Left Ventricular Hypertrophy Patterns and Incidence of Heart Failure With Preserved Versus Reduced Ejection Fraction

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Higher left ventricular (LV) mass, wall thickness, and internal dimension are associated with increased heart failure (HF) risk. Whether different LV hypertrophy patterns vary with respect to rates and types of HF incidence is unclear. In this study, 4,768 Framingham Heart Study participants (mean age 50 years, 56% women) were classified into 4 mutually exclusive LV hypertrophy pattern groups (normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy) using American Society of Echocardiography–recommended thresholds of echocardiographic LV mass indexed to body surface area and relative wall thickness, and these groups were related to HF incidence. Whether risk for HF types (HF with reduced ejection fraction [<45%] vs preserved ejection fraction [≥45%]) varied by hypertrophy pattern was then evaluated. On follow-up (mean 21 years), 458 participants (9.6%, 250 women) developed new-onset HF. The age- and gender-adjusted 20-year HF incidence increased from 6.96% in the normal left ventricle group to 8.67%, 13.38%, and 15.27% in the concentric remodeling, concentric hypertrophy, and eccentric hypertrophy groups, respectively. After adjustment for co-morbidities and incident myocardial infarction, LV hypertrophy patterns were associated with higher HF incidence relative to the normal left ventricle group ($p = 0.0002$); eccentric hypertrophy carried the greatest risk (hazard ratio [HR] 1.89, 95% confidence interval [CI] 1.41 to 2.54), followed by concentric hypertrophy (HR 1.40, 95% CI 1.04 to 1.87). Participants with eccentric hypertrophy had a higher propensity for HF with reduced ejection fraction (HR 2.23, 95% CI 1.48 to 3.37), whereas those with concentric hypertrophy were more prone to HF with preserved ejection fraction (HR 1.66, 95% CI 1.09 to 2.51). In conclusion, in this large community-based sample, HF risk varied by LV hypertrophy pattern, with eccentric and concentric hypertrophy predisposing to HF with reduced and preserved ejection fraction, respectively. **(Am J Cardiol 2014;113:117–122)**

We evaluated the long-term prognosis of left ventricular (LV) hypertrophy patterns with respect to heart failure (HF) risk. We hypothesized an increased risk for HF in patients with LV hypertrophy patterns (i.e., concentric remodeling, concentric hypertrophy, and eccentric hypertrophy) compared with those with normal left ventricles. Furthermore, we postulated an increasing gradient of HF risk across LV remodeling patterns that varies by type of HF, that is, risk for HF with reduced ejection fraction (HFREF) will increase from concentric remodeling to eccentric hypertrophy (intermediate incidence rates in those with concentric hypertrophy), whereas risk for HF with preserved ejection fraction (HFPEF) will increase from concentric remodeling to concentric hypertrophy (intermediate incidence rates in those with eccentric hypertrophy).

Methods

Attendees of the 16th examination cycle of the Framingham Heart Study Original Cohort[1] (1978 to 1980) and the 2nd examination cycle of the Offspring Cohort[2] (1979 to 1982) were eligible for our investigation (n = 6,214). After excluding participants with prevalent myocardial infarction (MI) or HF (n = 319), those missing follow-up (n = 14), and those with missing or unavailable echocardiographic data (n = 1,113), 4,768 subjects remained eligible. All participants were white of European descent and provided written informed consent, and the study protocol was

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See page 122 for disclosure information.

