LV hypertrophy were 143 g/m in men and 102 g/m in women (21).

Statistical analysis. Subjects were followed for up to 14 years after the initial echocardiographic examination. The incidence of sudden death was examined both as a function of increments in LV mass (adjusted for height) and as a function of the presence or absence of LV hypertrophy.

Crude incidence rates for sudden death were displayed for men and women according to quartiles of LV mass adjusted for height and according to LV hypertrophy status. The Cox proportional hazards model was used to examine these relations using several covariates chosen by stepwise selection (23). These were age, gender, antihypertensive treatment, smoking status, high-density lipoprotein cholesterol, diabetes mellitus and presence of coronary heart disease or congestive heart failure. Systolic blood pressure, diastolic blood pressure, total cholesterol and body mass index did not enter the stepwise models and therefore were not included as covariates in the final models. Risk factor–adjusted hazard ratios (HR) and 95 percent confidence intervals (CI) were calculated for every increment of 50 g/m in LV mass and for the presence (vs. absence) of LV hypertrophy.

Proportional hazards assumptions were verified by graphic displays and Cox models that included time-dependent interaction terms to permit HRs to increase or decrease as duration of follow-up increased. There were too few sudden deaths among women to test whether the relation of LV mass with sudden death was the same in both sexes; instead, we conducted a secondary analysis in men only. Because LV mass is associated with all manifestations of coronary heart disease, the development of myocardial infarction before sudden death in those with and without LV hypertrophy was also examined. A p value <0.05 was considered significant. Statistical analysis was performed using SAS software (24).

Results

Of the 4,853 men and women above 40 years of age who were seen at the baseline examination, an echocardiogram of adequate quality to measure LV mass was available for 3,663 subjects (75.5%). Those who had inadequate echocardiograms were older and more obese and had higher rates of sudden death compared with those with adequate echocardiograms (4.6 vs. 2.9 per 1,000 person-years of follow-up in men; corresponding rates in women were 1.1 vs. 0.5). Two subjects who had no follow-up contact were excluded from analysis. The study sample comprised 3,661 subjects (1,634 men and

Table 1. Baseline Characteristics of the Study Sample

	Men (n = 1,634)	Women (n = 2,027)
Age (yrs)	56 ± 10.8 (40–88)	58 ± 11.8 (40–91)
Body mass index (kg/m^2)	26.7 ± 3.5 (15.5–42.7)	25.5 ± 4.6 (15.6–49.5)
Systolic blood pressure (mm Hg)	132 ± 18 (92–225)	130 ± 20 (84–278)
Diastolic blood pressure (mm Hg)	81 ± 9 (50–140)	77 ± 10 (40–143)
Antihypertensive treatment (%)	18	23
Coronary disease or heart failure (%)	11	8
Diabetes mellitus (%)	8	5
Cigarette smoker (%)	30	30
Total cholesterol (mg/dl)	213 ± 38 (93–421)	221 ± 39 (52–511)
HDL cholesterol (mg/dl)	43 ± 12 (16–119)	55 ± 15 (18–112)
LV mass (g/m)	119 ± 38 (37–518)	89 ± 30 (33–439)
LV hypertrophy (%)	19	24

Values are means ± SD (range). HDL = high-density lipoprotein; LV = left ventricular.

Table 2. Left Ventricular Mass and Risk of Sudden Death

	Hazard Ratio*	95% Confidence Interval	
		Lower	Upper
Unadjusted	1.94	1.66	2.27
Age and sex adjusted	1.50	1.19	1.89
Age, sex and risk factor† adjusted	1.45	1.10	1.92
Age and risk factor† adjusted, men only	1.57	1.18	2.09

*Hazard ratio per 50 g/m increment in left ventricular mass. †Risk factors: age, gender, antihypertensive treatment, smoking status, high-density lipoprotein cholesterol, diabetes mellitus, coronary heart disease or congestive heart failure.

2,027 women) with a mean age of 57 ± 11 years. The characteristics of the study subjects are summarized in Table 1. Echocardiographic criteria for LV hypertrophy were fulfilled in 304 men (19%) and 477 women (24%).

In the study cohort 18% of men and 23% of women were receiving antihypertensive treatment. Among subjects without echocardiographic LV hypertrophy, 5% were taking beta-adrenergic blocking agents, 14% diuretics and 7% other agents for treatment of hypertension; 18% were being treated with at least one of these agents and 7% with two or more. In contrast, among subjects with echocardiographic LV hypertrophy, 13% were taking beta blockers, 29% diuretics and 19% other agents for treatment of hypertension; 42% were being treated with at least one of these agents and 16% with two or more.

