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Increased Left Ventricular Mass Is a Risk Factor for the Development of a Depressed Left Ventricular Ejection Fraction Within Five Years

The Cardiovascular Health Study

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OBJECTIVES Our aim in this study was to determine whether increased left ventricular mass (LVM) is a risk factor for the development of a reduced left ventricular ejection fraction (LVEF).

BACKGROUND Prior studies have shown that increased LVM is a risk factor for heart failure but not whether it is a risk factor for a low LVEF.

METHODS As part of the Cardiovascular Health Study, a prospective population-based longitudinal study, we performed echocardiograms upon participant enrollment and again at follow-up of 4.9 ± 0.14 years. In the present analysis, we identified 3,042 participants who had at baseline a normal LVEF and an assessment of LVM (either by electrocardiogram or echocardiogram), and at follow-up a measurable LVEF. The frequency of the development of a qualitatively depressed LVEF on two-dimensional echocardiography, corresponding approximately to an LVEF <55%, was analyzed by quartiles of baseline LVM. Multivariable regression determined whether LVM was independently associated with the development of depressed LVEF.

RESULTS Baseline quartile of echocardiographic LVM indexed to body surface area was associated with development of a depressed LVEF (4.8% in quartile 1, 4.4% in quartile 2, 7.5% in quartile 3, and 14.1% in quartile 4 [$p < 0.001$]). A similar relationship was seen in the subgroup of participants without myocardial infarction ($p < 0.001$). In multivariable regression that adjusted for confounders, both baseline echocardiographic ($p < 0.001$) and electrocardiographic ($p < 0.001$) LVM remained associated with development of depressed LVEF.

CONCLUSIONS Increased LVM as assessed by electrocardiography or echocardiography is an independent risk factor for the development of depressed LVEF. (J Am Coll Cardiol 2004;43:2207–15)

Increased left ventricular mass (LVM) and left ventricular (LV) hypertrophy are important independent predictors of cardiovascular morbidity including heart failure in population studies (1–7). However, prior studies have not reported how often the heart failure attributed to LV hypertrophy occurred in the setting of a depressed or preserved left ventricular ejection fraction (LVEF) (7). Preserved LVEF is present in a significant number of patients with heart failure in epidemiologic studies (8–10). Additionally, heart failure in the presence of LV hypertrophy and a preserved LVEF may be due to related diastolic dysfunction (11,12). To our knowledge, no large prospective cohort study has previously addressed whether increased LVM is an independent risk factor for a subsequent decrease in LVEF. The Cardiovascular Health Study (CHS), a large multicenter longitudinal study of elderly individuals in which echocardiograms were performed at baseline and repeated approximately five years later (13,14), afforded the opportunity to address this important question.

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METHODS

Study population. There were 5,201 participants in the baseline CHS cohort, a National Heart, Lung, and Blood Institute-sponsored prospective cohort study previously described in detail (15). Participants were ≥65 years of age,

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Abbreviations and Acronyms

BSA = body surface area
CHS = Cardiovascular Health Study
CI = confidence interval
FS = fractional shortening
LV = left ventricular
LVEF = left ventricular ejection fraction
LVM = left ventricular mass

non-institutionalized, and were recruited between 1989 and 1990. At baseline, subjects underwent a comprehensive battery of examinations including laboratory evaluations obtained after a 12-h fast (15,16), electrocardiography, and echocardiography. Subjects have been followed serially since the baseline evaluation including a repeat echocardiogram performed in 1994 to 1995 (4.9 ± 0.14 years after baseline study), herein termed "follow-up echocardiogram." The present analysis includes those 3,042 participants with a baseline echocardiographic (n = 2,190) or electrocardiographic (n = 2,944) assessment of LVM, normal LVEF as assessed qualitatively by two-dimensional echocardiography at baseline, and an assessment of LVEF on the follow-up echocardiogram (Fig. 1). A second cohort of African-American subjects was recruited into the CHS between 1992 and 1993 and had their baseline echocardiogram in 1994 and 1995; given the lack of a follow-up echocardiogram, they were not included in the present analysis.

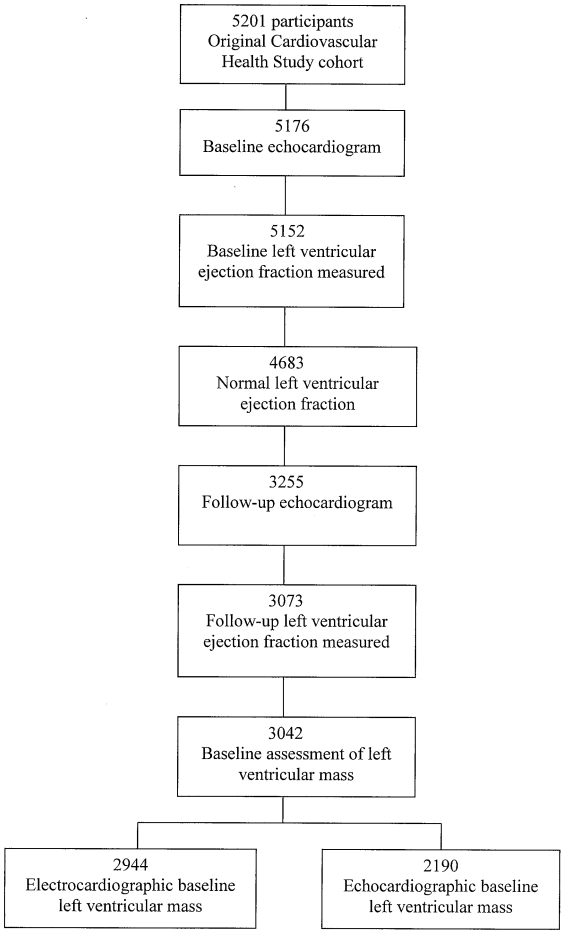

Figure 1. Number of participants meeting inclusion criteria.