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Table 1
Baseline characteristics of study sample by left ventricular hypertrophy pattern

Variable	All Participants (n = 4,768)	Normal Left Ventricle (n = 3,384)	Concentric Remodeling (n = 686)	Concentric Hypertrophy (n = 373)	Eccentric Hypertrophy (n = 325)
Age (yrs)	50 ± 14	47 ± 13	59 ± 13	64 ± 14	55 ± 15
Women	56%	57%	50%	57%	58%
Body mass index (kg/m^2)	25.7 ± 4.3	25.2 ± 4.1	26.7 ± 4.5	27.8 ± 4.4	26.4 ± 4.6
Systolic blood pressure (mm Hg)	126 ± 19	122 ± 17	134 ± 19	142 ± 21	134 ± 21
Total cholesterol (mg/dl)	210 ± 41	205 ± 41	223 ± 41	234 ± 8.9	213 ± 39
High-density lipoprotein cholesterol (mg/dl)	50 ± 14	50 ± 14	48 ± 14	47 ± 15	50 ± 14
Diabetes mellitus	3.9%	2.5%	6.0%	11.5%	5.7%
Lung disease	11.9%	5.4%	7.1%	8.0%	10.2%
Kidney disease	6.1%	6.4%	5.3%	5.4%	5.3%
Hypertension treatment	15.6%	10.4%	24.6%	39.7%	23.7%
Valve disease	1.4%	0.5%	0.6%	8.7%	4.0%
Smoking	33%	34%	30%	28%	34%
Interim MI*	9.7%	8.0%	14.6%	13.4%	13.5%
Stroke	7.8%	6.2%	11.8%	14.3%	8.7%

Data are expressed as mean ± SD or percentages.
* MI occurrence between baseline examination and diagnosis of HF or end of follow-up (whichever occurred earlier).

Table 2
Echocardiographic characteristics of study sample according to left ventricular hypertrophy pattern

Variable	Men (n = 2,098)				Women (n = 2,670)			
	Normal Left Ventricle	Concentric Remodeling	Concentric Hypertrophy	Eccentric Hypertrophy	Normal Left Ventricle	Concentric Remodeling	Concentric Hypertrophy	Eccentric Hypertrophy
LV mass/body surface area (g/m^2)	88 ± 13	96 ± 12	141 ± 34	130 ± 18	73 ± 11	79 ± 10	117 ± 26	109 ± 18
Interventricular septal thickness (cm)	0.92 ± 0.08	1.10 ± 0.10	1.31 ± 0.18	1.06 ± 0.08	0.81 ± 0.08	0.97 ± 0.09	1.23 ± 0.22	0.94 ± 0.07
LV posterior wall thickness (cm)	0.91 ± 0.08	1.09 ± 0.09	1.27 ± 0.16	1.06 ± 0.08	0.80 ± 0.08	0.97 ± 0.08	1.17 ± 0.16	0.93 ± 0.07
LV wall thickness (cm)	1.83 ± 0.16	2.19 ± 0.18	2.58 ± 0.32	2.12 ± 0.15	1.61 ± 0.16	1.94 ± 0.17	2.41 ± 0.34	1.87 ± 0.14
LVEDD (cm)	5.10 ± 0.35	4.74 ± 0.32	5.15 ± 0.44	5.79 ± 0.39	4.60 ± 0.30	4.15 ± 0.29	4.46 ± 0.45	5.14 ± 0.39
RWT	0.36 ± 0.04	0.46 ± 0.05	0.51 ± 0.09	0.37 ± 0.04	0.35 ± 0.04	0.47 ± 0.05	0.55 ± 0.11	0.37 ± 0.04
FS	0.36 ± 0.04	0.38 ± 0.04	0.37 ± 0.04	0.35 ± 0.05	0.38 ± 0.04	0.41 ± 0.04	0.40 ± 0.05	0.37 ± 0.05
FS ≤0.29	2.0%	0.9%	4.3%	7.3%	0.4%	0.3%	2.4%	3.2%

Data are expressed as mean ± SD or percentages.

approved by the institutional review board of Boston University Medical Center.

At the baseline examinations, study participants underwent 2-dimensionally guided M-mode echocardiography. LV end-diastolic dimension (LVEDD) and the end-diastolic thicknesses of the interventricular septum and LV posterior wall were measured according to American Society of Echocardiography recommendations.[3] LV mass (LVM)[4] and relative wall thickness (RWT) were calculated using the following formulae LVM (g) = 0.8[1.04 (LVEDD + interventricular septal thickness + LV posterior wall thickness)^3 − (LVEDD)^3] + 0.6, and RWT = (interventricular septal thickness + LV posterior wall thickness)/LVEDD.

