Left Ventricular Mass and the Risk of Sudden Cardiac Death: A Population-Based Study

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Background—Left ventricular (LV) mass ascertained using echocardiography may enhance risk stratification for sudden cardiac death. The objective of this study was to assess the association between left ventricular mass and the risk of sudden cardiac death in a population-based cohort and determine its incremental value beyond conventional risk predictors.

Methods and Results—Assessment of LV mass was based on echocardiography in a sample of 905 middle-aged men representative of the general population (aged 42 to 61 years). During the follow-up period of 20 years, there were a total of 63 sudden cardiac deaths. In a comparison of the top versus the bottom quartile of LV mass adjusted by body surface area (>120 versus <89 g/m^2), the multivariable adjusted hazard ratio was 2.57 (95% CI 1.24 to 5.31, $P=0.010$). Further adjustment for LV function only modestly attenuated the risk of sudden cardiac death among men with LV mass of >120 g/m^2 (hazard ratio 2.29, 95% CI 1.10 to 4.74, $P=0.026$). Addition of LV mass adjusted by body surface area to a conventional risk factor model for sudden cardiac death improved the integrated discrimination index by 0.033 (95% CI 0.009 to 0.057, $P=0.007$) and the category-free net reclassification index by 0.501 (95% CI 0.092 to 0.911, $P=0.016$).

Conclusions—Indexed LV mass by body surface area is an independent predictor of sudden cardiac death and may help improve the risk prediction of sudden cardiac death beyond conventional cardiovascular risk factors. (*J Am Heart Assoc*. 2014;3: e001285 doi: 10.1161/JAHA.114.001285)

Key Words: echocardiography • epidemiology • left ventricular mass • prospective study • sudden cardiac death

S udden cardiac death (SCD) typically occurs soon after the onset of the first symptoms with few or no early warning signs or symptoms, leaving little time for effective medical interventions.[1] Due to the high impact of SCD worldwide, prevention appears to be a desirable approach to decrease the risk of SCD at the population level.[2–4] Echocardiographic measures of left ventricular (LV) mass may help improve risk stratification for SCD beyond conventional cardiovascular risk factors. Some studies have observed that an elevated LV mass is associated with increased risk of cardiovascular diseases[5–9]

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and SCD.[10,11] However, there is limited prospective evidence available on the association of indexed LV mass and the risk of SCD. Previous case–control study suggested that body surface area (BSA) adjusted LV mass may have an additive effect on SCD risk irrespective of LV function.[12] The aim of this prospective study was to evaluate the association and prognostic significance of LV mass/BSA in relation to the risk of SCD in a representative population-based sample of men.

Methods

Subjects

The study was carried out with the participants of the Kuopio Ischaemic Heart Disease Risk Factor Study, a longitudinal population-based study initially designed to investigate risk factors for cardiovascular diseases and SCD. This prospective study focused on LV mass defined by echocardiography and SCD risk in the general population. The study population is a representative sample of men who were 42 to 61 years of age at baseline examinations performed between March 1984 and December 1989, and living in the city of Kuopio and its surrounding rural communities.[4] Of 3235 potentially eligible men, 2682 (83%) volunteered to participate in this study. The

Kuopio Ischaemic Heart Disease Risk Factor Study was approved by the Research Ethics Committee of the University of Kuopio, and each participant gave written informed consent. The study reported here is based on data obtained from 905 participants who had complete data on echocardiographic measurements available at baseline.[13] All men who visited consecutively from 1986 to 1988 participated in the study. There were no statistically significant differences in baseline characteristics between those who were included and those excluded from the current study. Although men who excluded were slightly older (age 53.8 versus 50.5 years, P=0.001) as compared with men who were included in the final analysis, all other key characteristics including body mass, cigarette smoking, serum lipids, blood pressure, and prevalent diseases did not differ statistically significantly at baseline.

Echocardiographic Assessment of LV Mass

Echocardiographic studies were performed with an ATL Ultramark IV system and the use of two-dimensional-guided M-mode measurements with a 3.0- or 3.5-MHz transducer. Two-dimensional-guided M-mode images were obtained from the parasternal window and a perpendicular projection across the heart, with participants lying in a modified left lateral decubitus position.[13] Left atrium diameter, LV end-diastolic and systolic internal dimension, end-diastolic thickness of the interventricular septum and the LV posterior wall and LV function (fractional shortening, percent) were among the measures collected. All measures were calculated from leading edge to leading edge. LV diameter and wall thicknesses were measured in the parasternal long-axis view. LV mass was calculated by using the Devereux formula (corrected American Society of Echocardiography cube method).[13–15] The reproducibility of this measure was tested at baseline in a random sample of 30 subjects re-examined at 3-week intervals, yielding a retest reliability of 0.82 between the 2 examinations. The change in LV mass was defined by repeating the assessment of LV mass in the midpoint of the follow-up in a random sample. LV mass was adjusted for BSA (calculated by $[weight^{0.425} \times height^{0.725}] \times 0.007184$).[16] We used BSA-adjusted approach defined by indexed LV mass of >125 g/m^2 as a cut-off for LV hypertrophy supported by previous evidence.[13,16] We also conducted analyses based on LV/mass divided by height.[17] All the echocardiographic measurements were performed and interpreted during the baseline and follow-up examination by 2 independent cardiologists according to the standardized protocol.