Electrocardiography. Twelve-lead electrocardiograms were obtained at baseline and at follow-up and were analyzed at a core facility. Left ventricular mass was estimated as previously described (17). Left ventricular hypertrophy, Q waves, and atrial fibrillation were defined based on Minnesota codes (18).

Echocardiography. Echocardiographic images were obtained using a standardized protocol and recorded onto super VHS tape (13,14). The core reading center for baseline echocardiograms was located at University of California-Irvine, and for follow-up echocardiograms at Georgetown University, Washington, DC. The LVM was calculated as described by Devereux et al. (19): LVM (g) = 0.80×1.04 [(ventricular septal thickness diastole + LV diastolic dimension + ventricular posterior wall thickness diastole)^3 − (LV diastolic dimension)^3] + 0.6. Expected LVM was calculated for men as $16.6 \times$ [weight (kg)]$^{0.51}$ and for women as $13.9 \times$ [weight (kg)]$^{0.51}$ as before (1,14). Left ventricular hypertrophy was defined as an observed/expected LVM >1.45 (1,14). Fractional shortening (FS) at the endocardium and midwall was calculated from M-mode measurements (20,21). Stress-adjusted FS was calculated, and ratios of observed/predicted FS in the lower 5% of a reference population deemed free of cardiac disease were considered to be depressed (1,21). Left ventricular geometry was categorized into four mutually exclusive categories depending upon the presence of LV hypertrophy (observed/expected LVM >1.45 as above) and/or increased relative wall thickness (defined as >0.48 [6]). As compared with normal geometry, concentric remodeling was defined as increased relative wall thickness but observed/expected LVM ≤1.45, eccentric hypertrophy as observed/expected LVM >1.45 but no increased relative wall thickness, and concentric hypertrophy as increased relative wall thickness with observed/expected LVM >1.45.

Qualitative assessment of LVEF was obtained by two-dimensional echocardiography (14). Left ventricular ejection fraction was classified as normal, borderline, or abnormal approximately corresponding to values ≥55%, ≥45% and <55%, or <45%, respectively (1,10,22). Regional wall motion was also qualitatively assessed as normal, borderline, or abnormal (14). To assess agreement for qualitative assessment of LVEF between the baseline and follow-up echocardiography core centers, 238 baseline echocardiograms were reinterpreted by the follow-up echocardiography core center in a blinded fashion. There was an 87.8% agreement (kappa = 0.344) for whether LVEF was normal or not. This is comparable with assessments of inter-reader agreement of the follow-up echocardiogram (n = 250, agreement = 86.8%, kappa = 0.432) and, as previously reported, the baseline echocardiogram (agreement = 94%, kappa = 0.32) (14). Using two sets of baseline echocardio-

grams (set one: n = 81, set two: n = 41), the endocardial FS was recalculated at follow-up blinded to the original results. In set one, the original mean FS was 43.2%, and, on blinded reassessment at follow-up, it was 44.6%. In set two, the original mean FS was 40.7%, and on reassessment it was 45.2%.

Definitions. Hypertension was categorized as present if seated systolic blood pressure was 140 mm Hg or higher, or diastolic blood pressure was 90 mm Hg or higher, or the patient self-reported a history of hypertension in combination with use of antihypertensive medication. Methods of ascertaining myocardial infarction (23) have been described. The outcome measure was the development of a depressed LVEF as defined by a borderline or abnormal LVEF on the follow-up echocardiogram (see preceding text). These were grouped together because we have previously shown that borderline LVEF is an independent risk factor for mortality (22). However, we also performed a sensitivity analysis by considering subjects with follow-up borderline LVEF as having not reached the outcome.

Statistical analysis. Continuous variables are expressed as mean ± SD or median (25th, 75th percentile). Differences in continuous variables were compared with the *t* test except for levels of C-reactive protein and serum insulin in which the Wilcoxon rank-sum test was used due to highly skewed distributions. The significance of differences in categorical variables was assessed by chi-square analysis. Analyses incorporating LVM were performed with crude LVM and LVM indexed to body surface area (BSA) or height. Pearson correlation coefficients between baseline electrocardiographic LVM or baseline echocardiographic parameters and follow-up echocardiographic parameters were calculated. The frequency of the development of depressed LVEF was calculated in the cohort by quartiles of baseline LVM. The Cochran-Armitrage test of trend was used to determine the significance of the association of LVM measures and the development of a depressed ejection fraction. Similar analyses were performed in important subgroups.