We calculated fractional shortening (FS; [LVEDD − LV systolic dimension]/LVEDD), and a value of ≤0.29 (corresponding to an ejection fraction of 50%) indicated decreased LV systolic function.[5]

We used American Society of Echocardiography–recommended thresholds for identifying normal and elevated LVM (indexed to body surface area; ≤115 vs >115 g/m^2 for men and ≤95 vs >95 g/m^2 for women) and RWT (≤0.42 vs >0.42) to classify participants into 4 mutually exclusive LV hypertrophy patterns: normal (LVM and RWT normal), concentric remodeling (LVM normal but RWT elevated), eccentric hypertrophy (LVM elevated but RWT normal), and concentric hypertrophy (LVM and RWT elevated).

Covariates were defined at the baseline examination. Body mass index was calculated as weight in kilograms divided by the square of height in meters. During the Framingham Heart Study clinic visit, a physician measured blood pressure twice in the left arm of the seated participant using a mercury-column sphygmomanometer and a cuff of appropriate size; the average of these 2 readings indicated the examination blood pressure. Serum lipids were measured using standardized assays. Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dl, random plasma glucose ≥200 mg/dl, or use of insulin or other hypoglycemic therapy. Cardiac valve disease was defined as presence of a systolic murmur of grade ≥3 or any diastolic murmur at the Framingham Heart Study examination.

An end points committee reviews Framingham Heart Study clinic charts and hospitalization and physician office records for all suspected cardiovascular events, including HF, and adjudicates incident events using prespecified

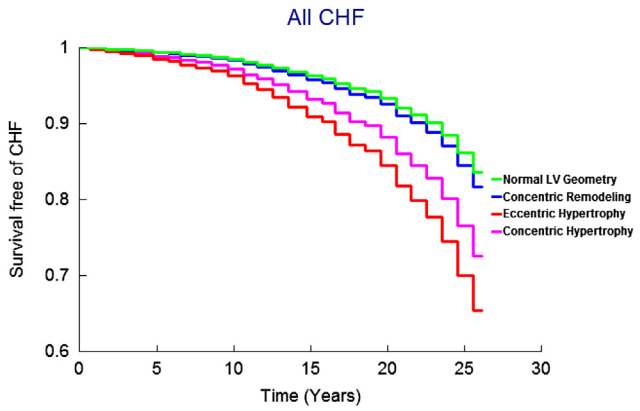

Figure 1. Age- and gender-adjusted survival free of HF according to LV hypertrophy pattern. CHF = congestive HF.

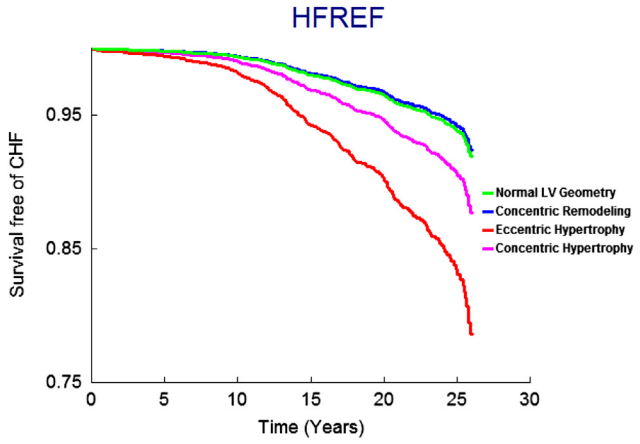

Figure 2. Age- and gender-adjusted survival free of HFREF according to LV hypertrophy pattern. CHF = congestive HF.