Assessment of Risk Factors and Clinical Diseases

The collection of blood specimens including measurement of fasting levels of serum lipids and assessment of smoking,

alcohol consumption, and the definition of type 2 diabetes are described elsewhere.[4,18] Resting blood pressure was measured by an experienced nurse using a random-zero sphygmomanometer (Hawskley, UK) after 5 and 10 minutes of rest in a seated position.[18] The lifelong exposure to smoking (cigarette pack-years) was estimated as the product of the number of smoking years multiplied by the number of tobacco products smoked daily. Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. Baseline diseases, family histories, and the regular use of antihypertensive medication were assessed by self-administered questionnaires, which were checked during a medical examination by a physician. Cardiorespiratory fitness was defined as the highest value or the plateau of directly measured oxygen uptake based on breathing gas exchange during the exercise testing.[4]

Definition of Follow-Up Events

Deaths that occurred by the end of 2010 were checked against the hospital documents, health centers, and death certificates. There were no losses to follow-up. A death was classified as SCD when it occurred within 24 hours of the onset of symptoms, including nonwitnessed cases when clinical and autopsy findings did not reveal a noncardiac cause of sudden death.[4] The witnessed subject was to have been seen alive and symptom free within 1 hour before the event. SCDs that occurred in out-of-hospital conditions were also defined as places in which the events that occurred had been reported accurately in hospital documents.[4] The deaths due to aortic aneurysm rupture or tamponade and pulmonary embolism were not included as SCD. The sources of information were interviews, hospital documents, death certificates, autopsy reports, and medicolegal reports. The diagnostic classification of events was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80% of all cardiac deaths), and history of coronary heart disease (CHD) together with the clinical and electrocardiographic findings of the paramedic staff. All the documents related to the death were cross-checked in detail by 2 physicians. Non-SCDs were also carefully documented using standardized criteria. Cardiac deaths that did not lead to death during the following 24 hours of the onset of symptoms were considered as non-SCD. Data on incident nonfatal acute coronary events were obtained by computer linkage to the national hospital register. The independent events committee, blind to clinical data, performed the classification of deaths. All coronary interventions including percutaneous coronary intervention and coronary artery bypass graft surgery performed due to clinical reasons were also defined during the follow-up. The information based on the interventions was collected from the hospital coronary intervention registry.

Statistical Analysis

Descriptive data are presented as means (SD) and percentages. Correlation coefficients are reported for LV mass/BSA and relevant risk factors. Means of continuous variables were compared using the *t* test, and χ^2 tests were used for categorical variables. Time-to-event analyses were conducted using Cox proportional hazard models adjusted for age, systolic blood pressure, cigarette smoking, serum low-density lipoprotein cholesterol, type 2 diabetes, BMI, previous myocardial infarction, family history of CHD, and cardiorespiratory fitness. Covariates were selected on the basis of their previously established role as a well-defined predictive factor on the basis of overall evidence and available data. To evaluate whether LV mass/BSA were associated with SCD independently of incident nonfatal coronary events during follow-up, we adjusted for acute coronary events, fitting these as time-dependent covariates in regression models. The proportional hazards assumption was evaluated by examining the Schoenfeld residuals.

To quantify within-person variability in LV mass indexed to BSA, which is the extent to which an individual's indexed LV mass varies around a long-term average level, the regression dilution ratio was estimated from a linear regression of the available repeat measurements made in samples collected at an 11-year follow-up interval in 579 individuals, approximately the midpoint of this study's follow-up duration. The usual levels of LV mass indexed to BSA were then generated using regression calibration models, which take into account the long-term within-person variability (eg, increase in LV mass). Regression dilution ratio assumed that the "usual levels" of LV mass represented the true long-term exposure of LV mass on SCD risk.[19]

The shape of association with SCD risk was assessed by plotting hazard ratios (HR) calculated within the prespecified quartiles of baseline LV mass to BSA against the mean value within each fourth. Floating variances were used to calculate 95% CI for the HR in each group, including the reference group, to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category (ie, bottom quartile). Appropriate interaction terms were introduced to examine for differences in HRs across levels of prespecified clinical characteristics (LV function, history of hypertension, CHD or pulmonary disease, BMI, the use of β-blockers, and age).

The C-index was calculated to assess the model discrimination (the ability of the model to correctly identify subjects with respect to SCD). The incremental value of indexed LV mass in addition to previously documented risk factors and diseases were evaluated using C-index. Additionally, the risk prediction models were compared using metrics of risk reclassification, including the integrated discrimination improvement and a category-free measure of the net reclassification index, which is a measure without predefined risk categories.[20] The change in C-index and the measures of risk reclassification were assessed for the model (age, systolic blood pressure, cigarette smoking, serum low density lipoprotein cholesterol, type 2 diabetes, BMI, previous myocardial infarction, family history of CHD, and cardiorespiratory fitness) with and without LV mass/BSA. A 2-sided $P<0.05$ was accepted as statistically significant for all analyses. Statistical analyses were performed using SPSS version 20.0 IBM Corp., Armonk, NY and STATA version 11.0 StataCorp LP, College Station, TX.