Logistic regression was used to determine the association of either baseline LVM or baseline presence of LV hypertrophy with incident depressed LVEF. Linear regression was used to determine the association of LVM with follow-up mid-wall FS. Potential confounders including demographics, baseline height and weight, hypertension status, presence of coronary heart disease, atrial fibrillation, and baseline endocardial FS were incorporated as covariates in multivariable models. We excluded major residual confounding by those variables that were not included in the final multivariable models but that differed significantly between participants who did or did not reach the outcome on univariate analysis by adding them back into the final model and verifying that the association of the covariate of interest and outcome was not changed appreciably. Models were also constructed in which LV diastolic dimension was entered as an independent variable in addition to either LV septal wall thickness or posterior wall thickness to determine which components of LVM were associated with the outcome. In a separate set of models, categorical patterns of LV geometry were entered as an independent variable. Analyses were performed with SPSS software (SPSS Inc., Chicago, Illinois), and $p < 0.05$ was used as criteria for statistical significance.

Missing data. A separate analysis was performed to address the impact of missing data introduced by the requirement to have a follow-up CHS echocardiogram. In 131 participants who did not have a follow-up CHS echocardiogram but were otherwise eligible for inclusion in the present study, we ascertained whether they had developed a depressed LVEF from echocardiograms that had been performed as part of clinical care (and had been reassessed by CHS investigators as previously described [1]). The baseline LVM of those who developed a depressed LVEF was compared with the baseline LVM of the remainder of the subjects without a follow-up echocardiogram who did not have a known history of heart failure (including heart failure as a cause of death).

RESULTS

Baseline characteristics, interim clinical events, and follow-up. The baseline characteristics are shown in Table 1, stratified by whether baseline LVM was above or below the median value (137 g). Subjects with higher LVM were more often men with a history of hypertension, diabetes mellitus, and prior coronary heart disease. As would be expected, the component measures of LVM (LV diastolic dimension and posterior wall and septal wall thickness) also differed significantly between the two groups. When stratifying the cohort into quartiles of baseline echocardiographic LVM, the component values of LVM in quartile four were: LV diastolic dimension 5.4 ± 0.6 cm, septal wall thickness 1.0 ± 0.2 cm, and posterior wall thickness 0.95 ± 0.1 cm. A correlation matrix of baseline electrocardiographic LVM and echocardiographic parameters with follow-up echocardiographic parameters is shown (Table 2) ($p < 0.001$ for all correlations). Baseline LV dimensions, echocardiographic LVM, and electrocardiographic LVM were strongly and directly related to follow-up LV dimensions and inversely with follow-up FS measures. Baseline FS measures were inversely related to follow-up LV dimensions and directly related to follow-up FS measures. During follow-up (Table 3), participants who had higher baseline LVM were more likely to have a clinical event related to coronary artery disease (composite measure of myocardial infarction, percutaneous coronary angioplasty, or coronary artery bypass graft). They also were more likely to develop atrial fibrillation. A number of parameters on the follow-up echocardiograms differed between those with a higher or lower baseline LVM.

Table 1. Baseline Clinical Characteristics*

Characteristics	Baseline Echo LV Mass Below the Median† n = 1,095	Baseline Echo LV Mass Above the Median† n = 1,095	p Value
Age (yrs)	71.2 ± 4.5	71.6 ± 4.7	0.038
Ethnicity			0.152
Caucasian	1,042 (95.2)	1,044 (95.3)	
African American	45 (4.1)	49 (4.5)	
Other	8 (0.7)	2 (0.2)	
Male gender	215 (19.6)	587 (53.6)	< 0.001
Diabetes mellitus			< 0.001
None	999 (92.0)	946 (86.6)	
Fasting blood glucose >125 mg/dl	47 (4.3)	82 (7.5)	
History of treated diabetes	40 (3.7)	65 (5.9)	
Fasting glucose (mg/dl)	103 ± 23	108 ± 28	< 0.001
Hypertensive	477 (43.8)	638 (58.4)	< 0.001
Smoking status			< 0.001
Never	579 (52.9)	489 (44.7)	
Former	388 (35.5)	509 (46.6)	
Current	127 (11.6)	95 (8.7)	
History of			
Coronary heart disease‡	134 (12.2)	171 (15.6)	0.026
Heart failure	14 (1.3)	21 (1.9)	0.307
Use of medications			
ACE-I	42 (3.8)	57 (5.2)	0.150
Beta-blockers	115 (10.5)	159 (14.5)	0.005
Diuretics	202 (18.5)	253 (23.1)	0.008
Calcium channel blockers	89 (8.1)	133 (12.1)	0.002
Systolic blood pressure (mm Hg)	131 ± 20	137 ± 21	< 0.001
Heart rate (beats/min)	64 ± 9	62 ± 10	< 0.001
Weight (kg)	65.0 ± 11.1	75.4 ± 12.7	< 0.001
Body mass index (kg/m^2)	25 ± 4	27 ± 4	< 0.001
Serum creatinine (mg/dl)	1.0 ± 0.2	1.1 ± 0.3	< 0.001
C-reactive protein (mg/l)	1.6 (0.8, 2.7)	1.7 (0.9, 3.0)	0.002
Serum cholesterol (mg/dl)	220 ± 38	207 ± 37	< 0.001
Serum insulin (IU/ml)	11 (9, 15)	13 (10, 17)	< 0.001
Electrocardiographic variables			
Atrial fibrillation	16 (1.5)	30 (2.7)	0.052
Q_waves	26 (2.5)	43 (4.0)	0.050
LV hypertrophy	14 (1.3)	44 (4.1)	< 0.001
LV mass (g)	134 ± 21	161 ± 27	< 0.001
Echocardiographic variables			
Left atrial dimension (cm)	3.6 ± 0.6	4.0 ± 0.6	< 0.001
Posterior wall thickness, diastole (cm)	0.77 ± 0.11	0.90 ± 0.13	< 0.001
Ventricular septal thickness, diastole (cm)	0.79 ± 0.12	0.96 ± 0.18	< 0.001
LV diastolic dimension (cm)	4.6 ± 0.4	5.2 ± 0.6	< 0.001
LV systolic dimension (cm)	2.6 ± 0.4	3.0 ± 0.6	< 0.001
Endocardial FS (%)	43 ± 7	42 ± 8	< 0.001
Midwall FS (%)	24 ± 3	23 ± 4	< 0.001