During follow-up (mean 10.32 years, range 0.00 to 14.41 years) sudden death occurred in 49 men (mean age 70.5 ± 11.5 years) and in 11 women (mean age 75 ± 9.4 years). Unadjusted sudden death rates per 1,000 person-years of follow-up ranged from 1.1% in men with an LV mass <95 g/m to 6.9% in those with values >135 g/m; the corresponding rates for women were 0% and 1.0%, respectively (Fig. 1). The age-, gender- and risk factor–adjusted HR for sudden death per 50-g/m increment in LV mass was 1.45 (95% CI 1.10 to 1.92, p = 0.008, Table 2).

The rates of sudden death in men with LV hypertrophy and in those without were 8.2 and 1.9 per 1,000 person-years, respectively. The corresponding rates for women were 0.9% and 0.4% (Fig. 2). Among subjects with LV hypertrophy the age-, gender- and risk factor–adjusted HR for sudden death was 2.16 (95% CI 1.22 to 3.81, p = 0.008, Table 3). The frequency of interim myocardial infarction in sudden death victims with and without LV hypertrophy was 28% and 20%, respectively. In secondary analyses of men only, the associations of LV mass and LV hypertrophy with sudden death risk were stronger than in the analyses with both sexes combined (Tables 2 and 3).

A pattern of electrocardiographic LV hypertrophy with repolarization abnormality (strain pattern) was uncommon. Only 47 subjects (1.3%) had definite electrocardiographic LV hypertrophy; 39 (83.0%) of these also had echocardiographic LV hypertrophy and 3 (6.4%) had sudden death. In contrast,

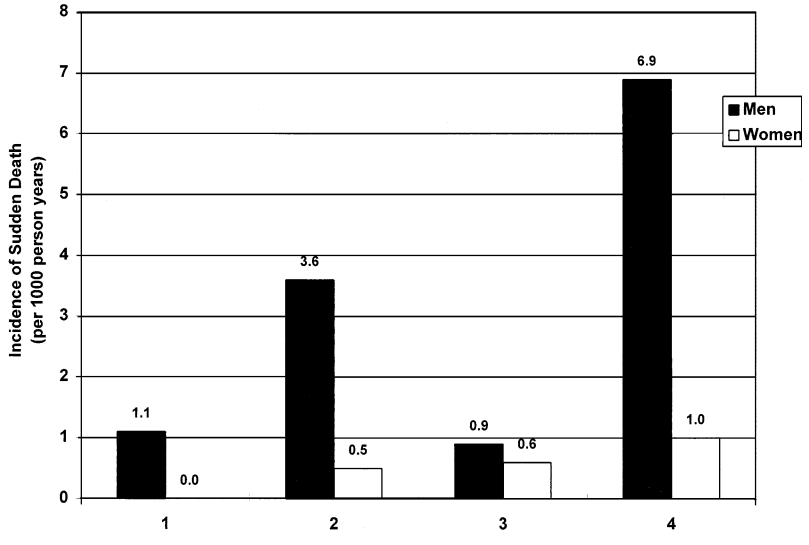

Figure 1. Incidence (unadjusted) of sudden death according to quartiles of LV mass (adjusted for height). Quartile partition values for LV mass were: Q1, <95 g/m in men and <70 g/m in women; Q2, 95 to 109 and 70 to 84; Q3, 110 to 134 and 85 to 99; Q4, ≥135 and ≥100.