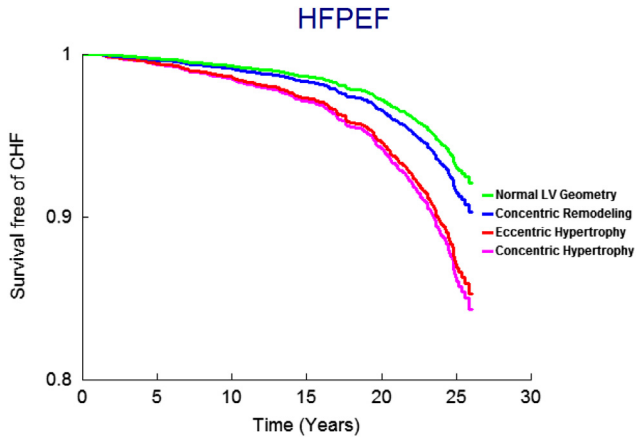

Figure 3. Age- and gender-adjusted survival free of HFPEF according to LV hypertrophy pattern. CHF = congestive HF.

criteria.[6] We used Framingham criteria[7] (Supplementary Table 1) to determine HF occurrence. We defined HF as HFREF if the ejection fraction (at the time of HF event) was <45% and as HFPEF if the ejection fraction was ≥45%.[8]

We estimated the age- and gender-adjusted 10-year cumulative and 20-year cumulative HF incidence for each LV pattern. We used Cox regression to compare HF hazards in each LV group (with the normal group serving as the referent), after confirming that the assumption of proportionality of hazards was met. We constructed a multivariable model adjusting for age, gender, body mass index, systolic blood pressure, hypertension treatment, diabetes, total cholesterol/high-density lipoprotein ratio, smoking, valve disease, reduced baseline FS (≤0.29 vs >0.29), and MI occurrence on follow-up; all variables were entered simultaneously into the Cox models. Because values of covariates (such as blood pressure) and proportions of participants who receive therapy that modifies HF risk (such as antihypertensive therapy) change over time, we updated the covariate profile at each subsequent examination attended by each participant (i.e., all variables, except for age, gender, and LV hypertrophy patterns, were entered as time-dependent covariates in the Cox regression models).

To control for potential confounding in the relations of hypertrophy patterns to HF risk, we performed the following secondary analyses. Because LV hypertrophy patterns may be associated with low FS, we repeated analyses excluding subjects with reduced FS at the baseline examination. To eliminate potential confounding by prevalent valve disease, we repeated our analysis excluding participants with clinical valve disease. To evaluate the impact of gender and age on the relations of hypertrophy patterns to HF risk, we repeated the analyses including appropriate interaction terms (hypertrophy pattern × gender and hypertrophy pattern × age dichotomized at the median).

To evaluate if a differential gradient of HF risk existed across the LV hypertrophy patterns and if this gradient varied by type of HF, we related LV hypertrophy patterns to HFREF and HFPEF in separate Cox regression analyses using the statistical model described previously. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina), and p values <0.05 were considered statistically significant.

Results

The baseline clinical and echocardiographic characteristics of participants are listed in Tables 1 and 2. Participants excluded for unavailable echocardiographic data were older, had higher mean systolic blood pressures, had higher total/high-density lipoprotein cholesterol ratios, and had a higher prevalence of diabetes and hypertension treatment, compared with the study sample as a whole. In the study sample, mean LVM, LV dimensions, and wall thicknesses were higher in men than in women.

On follow-up (mean 21 years, maximum 28 years), 458 participants (9.6%, 250 women) developed new-onset HF. Figure 1 displays age- and gender-adjusted survival free of HF in the 4 groups and demonstrates the highest incidence of HF in those with eccentric hypertrophy, followed by concentric hypertrophy, with participants with concentric remodeling having a risk intermediate between the normal group and these groups; Figures 2 and 3 display analogous data for the HFREF and HFPEF. Age- and gender-adjusted incidence was highest for those with eccentric hypertrophy (Table 3).