*Data are presented as n (%) or means ± SD except for C-reactive protein and serum insulin where median (25th, 75th percentile) is reported; †median left ventricular (LV) mass = 137 g; ‡coronary heart disease includes myocardial infarction, angina, coronary artery bypass grafting, or percutaneous transluminal angioplasty.
ACE-I = angiotensin-converting enzyme inhibitors; FS = fractional shortening.

Follow-up LV function and its association with baseline LVM. Of the 3,042 participants with baseline assessment of LVM, 265 (8.7%) developed depressed LVEF during the ~5 years of follow-up. Those participants who did reach the outcome were more likely to have an interval myocardial infarction (16%) than those who did not reach the outcome (3%, $p < 0.001$). As would be expected, there were a number of significant differences in measurements from the follow-up echocardiograms of participants who reached the outcome as compared with those who did not. These included a larger LV diastolic dimension (5.3 ± 0.8 vs. 4.7 ± 0.5), LV systolic dimension (3.6 ± 1.0 vs. 2.7 ± 0.5), and left atrial dimension (4.2 ± 0.8 vs. 4.0 ± 0.9), and lower endocardial FS (33 ± 11 vs. 43 ± 8), and midwall FS (21 ± 7 vs. 23 ± 4), respectively ($p < 0.001$ for all comparisons).

The percentage of participants who developed a depressed LVEF, stratified by quartiles of baseline LVM (Fig. 2A), LVM indexed to BSA (Fig. 2B), and LVM indexed to height (Fig. 2C), are shown. Irrespective of indexation

Table 2. Correlation Matrix of Baseline Echocardiographic Parameters or Electrocardiographic LV Mass With Follow-Up Echocardiographic Parameters*

Follow-Up Echocardiographic Parameter	Baseline Echocardiogram					Baseline Electrocardiographic LV Mass
	LV Diastolic Dimension	LV Systolic Dimension	FS (Endocardial)	FS (Midwall)	LV Mass	
LV diastolic dimension	0.506	0.470	−0.228	−0.093	0.472	0.434
LV systolic dimension	0.397	0.466	−0.319	−0.184	0.363	0.346
FS (endocardial)	−0.152	−0.281	0.276	0.188	−0.125	−0.142
FS (midwall)	−0.077	−0.145	0.144	0.151	−0.144	−0.133
LV mass	0.496	0.392	−0.123	−0.084	0.603	0.534

*Pearson correlations are shown. Number of observations for correlations ranges from 1,656 to 2,126. $p < 0.001$ for all correlations.
FS = fractional shortening; LV = left ventricular.

method, increasing quartile of LVM was associated with the development of a depressed ejection fraction. This association remained true in a variety of subgroups (Fig. 3). Baseline echocardiographic LVM indexed to BSA was also associated with a decrease in FS from baseline to follow-up (change in FS: 0 ± 9.4 in quartile 1 vs. −1.5 ± 9.9 in quartile 4 of baseline LVM, $p < 0.03$). In unadjusted regression models using the entire cohort, baseline electrocardiographic and echocardiographic LVM (Table 4) and LV hypertrophy were also each significantly associated with incident depressed LVEF and inversely with follow-up mid-wall FS ($p < 0.005$ for all).

Sensitivity analysis. A sensitivity analysis was performed in which subjects with follow-up borderline LVEF were classified as having not reached the outcome. A depressed LVEF at follow-up occurred in 2% of participants using this definition. Baseline LVM indexed to BSA remained associated with the outcome (percentage developing a depressed LVEF in quartiles 1 through 4 of baseline echocardiographic LVM indexed to BSA was: 1.1%, 0.5%, 1.1%, and 4.6%, respectively; $p < 0.001$). Using quartiles of baseline electrocardiographic LVM index, the percentage of participants developing a depressed LVEF was 0.3%, 1.4%, 2.7%, and 3.4%, respectively ($p < 0.001$). The risk ratio for the development of a depressed LVEF associated with quartile 4 of baseline echocardiographic LVM index as compared with quartile 1 was 4.3 (95% confidence interval (CI) 1.8 to 10.6; $p < 0.001$).