Results

Characteristics

The mean age of participants was 50.5 (SD 6.6) years, and mean LV mass was 207 g (SD 54, range 92 to 525 g). Both LV end-diastolic ($r=0.659$, $P<0.001$) and end-systolic ($r=0.536$, $P<0.001$) diameter were correlated with LV mass. Baseline characteristics and their correlation with LV mass/BSA are shown in Table 1. Prevalence of LV hypertrophy, defined as LV mass >125 g/m^2, was 19.3% (n=175).

Outcomes

Overall, 63 SCDs were recorded during an average follow-up of 20.2 years (interquartile range 18.8 to 21.3 years=53 623.6 person-years). A total of 55 SCDs (83% of all events) occurred in out-of-hospital situations, and most of these cases were due to documented ventricular tachycardia, ventricular fibrillation, or death with autopsy revealing no other reason for death. Echocardiographic characteristics are shown according to subsequent SCD in Table 2.

LV Mass and the Risk of SCD

Cumulative hazard curves demonstrated the highest risk of SCD among males in the top fourth indexed LV mass to BSA compared to those in the bottom fourth (*P*-value for log-rank test <0.001: Figure 1). Men with LV mass/BSA of >120 g/m^2 had 2.57-fold risk of SCD compared to men with LV mass/BSA of <89 g/m^2, after adjusting for the multivariable model with age, systolic blood pressure, cigarette smoking, serum low-density lipoprotein cholesterol, type 2 diabetes, BMI, previous myocardial infarction, family history of CHD, and cardiorespiratory fitness (Table 3). The highest fourth of LV mass/BSA showed a higher rate of SCD, whereas the risk was not significantly increased among subjects in the second and

Table 1. Baseline Demographic Characteristics and Correlations With Left Ventricular (LV) Mass/Body Surface Area (BSA) (n=905)

	Mean (SD) or Proportion	LV Mass/BSA
Characteristics		Correlation (95% CI)[†]
Age, y	50.5 (6.6)	0.15 (0.08, 0.21)*
Body weight, kg	80.6 (11.3)	0.15 (0.09, 0.22)*
Body mass index, kg/m^2	26.7 (3.1)	0.14 (0.08, 0.21)*
BSA, m^2	1.94 (0.15)	0.14 (0.07, 0.20)*
Cigarette pack-years of smoking[‡]	7.6 (15.7)	−0.04 (−0.10, 0.03)
Systolic blood pressure, mm Hg	132.3 (15.4)	0.14 (0.07, 0.20)*
Diastolic blood pressure, mm Hg	88.7 (10.2)	0.07 (0.01, 0.14)*
Serum total cholesterol, mmol/L	5.78 (1.00)	−0.01 (−0.07, 0.06)
Serum LDL-cholesterol, mmol/L	3.87 (0.92)	−0.03 (−0.10, 0.03)
Serum HDL-cholesterol, mmol/L	1.27 (0.29)	0.09 (0.02, 0.15)*
Cardiorespiratory fitness, mL/kg per minute[§]	32.1 (7.8)	0.04 (−0.03, 0.10)
Categorical variable		Change relative to ref category[‖]
Smoker, %	31.2	−2.22 (−5.78, 1.34)
Diabetes, %[¶]	4.9	2.56 (−5.34, 10.45)
Atrial fibrillation, %	1.2	4.45 (−7.44, 16.33)
Hypertension, %	25.8	2.77 (−0.55, 6.09)
Family history of coronary heart disease, %	48.9	−1.42 (−4.74, 1.89)
Regular use of medication		
Antihypertensive drugs, %	13.9	9.95 (5.56, 14.35)*
Statins,%	6.2	−5.94 (−26.39, 14.52)
β-Blockers, %	9.6	7.68 (2.75, 12.62)*
Aspirin, %	9.5	−1.29 (−6.68, 4.11)

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

*P<0.05 for statistical significance.

[†]Correlation coefficient (95% CI).

[‡]Pack-years denotes the lifelong exposure to smoking which was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination.

[§]Cardiorespiratory fitness was defined as the highest value or the plateau of oxygen uptake during the exercise testing.

[‖]Reference is the category without the characteristic (eg, change relative to the reference).

[¶]Diabetes was defined as fasting blood glucose ≥6.1 mmol/L or a clinical diagnosis of diabetes with either dietary, oral, or insulin treatment.

third fourths. LV function at baseline and acute coronary events during the interim period were additionally taken into account, and HRs were still more than 2-fold for men in the highest fourth, respectively. The respective relation between the highest fourth of LV mass/BSA and SCD was significant after adjustment for coronary interventions during the follow-up (adjusted HR 2.07, 95% CI 1.34 to 3.19, P=0.001 for men in the highest quartile). Estimated regression dilution ratio was 0.84 (CI 0.79 to 0.88) for LV mass adjusted to BSA, indicating the changes in LV mass over the time. The shapes of the association of the usual level of LV mass to BSA with the risk of SCD are shown in Figure 2 when the regression dilution ratio was included in the model. The relationship between LV mass/BSA (in quartiles) and the risk of non-SCD was not significant (P=0.229).