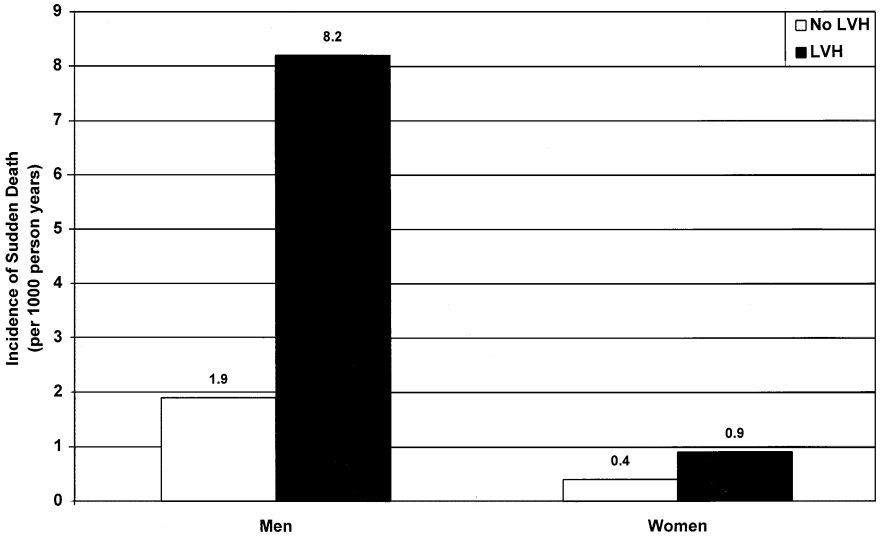

Figure 2. Incidence (unadjusted) of sudden death in men and women according to LV hypertrophy status. The cutoff values for LV hypertrophy were 143 g/m in men and 102 g/m in women (21).

among subjects without electrocardiographic LV hypertrophy, 736 (20.4%) had echocardiographic LV hypertrophy and 57 (1.6%) had sudden death. In a secondary analysis, when electrocardiographic LV hypertrophy was included as a covariate in the multivariable model, the HRs for echocardiographic LV hypertrophy and LV mass were essentially unchanged (HR 2.13, 95% CI 1.19 to 3.80, p = 0.011 and HR 1.43, 95% CI 1.07 to 1.89, p = 0.015, respectively).

There were 27 sudden deaths in the first 4 years of follow-up and 33 thereafter. Neither LV mass (HR 1.34/50 g per m, 95% CI 0.91 to 1.98, p = 0.14) nor LV hypertrophy (HR 1.08, 95% CI 0.44 to 2.69, p = 0.86) conferred significant risk during the first 4 years of follow-up. After excluding the first 4 years of follow-up, risk of sudden death was substantially increased in the long term, both for increased LV mass (HR 1.53/50 g per m, 95% CI 1.01 to 2.28, p = 0.047) and in association with LV hypertrophy (HR 3.28, 95% CI 1.58 to 6.83, p = 0.002).

Discussion

Prognostic implications of LV hypertrophy and increased LV mass. Previous studies have reported an increased risk for cardiovascular disease in subjects with echocardiographic evidence of LV hypertrophy (3,4,8,10,11,14–17,25–29). Studies from Framingham and elsewhere have demonstrated an association between echocardiographically determined LV mass and the risk for coronary heart disease in middle-aged and elderly subjects (3,4,30). However, the association of echocardiographic LV hypertrophy with sudden death has not been examined thoroughly in a general population sample. This study was undertaken to examine the associations of LV mass and LV hypertrophy with sudden death risk in a large group of middle-aged and elderly subjects enrolled in the Framingham Heart Study. This long-term follow-up study of a carefully monitored cohort supports the hypothesis that LV hypertrophy is an independent risk factor for sudden death and the hazards increase with increasing LV mass. With a mean follow-up of 10.32 years, this study also demonstrates that LV hypertrophy confers long-term risk for sudden death. These findings may enhance our understanding of pathophysiologic mechanisms and predisposing factors for sudden death.

Table 3. Left Ventricular Hypertrophy and Risk of Sudden Death

	Hazard Ratio*	95% Confidence Interval	
		Lower	Upper
Unadjusted	3.40	2.04	5.66
Age and sex adjusted	2.63	1.56	4.45
Age, sex and risk factor† adjusted	2.16	1.22	3.81
Age and risk factor† adjusted, men only	2.89	1.56	5.38

*Hazard ratio comparing subjects with and those without left ventricular hypertrophy. †Risk factors: age, gender, antihypertensive treatment, smoking status, high-density lipoprotein cholesterol, diabetes mellitus, coronary heart disease or congestive heart failure.

Left ventricular hypertrophy on the electrocardiogram is well known to predict morbidity and mortality both in the general population and in patients with hypertension (5–7,9,12–14). Individuals with electrocardiographic evidence of LV hypertrophy also have been shown to be at increased risk for sudden death (14,31,32). Electrocardiographic LV hypertrophy was found to be a short- and long-term predictor of sudden death in a previous study from Framingham (32). The association persists after taking into account the traditional coronary disease risk factors that may have promoted LV hypertrophy (14,32).