Multivariable analysis. In multivariable models that adjusted for potential confounders, baseline electrocardiographic and echocardiographic LVM were each independently associated with the development of depressed LVEF and inversely with follow-up midwall FS (Table 4). The results were nearly identical when baseline midwall FS was

Table 3. Interim Clinical Events and Follow-Up Assessment*

Variables	Baseline Echo LV Mass Below the Median n = 1,095	Baseline Echo LV Mass Above the Median n = 1,095	p Value
Systolic blood pressure on follow-up (mm Hg)	132 ± 20	135 ± 21	0.003
Diastolic blood pressure on follow-up (mm Hg)	69 ± 11	69 ± 11	0.345
Interim clinical events (%)			
Myocardial infarction	38 (3.6)	53 (5.1)	0.108
Heart failure	30 (2.8)	75 (6.9)	< 0.001
Coronary artery bypass graft	14 (1.3)	47 (4.4)	< 0.001
Composite CAD event†	48 (4.6)	88 (8.6)	< 0.001
Angina	89 (8.8)	153 (15.4)	< 0.001
Follow-up electrocardiogram (%)			
Interim Q_waves	60 (5.6)	100 (9.6)	0.001
Interim atrial fibrillation	17 (1.6)	41 (3.8)	0.001
Follow-up echocardiogram			
Midwall FS (%)	23 ± 4	23 ± 4	< 0.001
Endocardial FS (%)	43 ± 8	42 ± 9	< 0.001
LV hypertrophy† (%)	74 (8.3)	176 (21.9)	< 0.001
LV mass (g)	127 ± 32	170 ± 47	< 0.001
Left atrial dimension (cm)	3.8 ± 0.6	4.2 ± 1.2	< 0.001
LV diastolic dimension (cm)	4.5 ± 0.5	5.0 ± 0.6	< 0.001
LV systolic dimension (cm)	2.6 ± 0.5	3.0 ± 0.7	< 0.001
LV function			< 0.001
Normal	1,048 (95.7)	973 (88.9)	
Mild decrease	37 (3.4)	92 (8.4)	
Moderate/severe decrease	10 (0.9)	30 (2.7)	

*Data are presented as n (%) or mean ± SD; †interim composite coronary artery disease (CAD) event included myocardial infarction, coronary artery bypass graft, or percutaneous transluminal angioplasty. Left ventricular (LV) hypertrophy was defined as observed/expected LV mass ratio >1.45 as before (1,14).
FS = fractional shortening.