The age and risk-factor adjusted HR for LV hypertrophy defined by categorized LV mass of >125 g/m^2 was 2.72 (95% CI 1.59 to 4.65, P<0.001) for the risk of SCD. Additional adjustment for LV function did not change considerably the association between LV mass of >125 g/m^2 and the risk of SCD (HR 2.50, 95% CI 1.46 to 4.29, P=0.001). When using the lower cut-off of >116 g/m^2 for LV hypertrophy, the respective HRs were 1.84 (95% CI 1.09 to 3.10, P=0.023) and 1.69 (95% CI 1.01 to 2.86, P=0.049) after additional adjustment for LV function. LV mass was a significant predictor of SCD risk among subjects without previous history of CHD, hypertension, pulmonary disease, or the use of β-blockers (Figure 3). In general, the association between LV hypertrophy (>125 kg/m^2) and the risk of SCD was consistent across several subgroups without a statistically significant interac-

Table 2. Echocardiographic Characteristics With and Without Sudden Cardiac Death (SCD) During Follow-Up (n=905)

	SCD (63 Men)	Others (842 Men)	
	Mean (SD)	Mean (SD)	P Value for the Difference
Left ventricular mass, g*	241.4 (73.8)	204.3 (51.2)	<0.001
Left ventricular mass/BSA, g/m^2	125.1 (37.5)	104.8 (23.9)	<0.001
Left ventricular posterior wall at end diastole, mm	11.6 (2.0)	10.7 (1.5)	<0.001
Ventricular septum at end diastole, mm	11.0 (2.3)	10.2 (1.7)	0.001
Left ventricular end-diastolic diameter, mm	53.2 (6.7)	51.3 (4.3)	0.001
Left ventricular end-systolic diameter, mm	36.8 (7.6)	34.0 (4.6)	<0.001
Left ventricular function, fractional shortening, %	31.1	34.9	<0.001
Aortic diameter, mm	35.9 (4.2)	35.3 (3.6)	0.233
Left atrium diameter, mm	44.9 (6.2)	41.1 (5.2)	<0.001

BSA indicates body surface area.

*Left ventricular mass calculated by using the Devereux formula (corrected American Society of Echocardiography cube method).[14]

tion. In addition, LV diameter (mm) was related to risk of SCD (adjusted HR 1.21, 95% CI 1.06 to 1.37, *P*=0.004). Men in the highest quartile of LV diastolic diameter (>54 mm) had a 2.27-fold (95% CI 1.37 to 3.77, *P*=0.001) risk of SCD, compared to those in the lowest quartile of LV diastolic diameter (>48 mm). LV diastolic diameter/BSA (mean 27 mm/m^2) as a continuous variable was also related to the risk of SCD (adjusted HR 1.13, 95% CI 1.05 to 1.22, *P*=0.002 per mm/m^2 change).

Men in the highest fourth of LV mass indexed to BSA (>120 g/m^2) had an adjusted HR of 3.39 (95% CI 1.32 to 8.73, *P*=0.010) for out-of-hospital SCD compared to men with LV mass indexed to BSA (<89 g/m^2) in the lowest fourth. Similarly, men with LV mass indexed to BSA >125 g/m^2 had
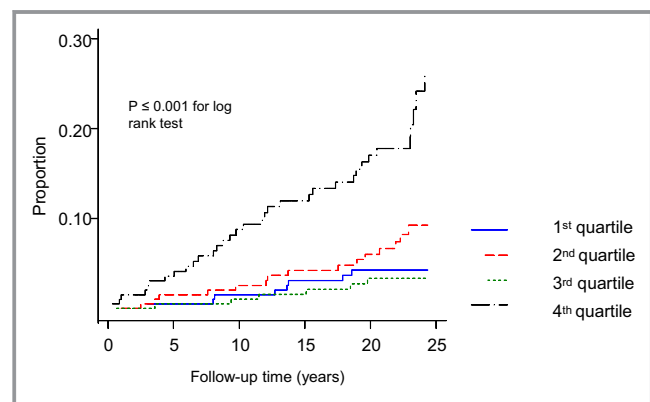
an adjusted HR of 2.62 (95% CI 1.40 to 4.91, *P*=0.003) for out-of-hospital SCD compared to men with LV mass index to BSA ≤125 g/m^2. Prevalence of LV hypertrophy, as by defined LV mass indexed to height (LV mass per height$^{2.7}$) of >51 g/m, was 29.8% (n=270). The age and risk-factor adjusted HR for LV hypertrophy defined by height-categorized LV mass of >51 g/m was 1.72 (95% CI 1.01 to 2.93, *P*=0.046) for the risk of SCD. Additional adjustment for LV function weakened the association between LV hypertrophy of >51 g/m and the risk of SCD (HR 1.56, 95% CI 0.91 to 2.65, *P*=0.104).

Risk prediction models for SCD that added indexed LV mass/BSA to the previously established risk factors, as described earlier, increased integrated discrimination improvement by 0.033 (95% CI 0.009 to 0.057, *P*=0.007) and the category-free measure of the net reclassification index by 0.501 (95% CI 0.092 to 0.911, *P*=0.016). Inclusion of indexed LV mass/BSA in the model with age and previously established risk factors did not yield a statistically significant C-index change (0.007) (95% CI –0.009 to 0.023, *P*=0.418).