Electrocardiographic criteria for LV hypertrophy that are based on voltage and repolarization abnormalities have high specificity but low sensitivity for the detection of echocardiographic LV hypertrophy (25,26,28,33,34). Echocardiography has provided an accurate, noninvasive means of estimation of LV mass and has proved to be a more reliable tool for the detection of LV hypertrophy (25,33–35). In this study the application of gender-specific criteria for LV hypertrophy,

based on the distribution of LV mass in a healthy reference sample (21), revealed a prevalence of LV hypertrophy of 19% in men and 24% in women.

Potential mechanisms. The mechanisms by which cardiac hypertrophy may increase risk for sudden death are inadequately understood. Left ventricular hypertrophy reduces coronary flow reserve while increasing myocardial oxygen consumption (36,37). This imbalance also may predispose to ischemia (38), arrhythmias (39–41) and sudden death (3,15,39,40,42,43). Coronary blood supply also may be impaired by atherosclerosis in persons with LV hypertrophy because some factors associated with myocardial hypertrophy are atherogenic. Studies in laboratory animals with hypertensive LV hypertrophy have demonstrated a threefold risk of sudden death as well as increased myocardial infarct size after coronary occlusion (44–46). Moreover, hypertensive LV hypertrophy is associated with vascular hypertrophy and subclinical disease, which may increase the consequences of coronary artery obstruction (45,47,48).

The correlation between heart weight and severity of coronary heart disease in sudden death victims is not strong (49); heart weights are higher in sudden death victims than in those with nonsudden death, despite a similar prevalence of hypertension before death (50). Cooper et al. (16) and Ghali et al. (51) documented that increased LV mass predicts subsequent mortality more strongly in patients without angiographic evidence of obstructive coronary artery disease than in those with stenosis of epicardial coronary arteries. These findings have been interpreted to suggest that LV mass reflects the integrated adverse effects on the heart of increased hemodynamic load and vascular damage.

The small number of sudden deaths in women may partly reflect the definition used for sudden death (e.g. witnessed death). The mean age of sudden death cases was 70.5 years in men and 75.4 years in women. The older age at sudden death in women implies that a greater proportion of women than men would have outlived their spouse; consequently, witnessed sudden death would have been difficult to document in these circumstances. Our observations are also consistent with previous studies that sudden death has a preponderance in men compared with women (14,52). A 3.8-fold incidence of sudden death in men compared with women at 20 years of follow-up was reported in Framingham Heart Study participants (52).

Strengths and limitations. The Framingham Heart Study provides a large sample in which risk factors are routinely assessed at periodic examination cycles. The study includes both men and women and consists of a population-based sample in which referral bias is inherently low. Some limitations of the present study need to be considered. Left ventricular mass was assessed using M-mode echocardiography, which may misclassify subjects in the setting of abnormal LV geometry. Because of the largely Caucasian composition of the study sample, these findings may not be generalizable to other groups. Over a long follow-up period (mean 10.32 years) a single baseline assessment of LV hypertrophy may lose its prognostic value because of alterations in LV mass over time. However, baseline LV mass remained predictive of increased long-term risk of sudden death in this study. Further studies are warranted to examine the association of serial changes in LV mass with sudden death, because in previous studies, an increase in LV hypertrophy on the electrocardiogram (13) or echocardiogram (53) was predictive of adverse outcomes compared with no change or a decrease. This is an observational study and outside physicians selected antihypertensive therapy according to their patients' characteristics; this may introduce bias. Finally, a considerable number of subjects (24.5%) were excluded from this study because of inadequate quality of echocardiograms. The cumulative incidence of sudden death for subjects with inadequate echocardiograms was 2.2%, an intermediate value between those with LV hypertrophy and those without LV hypertrophy (3.1% and 0.8%, respectively). Therefore, it is not likely that the inability to obtain adequate echocardiograms in the entire study sample materially affected the conclusions of this investigation.

Conclusions. Increased LV mass and hypertrophy on the echocardiogram are associated with increased risk for sudden death after accounting for other known coronary disease risk factors. To our knowledge this is the first study demonstrating a long-term association between LV mass and sudden death in a community-based cohort. It is unclear whether antihypertensive therapies that promote regression of LV hypertrophy will reduce the risk for sudden death. Left ventricular hypertrophy, however, was not always an indication of coexisting hypertension in our study participants. Clinical trials are underway to assess the benefits of LV hypertrophy regression.

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