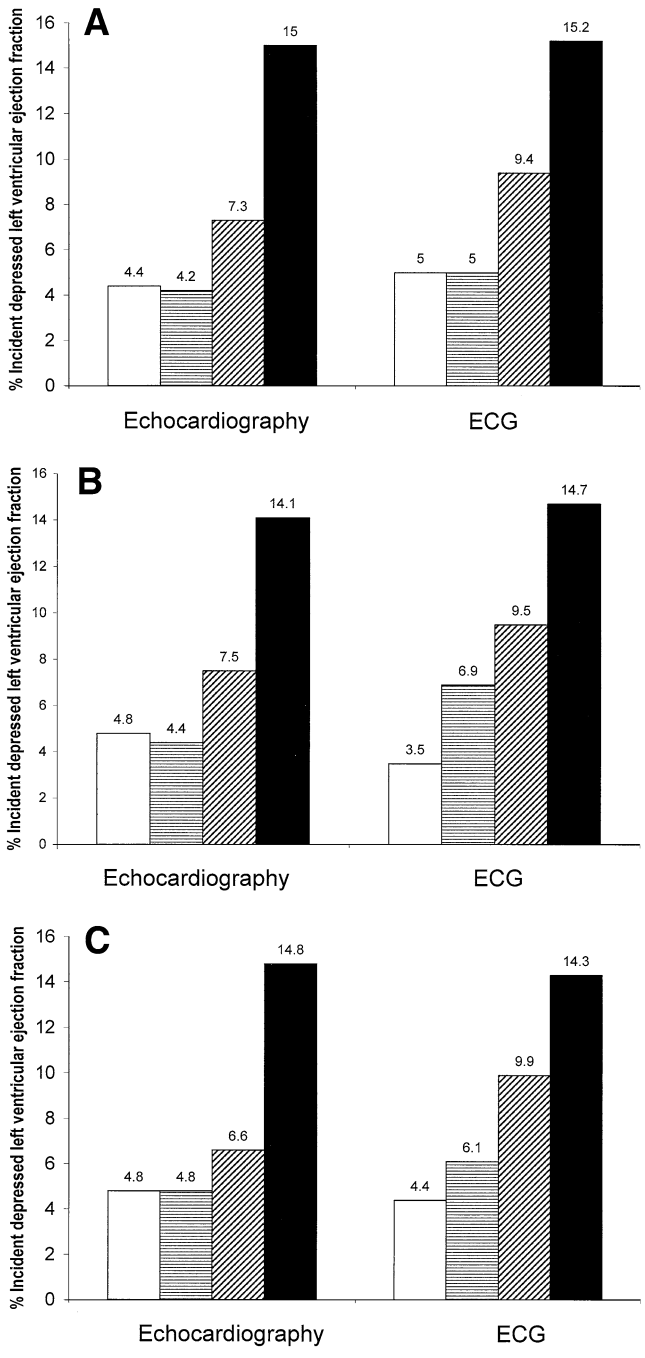

Figure 2. Percentage of participants developing a depressed left ventricular ejection fraction by baseline quartile of left ventricular mass (LVM) **(A)** and LVM indexed to body surface area (BSA) **(B)** or height **(C)**. Baseline LVM was assessed by echocardiography or electrocardiography (ECG). P < 0.001 for the association of LVM irrespective of indexation method with incident depressed ejection fraction in all cases. **White bars** = quartile 1; **bars with horizontal lines** = quartile 2; **bars with diagonal lines** = quartile 3; **black bars** = quartile 4. Quartiles of echocardiographic LVM (g): ≤114.7, 114.8 to 137.2, 137.4 to 165.7, >165.7, respectively. Quartiles of electrocardiographic LVM (g): <128.1, 128.1 to 145.4, 145.43 to 167.2, and >167.2, respectively. Quartiles of echocardiographic LVM/BSA (g/m^2): ≤67.7, 67.8 to 79.2, 79.3 to 93.5, and >93.5, respectively. Quartiles of electrocardiographic LVM/BSA (g/m^2): <76.9, 76.9 to 83, 83.1 to 90.3, and >90.3, respectively. Quartiles of echocardiographic LVM/height (g/m): ≤70.40, 70.42 to 84.13, 84.14 to 99.97, and >99.97, respectively. Quartiles of electrocardiographic LVM/height (g/m): ≤79.48, 79.49 to 88.51, 88.52 to 99.49, and >99.49, respectively.

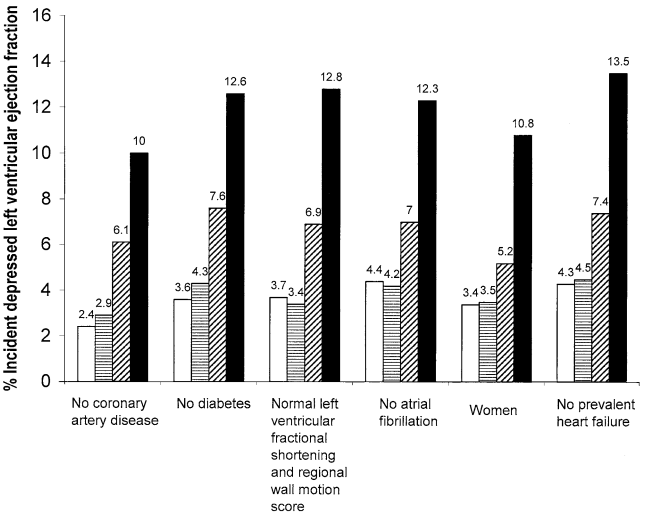

Figure 3. Subgroup analysis: percentage of participants developing a depressed left ventricular ejection fraction by baseline quartile of echocardiographic left ventricular mass (LVM) indexed to body surface area (BSA). "No coronary artery disease" subgroup consisted of participants without prevalent or interval myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal angioplasty. "No diabetes" and "no heart failure" excluded participants with these conditions present at baseline, and "no atrial fibrillation" excluded those with atrial fibrillation at baseline or during follow-up. P < 0.001 for the association of LVM/BSA and incident depressed ejection fraction for all groups shown. **White bars** = quartile 1; **bars with horizontal lines** = quartile 2; **bars with diagonal lines** = quartile 3; **black bars** = quartile 4. Quartile values of echocardiographic LVM/BSA are as reported in Figure 2.

incorporated as a covariate instead of baseline endocardial FS. Similarly, when LVM indexed to BSA was entered as a covariate instead of crude LVM (height and weight removed from models) or when baseline blood glucose or blood pressure were entered into the models as covariates instead of diabetes or hypertension status, the results were essentially identical to those shown in Table 4. The risk ratio associated with baseline echocardiographic LV hypertrophy for incident depressed LVEF in multivariable analysis using the same confounders as in Table 4 was 2.2 (95% CI 1.3 to 3.4; p = 0.001). In multivariable analyses stratified by gender using the same covariates as in Table 4, the association between LVM (per 50.9 g) and development of a depressed LVEF persisted in women (risk ratio 1.6 [95% CI 1.1 to 2.4; p = 0.02]) and in men (risk ratio, 1.5 [95% CI 1.1 to 2.1; p = 0.02]).

Ventricular diastolic dimension, wall thickness, and their association with depressed ejection fraction. Because echocardiographic LVM is a calculation derived from LV diastolic dimension and wall thickness (ventricular septum and LV posterior wall), we assessed which of these subcomponents of calculated LVM was associated with the outcome. A series of models was constructed in which LV diastolic dimension was entered with either ventricular septal or posterior wall thickness as independent variables (Table 4). In the analyses that included diastolic dimension and septal wall thickness, both remained associated with the development of a depressed LVEF and lower follow-up