Figure 1. The cumulative hazard curves during the follow-up according to the quartiles of ratio of left ventricular mass to body surface area. The cut-off values for quartiles were as follows: left ventricular mass/body surface area first <89 g/m^2, second 89 to 103 g/m^2, third 104 to 120 g/m^2, fourth >120 g/m^2 (n=905).

Discussion

LV mass indexed by BSA was independently associated with the risk of SCD; most of the SCDs occurred in out-of-hospital conditions. Indexed LV mass defined by echocardiography incrementally improved SCD risk prediction beyond conventional risk factors.

The presence and severity of underlying heart disease including myocardial infarction with LV dysfunction has been the single most predictive risk factor for SCD.[3,21] The availability of LV function in the risk prediction for SCD has been limited by low sensitivity in the general population, as

Table 3. Association of Indexed LV Mass to Body Surface Area With the Risk of Sudden Cardiac Death (n=905)

|	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
LV mass/BSA, g/m^2								
Q1, <89 g/m^2	Ref		Ref		Ref		Ref	
Q2, 89 to 103 g/m^2	0.87 (0.37 to 2.04)	0.746	1.02 (0.43 to 2.47)	0.949	0.99 (0.41 to 2.40)	0.991	0.97 (0.40 to 2.35)	0.953
Q3, 104 to 120 g/m^2	1.39 (0.64 to 3.03)	0.405	1.36 (0.59 to 3.08)	0.465	1.25 (0.55 to 2.85)	0.595	1.24 (0.55 to 2.84)	0.602
Q4, >120 g/m^2	3.66 (1.86 to 7.18)	<0.001	2.57 (1.24 to 5.31)	0.010	2.29 (1.10 to 4.74)	0.026	2.28 (1.10 to 4.72)	0.027

Model 1: Unadjusted. Model 2: Adjusted age, cigarette smoking, serum low-density lipoprotein cholesterol, systolic blood pressure, type 2 diabetes, body mass index, previous myocardial infarction, family history of coronary heart disease, and cardiorespiratory fitness. Model 3: Model 2 plus left ventricular function. Model 4: Model 3 plus time-varying incident coronary events. BSA indicates body surface area; HR, hazard ratio; LV, left ventricular; Q1 to Q4, quartiles from 1 to 4.

the majority of subjects who suffer from SCD seem to have a preserved LV systolic function.[22] In this study of men from the general population, the assessment of LV mass by echocardiography with the definition of LV function provided valuable additional prognostic information for the risk of SCD.
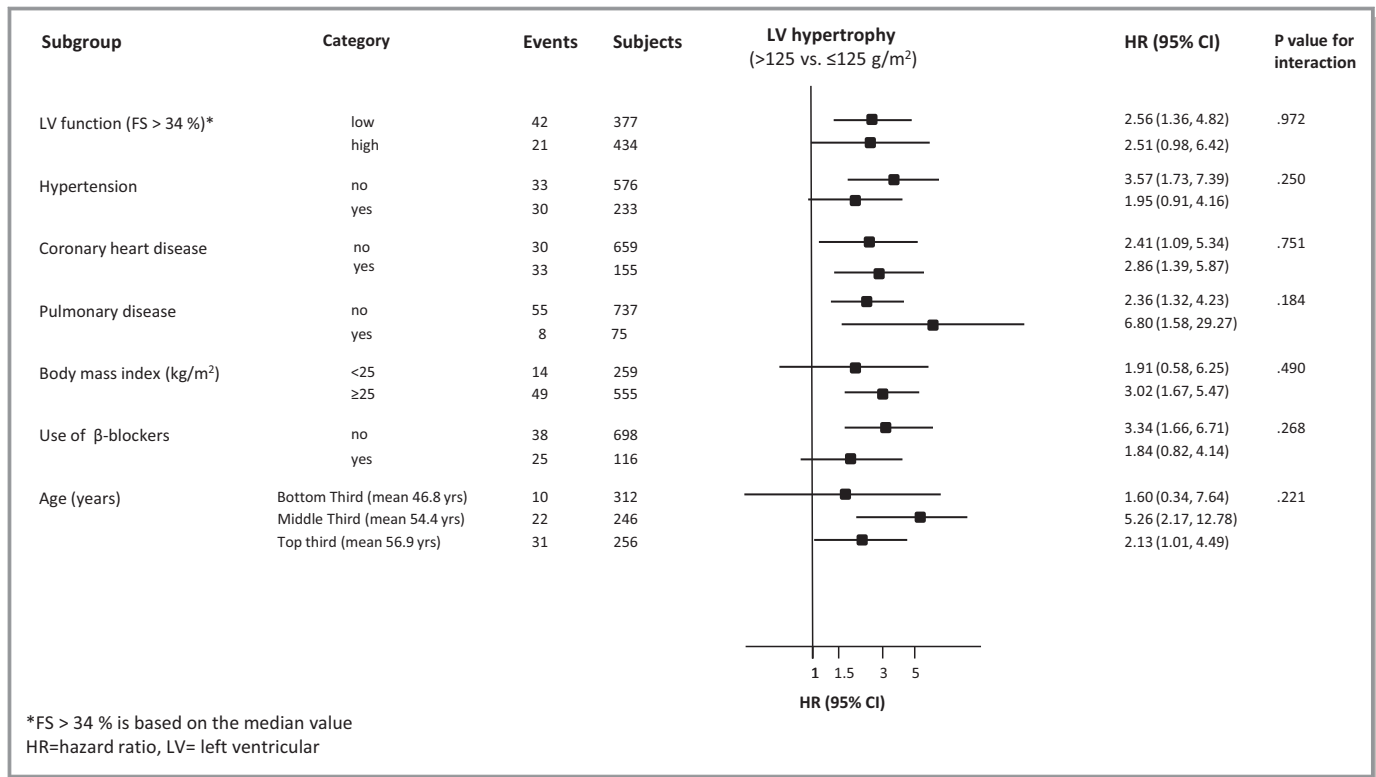
The observed association between LV mass and the risk of non-SCD was not statistically significant, indicating that LV mass is a more specific risk factor for SCD. The elevated risk of SCD seems to be limited in the top quartile of LV mass/ BSA, which was significantly different from the bottom quartile, and the association was significant after progressive adjustment for LV function and incident nonfatal coronary events occurring during the follow-up. On the basis of