In multivariate-adjusted Cox regression models, LV hypertrophy patterns were associated with increased HF

Table 3
Age- and gender-adjusted heart failure incidence by left ventricular hypertrophy pattern

Variable	Normal Left Ventricle	Concentric Remodeling	Concentric Hypertrophy	Eccentric Hypertrophy
No. of events/no. at risk	216/3,384	97/686	81/373	64/325
Age- and gender-adjusted 10-yr incidence*	1.58 (0.98−2.17)	1.99 (1.08−2.86)	3.91 (2.45−5.28)	5.19 (3.00−7.20)
Age- and gender-adjusted 20-yr incidence*	6.96 (5.45−8.36)	8.67 (6.45−10.70)	13.38 (9.90−16.43)	15.27 (11.01−18.90)

* HF incidence are age and gender adjusted per 100 patients; values in parentheses are 95% confidence intervals.

Table 4
Multivariate analyses relating left ventricular hypertrophy patterns to incident heart failure

Adjusted Hazard Ratio* for HF (95% Confidence Interval)				
Normal Left Ventricle	Concentric Remodeling	Concentric Hypertrophy	Eccentric Hypertrophy	p Value†
All participants (n = 4,768)				
Referent	1.09 (0.85−1.40)	1.40 (1.04−1.87)	1.89 (1.41−2.54)	0.0002
Participants with normal FS (>0.29) (n = 4,700)				
Referent	1.21 (0.94−1.57)	1.52 (1.13−2.05)	1.78 (1.31−2.41)	0.0009
Participants without clinical valve disease (n = 4,678)				
Referent	1.16 (0.90−1.50)	1.38 (1.02−1.87)	1.70 (1.25−2.32)	0.005

* HRs indicate HF risk associated with individual hypertrophy patterns compared with the group with normal left ventricles (referent) and adjusted for the following covariates: age, gender, body mass index, systolic blood pressure, valve disease, hypertension treatment, diabetes, total cholesterol/high-density lipoprotein cholesterol ratio, smoking status, FS, and interim MI.

† Statistical significance ($p < 0.05$) for the global test for differences among the 4 LV patterns with respect to HF risk.

Table 5
Age- and gender-adjusted heart failure incidence by left ventricular hypertrophy pattern and heart failure type

Variable	Normal Left Ventricle	Concentric Remodeling	Concentric Hypertrophy	Eccentric Hypertrophy	p Value*
HFREF†					
No. of events/no. at risk	101/3,384	36/686	28/373	33/325	
Age- and gender-adjusted 10-yr incidence§	0.63 (0.25−1.01)	0.62 (0.10−1.13)	1.38 (0.41−2.31)	2.70 (0.93−4.34)	
HR (95% CI)‖	Referent	0.96 (0.64−1.44)	1.32 (0.84−2.07)	2.23 (1.48−3.37)	0.02
HFPEF‡					
No. of events/no. at risk	93/3,384	46/686	23/325	44/373	
Age- and gender-adjusted 10-yr incidence§	0.77 (0.33−1.21)	1.17 (0.43−1.87)	1.57 (0.37−2.72)	2.11 (1.03−3.14)	
HR (95% CI)‖	Referent	1.25 (0.86−1.81)	1.63 (1.02−2.61)	1.66 (1.09−2.51)	0.007

CI = confidence interval; HR = hazard ratio.

* Statistical significance ($p < 0.05$) for trend test across the 4 LV patterns with respect to HF risk.

† Participants who developed HFPEF on follow-up were censored at the time of the HF event.

‡ Participants who developed HFREF on follow-up were censored at the time of the HF event.

§ Incidences are age and gender adjusted calculated per 100 patients.