Table 4. Unadjusted and Adjusted Regression Analysis

Outcome: Depressed LV Ejection Fraction*							
Independent Variables†		Unadjusted Risk Ratio	95% Confidence Intervals	p Value	Adjusted‡ Risk Ratio	95% Confidence Intervals	p Value
Echocardiographic LV mass (per 50.9 g)		1.8	1.5, 2.0	< 0.001	1.5	1.2, 1.8	< 0.001
Electrocardiographic LV mass (per 39.2 g)		2.0	1.7, 2.3	< 0.001	1.5	1.2, 1.8	< 0.001
LV diastolic dimension and septal wall thickness§	Diastolic dimension (per 0.8 cm)	2.0	1.7, 2.4	< 0.001	1.8	1.4, 2.2	< 0.001
	Septal thickness (per 0.2 cm)	1.3	1.1, 1.6	0.001	1.2	1.0, 1.5	< 0.05
LV diastolic dimension and posterior wall thickness§	Diastolic dimension (per 0.8 cm)	2.0	1.6, 2.4	< 0.001	1.7	1.4, 2.1	< 0.001
	Posterior wall thickness (per 0.2 cm)	1.3	1.1, 1.6	0.005	1.1	0.9, 1.4	0.27
Outcome: Follow-Up Midwall Fractional Shortening Percent*							
Independent Variables†		Unadjusted β-Coefficient	95% Confidence Intervals	p Value	Adjusted‡ β-Coefficient	95% Confidence Intervals	p Value
Echocardiographic LV mass (per 50.9 g)		−0.6	−0.86, −0.4	< 0.001	−0.5	−0.7, −0.1	0.001
Electrocardiographic LV mass (per 39.2 g)		−0.6	−0.9, −0.4	< 0.001	−0.1	−0.4, 0.02	0.4
LV diastolic dimension and septal wall thickness§	Diastolic dimension (per 0.8 cm)	−0.5	−0.8, −0.2	< 0.001	−0.4	−0.7, −0.1	0.01
	Septal thickness (per 0.2 cm)	−0.7	−0.9, −0.4	< 0.001	−0.5	−0.8, −0.3	< 0.001
LV diastolic dimension and posterior wall thickness§	Diastolic dimension (per 0.8 cm)	−0.5	−0.7, −0.2	0.001	−0.3	−0.6, −0.05	0.02
	Posterior wall thickness (per 0.2 cm)	−0.4	−0.7, −0.2	< 0.001	−0.3	−0.5, 0.01	0.06

*Logistic regression was used for the outcome of depressed ejection fraction and linear regression for midwall fractional shortening; †Interquartile ranges were used as the unit of change for all independent variables; ‡Adjusted for age, gender, white race, height, baseline weight, diabetes or hypertension at baseline, baseline and interval coronary artery status (including myocardial infarction, percutaneous angioplasty, or coronary artery bypass graft), and presence of Q waves or atrial fibrillation on electrocardiogram (either at baseline or during follow-up). Models incorporating echocardiographic and electrocardiographic left ventricular (LV) mass were also adjusted for baseline endocardial fractional shortening; §Both LV diastolic dimension and wall thickness (either septal or posterior wall) were entered as covariates in the same model.

midwall FS. However, in the adjusted models in which both LV diastolic dimension and posterior wall thickness were included as independent variables, there was no significant association of posterior wall thickness with incident depressed LVEF.

The baseline geometry of the LV was classified as being normal (n = 1,856) or as having concentric remodeling (n = 84), eccentric hypertrophy (n = 218), or concentric hypertrophy (n = 26). The percentage of participants who developed a depressed LVEF at follow-up among these four groups was 6.7%, 8.3%, 16.5%, and 3.8%, respectively ($p < 0.001$). In adjusted multivariable models using the same covariates as in Table 4, eccentric hypertrophy remained associated with the development of a depressed LVEF (relative risk 2.3; 95% CI 1.4 to 3.6) but concentric remodeling (relative risk 1.2; 95% CI 0.4 to 3.5) and concentric hypertrophy (relative risk 0.8; 95% CI 0.1 to 6.3) did not.

Participants excluded due to a missing follow-up echocardiogram. Of 5,201 participants in CHS, 1,581 were excluded from analysis in this study due to the lack of a follow-up echocardiogram with an assessment of LVEF as a result of death (n = 533), loss of contact (n = 229), a follow-up echocardiogram without assessment of LVEF (n = 179), and a follow-up visit with no echocardiogram obtained (e.g., home visit, nursing home visit, or phone information only; n = 640). In comparing participants who did not have a follow-up echocardiogram with an LVEF assessment to those who did, the former were older (74 ± 6 years vs. 72 ± 5 years, respectively), had a higher proportion of men (44% vs. 39%), diabetes (10.2% vs. 5.3%), hypertension (62% vs. 53%), atrial fibrillation (3.7% vs. 1.8%), larger echocardiographic baseline LVM (154 ± 54 g vs. 145 ± 44 g), and lower baseline mid-wall FS (23 ± 4% vs. 24 ± 4%); $p < 0.005$ for all comparisons.

Of 1,581 subjects without a CHS follow-up echocardiogram, 131 had an echocardiogram performed for clinical care that subsequently had been reviewed by CHS investigators (1). Of these, 69 subjects had a depressed LVEF. The baseline echocardiographic LVM indexed to BSA was higher in those subjects who developed a depressed LVEF (n = 42) as compared with the remainder of the subjects (n = 748) without a CHS follow-up

echocardiogram and no history of heart failure (LVM/BSA 98 ± 29 g/m^2 vs. 86 ± 26 g/m^2, respectively; p = 0.002). A similar relationship was seen with baseline electrocardiographic LVM indexed to BSA in comparing these two groups (92 ± 15 [n = 67] g/m^2 vs. 85 ± 12 [n = 1,225] g/m^2, respectively; p < 0.001).