supplementary analysis, LV mass was consistently related to SCD among subjects without previous history of hypertension, CHD or pulmonary disease, or the use of β-blockers, although the number of SCDs was limited for very detailed subgroup analysis.

In our study with the population sample of middle-aged men, the prevalence of BSA-adjusted LV hypertrophy, as defined by LV mass of >125 g/m^2, was in accordance with previous studies.[9,12,13,21–23] The American and European guidelines for echocardiography have suggested that LV mass indexed by BSA from 117 to 130 g/m^2 is a moderately abnormal finding.[24] In our study, the results were consistent while using the cut-off of >116 g/m^2. LV hypertrophy has
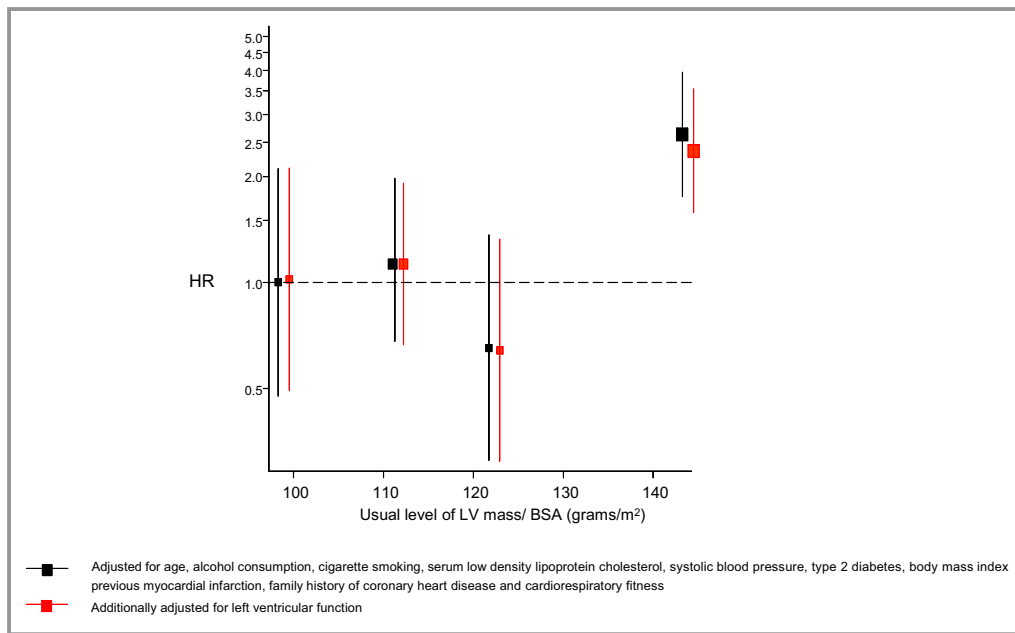
Figure 2. Hazard ratios (HRs) for sudden cardiac death by the quartiles of usual levels of ratio of left ventricular (LV) mass to body surface area (BSA). HRs and their 95% "floating absolute" CIs per LV mass/ BSA are shown. The size of the box is proportional to the inverse of the variance of HR. The first category is the reference (n=905).

Subgroup	Category	Events	Subjects	LV hypertrophy (>125 vs. ≤125 g/m^2)	HR (95% CI)	P value for interaction
LV function (FS > 34 %)*	low	42	377		2.56 (1.36, 4.82)	.972
	high	21	434		2.51 (0.98, 6.42)	
Hypertension	no	33	576		3.57 (1.73, 7.39)	.250
	yes	30	233		1.95 (0.91, 4.16)	
Coronary heart disease	no	30	659		2.41 (1.09, 5.34)	.751
	yes	33	155		2.86 (1.39, 5.87)	
Pulmonary disease	no	55	737		2.36 (1.32, 4.23)	.184
	yes	8	75		6.80 (1.58, 29.27)	
Body mass index (kg/m^2)	<25	14	259		1.91 (0.58, 6.25)	.490
	≥25	49	555		3.02 (1.67, 5.47)	
Use of β-blockers	no	38	698		3.34 (1.66, 6.71)	.268
	yes	25	116		1.84 (0.82, 4.14)	
Age (years)	Bottom Third (mean 46.8 yrs)	10	312		1.60 (0.34, 7.64)	.221
	Middle Third (mean 54.4 yrs)	22	246		5.26 (2.17, 12.78)	
	Top third (mean 56.9 yrs)	31	256		2.13 (1.01, 4.49)	

HR (95% CI): 1 1.5 3 5

*FS > 34 % is based on the median value
HR=hazard ratio, LV= left ventricular

Figure 3. Association of left ventricular (LV) hypertrophy (LV mass/body surface area of >125 g/m^2) in the clinical subgroups. FS indicates fractional shortening; HR, hazard ratios.

been detected by echocardiography in 16% to 19% of a general population and at least 20% to 23% or even more often among hypertensive subjects.[9,13,22,25] Repeated assessment of LV mass indicated that the change in LV mass in the general male population was very slight over many years. We also demonstrated that LV adjusted by height was also related to the risk of SCD. However, LV mass per height[2.7] index is not considered to be an adequate method for normalization of LV mass for body size.[17] It has been proposed that the indexation per height may misclassify very tall or short subjects.[17]

The electrophysiological alterations induced by the increased LV mass may initiate fatal arrhythmias among patients with LV hypertrophy,[24] which has been shown to increase in the frequency and complexity of fatal ventricular arrhythmias,[24–26] and the risk of SCD could be independent from the level of LV function.[12] LV hypertrophy has been associated with longer action potential durations, increased dispersion of repolarization, and vulnerability to fatal arrhythmias.[27,28] These pathophysiologies may be fostered by the development of myocardial fibrosis in subjects with LV hypertrophy, which are important contributing mechanisms of SCD without significant occlusion of coronary arteries. The increase in LV mass lowers coronary-flow reserve with increased oxygen requirements, reduces endothelial

vasodilatory capacity, and impairs LV muscle filling and contractility.[29] Some SCDs may be caused by unexpected plaque rupture that has been found among patients with the presence of both LV hypertrophy and coronary artery disease.[30,31] Hypertensive LV hypertrophy is associated with vascular hypertrophy, which may increase the serious consequences of coronary artery occlusion by sudden plaque rupture and/or thrombosis.[12,31] Electrocardiographically defined LV hypertrophy during antihypertensive therapy is associated with a lower likelihood of SCD independently of blood pressure among hypertensive patients.[32] On the basis of both animal and human studies, antihypertensive therapy could cause regression of LV hypertrophy, leading to lowered risk of cardiovascular events.[32,33] As the pathophysiology of underlying LV hypertrophy is multifactorial, however, there are no specific therapeutic agents that are specifically targeted to LV hypertrophy independently of blood-pressure–lowering therapies.[34]

This representative sample of men makes it possible to generalize the observed results in the male population, although these findings need to be reaffirmed in females and non-European ethnic groups. However, prior findings based on women and other ethnic groups have found no evidence to suggest an altered mechanism of SCD by race or gender.[35] The within-person variability of LV mass was taken

into account in multivariable analysis showing the effect of long-term exposure on SCD risk (eg, due to changes in health habits and medications). LV mass with the definition of LV diameter was assessed using the standardized M-mode echocardiography, which is a widely accepted method for the assessment of LV mass. The definition of LV mass by using M-mode echocardiography is a standard method, emphasizing the utilities of LV mass defined by M-mode for risk prediction.[14,24] The availability of more advanced cardiac imaging modalities to define better descriptors of LV function is a valuable asset in clinical studies, but cost tends to be a limiting factor in population-based studies. Other imaging modalities were not used to assess cardiac function and structure at the time of baseline examination. In addition to LV mass, we limited the use of the number of echocardiographic variables to avoid overadjustment from highly collinear variables.

In conclusion, this study provides evidence that LV mass is a noninvasive echocardiographic parameter that improves risk stratification for SCD in a population-based sample of men. Identification of subjects with LV hypertrophy, which can be easily defined in clinical practice, could provide an additional tool in the prediction of the risk of SCD. Additional evidence is still needed to support the assessment of LV mass for screening individuals at higher risk of SCD.

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Disclosures

None.

References

1. Albert CM, Ruskin JN. Risk stratifiers for sudden cardiac death (SCD) in the community: primary prevention of SCD. *Cardiovasc Res*. 2001;50:186–196.

2. Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population: the Paris Prospective Study I. *Circulation*. 1999;99:1978–1983.

3. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med*. 2001;345:1473–1482.

4. Laukkanen JA, Mäkikallio TH, Rauramaa R, Kiviniemi V, Ronkainen K, Kurl S. Cardiorespiratory fitness is related to the risk of sudden cardiac death: a population-based follow-up study. *J Am Coll Cardiol*. 2010;56:1476–1483.

5. Kannel WB. Hypertension: reflections on risks and prognostication. *Med Clin North Am*. 2009;93:541–558.

6. Yiu KH, Tse HF. Hypertension and cardiac arrhythmias: a review of the epidemiology, pathophysiology and clinical implications. *J Hum Hypertens*. 2008;22:380–388.

7. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Left ventricular mass and incidence of coronary heart disease in an elderly cohort: The Framingham Heart Study. *Ann Intern Med*. 1989;110:101–107.

8. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;322:1561–1566.