DISCUSSION

Left ventricular hypertrophy is associated with a number of adverse clinical outcomes including the development of heart failure (1–7). However, because LV hypertrophy is also associated with diastolic dysfunction, which may also cause heart failure (11,12), it has been unclear whether increased LVM and LV hypertrophy predispose to a depressed LVEF in humans. Echocardiographic studies that have associated increased LVM with subtle abnormalities in systolic function, such as midwall FS (20,21,24), and earlier, small case series of patients with various stages of hypertensive heart disease (25,26) have been cross-sectional in nature. As such, they did not clarify whether ventricular hypertrophy led to the ventricular systolic dysfunction, or whether the hypertrophy resulted from changes in systolic function and ventricular dilation (27). Recent data have shown that changes in LVM while on antihypertensive therapy are inversely related to changes in systolic function (28,29).

The CHS database has detailed measurements of cardiac dimensions including LVM, and, by restricting our analysis to those subjects with a normal LVEF at baseline, we found an association between baseline LVM and LV hypertrophy with incident depressed LVEF at a follow-up of ~5 years. The LVM remained associated with incident depressed LVEF in important subgroups including women; those with no evident baseline abnormalities of systolic function as measured by stress-adjusted FS and regional wall motion score; those free of coronary heart disease at baseline and at follow-up; those without diabetes, prevalent heart failure, or atrial fibrillation. In addition to its association with the development of a depressed LVEF, baseline LVM was also associated with lower midwall FS at follow-up. The association of LVM and LV hypertrophy with incident depressed LVEF was independent of potential confounders in multivariable analysis. In total, these data show that LVM and LV hypertrophy are risk factors for the development of a depressed LVEF within five years in older adults.

Factors contributing to fall in LVEF. The mechanisms by which increased LVM leads to a depressed LVEF remain ill-defined. Myocardial infarction is traditionally viewed as an obligatory event in the transition to depressed systolic function (30), and is an important risk factor, occurring in 16% of those who did develop a depressed LVEF as compared with 3% of those who did not. However, the present study also demonstrates that there must be other mechanisms operative, because increased LVM remained associated with the development of depressed LVEF in participants free of clinically manifest coronary heart disease including myocardial infarction (Fig. 3). Potential mechanisms that have previously been shown to be associated with increased LVM are neurohormonal activation (31) and abnormalities in myocyte perfusion even in the absence of epicardial coronary artery stenoses (32).

Ventricular wall thickness and chamber dimension. An increase in LVM may occur either through an increase in LV chamber dimensions or wall thickness. Previous data showing increased echocardiographic LVM to be associated with adverse clinical outcomes have not assessed whether these relationships were true for both chamber dilation and increased wall thickness (3–5). The Framingham Heart Study investigators have shown that increased LV cavity size is associated with a number of adverse outcomes including heart failure (33,34). Our study is the first to our knowledge to show that LV diastolic dimension and ventricular septal wall thickness are associated, independently of each other, with the development of a depressed LVEF and a decrease in mid-wall FS. The importance of LV dilation as a risk factor for the subsequent fall in LVEF is reinforced by the association of eccentric hypertrophy (increased LVM due to increased LV volume with normal relative wall thickness) but not concentric hypertrophy with the development of a depressed LVEF in multivariable models.

Study limitations. There are important limitations in this analysis. The development of a depressed LVEF may be secondary to a difference in echocardiographic interpretation that occurred over the five years of follow-up. However, other echocardiographic parameters were consistent with a true difference between the two groups, and blinded reinterpretation at follow-up of baseline studies had estimates of FS that were higher rather than lower than the original values. The true incidence of depressed LVEF cannot be calculated due to the lack of a follow-up echocardiogram in a sizable fraction of the participants. Given that the participants who did not have follow-up echocardiograms had lower midwall FS at baseline than the participants who did have follow-up echocardiograms, the true percentage of participants who progressed to a depressed LVEF is likely higher than we found. Although a considerable number of subjects had missing follow-up CHS echocardiograms and were excluded from the primary analysis, the association of LVM and depressed LVEF appeared robust in those participants as ascertained by an analysis of echocardiograms obtained for clinical care. The LVEF is afterload-dependent and likely underestimated the baseline presence of LV systolic dysfunction (21). However, the LVEF is the most common measure of systolic function, and a reduced LVEF has immediate clinical applicability.

Conclusions. We have shown that increased LVM, whether measured by the electrocardiogram or echocardiogram, is an independent risk factor for the subsequent development of a depressed LVEF in older adults at ~5 years of follow-up. An eccentric pattern of cardiac hypertrophy as occurs with LV chamber dilation is a particularly

strong risk factor for this outcome. The association between increased LVM and development of depressed LVEF persists even among subjects without myocardial infarction, suggesting that there are additional pathophysiologic mechanisms through which increased LVM is associated with a subsequent fall in the LVEF.

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