9. Sundstrom J, Lind L, Arnlov J, Zethelius B, Andren B, Lithell HO. Echocardiographic and electrocardiographic diagnoses of left ventricular hypertrophy predict mortality independently of each other in a population of elderly men. *Circulation*. 2001;103:2346–2351.

10. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol*. 1998;32:1454–1459.

11. Aronow WS, Epstein S, Koenigsberg M, Schwartz KS. Usefulness of echocardiographic left ventricular hypertrophy, ventricular tachycardia and complex ventricular arrhythmias in predicting ventricular fibrillation or sudden cardiac death in elderly patients. *Am J Cardiol*. 1988;62:1124–1125.

12. Reinier K, Dervan C, Singh T, Uy-Evanado A, Lai S, Gunson K, Jui J, Chugh SS. Increased left ventricular mass and decreased left ventricular systolic function have independent pathways to ventricular arrhythmogenesis in coronary artery disease. *Heart Rhythm*. 2011;8:1177–1182.

13. Laukkanen JA, Kurl S, Eränen J, Huttunen M, Salonen JT. Left atrium size and the risk of cardiovascular death in middle-aged men. *Arch Intern Med*. 2005;165:1788–1793.

14. Devereux RB. Detection of left ventricular hypertrophy by M-mode echocardiography: anatomic validation, standardization, and comparison to other methods. *Hypertension*. 1987;9:II9–II26.

15. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–458.

16. Kamarck TW, Eränen J, Jennings JR, Manuck SB, Everson SA, Kaplan GA, Salonen JT. Anticipatory blood pressure responses to exercise are associated with left ventricular mass in Finnish men: Kuopio Ischemic Heart Disease Risk Factor Study. *Circulation*. 2000;102:1394–1399.

17. Chirinos JA, Segers P, De Buyzere ML, Kronmal RA, Raja MW, De Bacquer D, Claessens T, Gillebert TC, St John-Sutton M, Rietzschel ER. Left ventricular mass: allometric scaling, normative values, effect of obesity, and prognostic performance. *Hypertension*. 2010;56:91–98.

18. Everson SA, Kaplan GA, Goldberg DE, Salonen JT. Anticipatory blood pressure response to exercise predicts future high blood pressure in middle-aged men. *Hypertension*. 1996;27:1059–1064.

19. Fibrinogen Studies Collaboration. Correcting for multivariate measurement error by regression calibration in meta-analyses of epidemiological studies. *Stat Med*. 2009;28:1067–1092.

20. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30:11–21.

21. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, Maron BJ, Page RL, Passman RS, Siscovick D, Stevenson WG, Zipes DP. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. *J Am Coll Cardiol*. 2008;52:1179–1199.

22. Gosse P, Dallocchio M. Left ventricular hypertrophy: epidemiological prognosis and associated critical factors. *Eur Heart J*. 1993;14(suppl):16–21.

23. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. *J Am Coll Cardiol*. 2003;41:1036–1043.

24. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of

Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.

25. Casale PN, Devereux RB, Milner M, Zullo G, Harshfield GA, Pickering TG, Laragh JH. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med*. 1986;105:173–178.

26. Ghali JK, Kadakia S, Cooper RS, Liao YL. Impact of left ventricular hypertrophy on ventricular arrhythmias in the absence of coronary artery disease. *J Am Coll Cardiol*. 1991;17:1277–1282.

27. Frohlich ED, Apstein C, Chobanian AV, Devereux RB, Dustan HP, Dzau V, Fauad-Tarazi F, Horan MJ, Marcus M, Massie B. The heart in hypertension. *N Engl J Med*. 1992;327:998–1008.

28. Biagetti MO, Quinteiro RA. Gender differences in electrical remodeling and susceptibility to ventricular arrhythmias in rabbits with left ventricular hypertrophy. *Heart Rhythm*. 2006;3:832–839.

29. Antony I, Nitenberg A, Foult JM, Aptecar E. Coronary vasodilator reserve in untreated and treated hypertensive patients with and without left ventricular hypertrophy. *J Am Coll Cardiol*. 1993;22:514–520.

30. Messerli FH, Ketelhut R. Left ventricular hypertrophy: a pressure-independent cardiovascular risk factor. *J Cardiovasc Pharmacol*. 1993;22(suppl):S7–S13.

31. Burke AP, Farb A, Liang YH, Smialek J, Virmani R. Effect of hypertension and cardiac hypertrophy on coronary artery morphology in sudden cardiac death. *Circulation*. 1996;94:3138–3145.

32. Wachtell K, Okin PM, Olsen MH, Dahlöf B, Devereux RB, Ibsen H, Kjeldsen SE, Lindholm LH, Nieminen MS, Thygesen K. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: the LIFE Study. *Circulation*. 2007;116:700–705.

33. Artham SM, Lavie CJ, Milani RV, Patel DA, Verma A, Ventura HO. Clinical impact of left ventricular hypertrophy and implications for regression. *Prog Cardiovasc Dis*. 2009;52:153–167.

34. Stevens SM, Reinier K, Chugh SS. Increased left ventricular mass as a predictor of sudden cardiac death: is it time to put it to the test? *Circ Arrhythm Electrophysiol*. 2013;6:212–217.

35. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336:1276–1282.