‖ HRs are from multivariate models adjusting for age, gender, body mass index, systolic blood pressure, valve disease, hypertension treatment, diabetes, total cholesterol/high-density lipoprotein ratio, smoking status, and FS and indicate HF risk associated with individual hypertrophy patterns compared with the group with normal left ventricles (referent).

incidence compared with the normal left ventricle group (Table 4). Eccentric hypertrophy and concentric hypertrophy were associated with increased risk, whereas concentric remodeling was not independently associated with HF risk. Qualitatively similar results were obtained when analyses were repeated in the subgroup of participants with normal FS (>0.29) (Table 4) and in analyses excluding participants with valve disease (Table 4). We did not observe any statistically significant gender interaction (p for interaction term = 0.53). The interaction term for age was statistically significant (p = 0.02), suggesting that the relations of hypertrophy patterns to HF risk may vary by age. However, when our main multivariate model relating hypertrophy pattern to HF risk was repeated separately in participants older and younger than the median age, the results were similar (data not shown). Of note, most of the covariates were also statistically significantly associated with incident HF, and the results are provided in Supplementary Table 2.

Ejection fractions at the time of HF diagnosis were available for 404 of the 458 participants (88%) who developed the incident HF event. HFREF was most common in the group with eccentric hypertrophy (Table 5), whereas HFPEF incidence was highest in those with concentric hypertrophy (Table 5).

In multivariate analyses, we observed an increasing gradient of risk for HFREF from concentric remodeling to

concentric hypertrophy to eccentric hypertrophy (Table 5). Specifically, eccentric hypertrophy was associated with a more than twofold greater risk for HFREF relative to those with normal left ventricles. In contrast, we observed an increasing gradient of risk for HFPEF from concentric remodeling to concentric hypertrophy (Table 5), with eccentric hypertrophy and concentric hypertrophy associated with a statistically significant increase in HFPEF risk.

Discussion

In our community-based sample free of prevalent MI or HF, LV hypertrophy patterns were associated with increased HF risk. Participants with eccentric hypertrophy experienced an approximately 90% higher HF risk, whereas concentric hypertrophy was associated with a statistically significant 40% increased risk for HF, findings that remained robust in the subgroup with normal FS and in those without clinical valve disease. Although HF rates were higher in participants with concentric remodeling, the association of this pattern with HF was attenuated in multivariate analyses, suggesting that a greater burden of risk factors (including interim MI) may have contributed to higher HF incidence in this group. Previous investigations from Framingham reported the strong effect of age on longitudinal change in measures of cardiac structure over the adult life course.[9−11] However, the results of our main analysis were similar in participants older and younger than the median age. In analyses of the subset of patients with available echocardiographic ejection fractions after the onset of HF, participants with eccentric hypertrophy were more likely to develop HFREF, and those with concentric hypertrophy were at higher risk for HFPEF, and there was an increasing gradient of risk by HF type across the 4 groups, consistent with our hypothesis.

Our investigation is strengthened by several design elements. We demonstrate prospectively the relationship between pattern of LV hypertrophy and HF risk and the relative preponderance of type of HF between concentric and eccentric hypertrophy, using a large sample size from 2 cohorts uniformly followed over a long period. The echocardiographic data were derived from routine studies performed on a community-based sample, thereby removing selection bias; however, this may limit the generalizability of our findings, because similar patients in a primary care setting may not have undergone echocardiography because of the lack of a clinical indication. The baseline examinations for our investigation were performed from 1978 to 1982, which permitted long-term follow-up and the accrual of a large number of HF events to have adequate statistical power to analyze incident HF. In addition, information about co-morbid conditions and other cardiovascular outcomes was available at serial time points, thus enabling us to fit Cox regression models with time-dependent clinical covariates. We were thus able to identify the prognoses of LV hypertrophy patterns over the adult life course independent of changing co-morbidity profiles and to assess the relative contributions of LV remodeling versus the associated burden of cardiovascular risk factors to the propensity for overall HF and types of HF.

Several previous reports related the individual components of LV hypertrophy (i.e., LVM, wall thickness, and internal dimensions) to HF risk. We previously reported that higher LV internal dimensions were positively related to HF risk in participants without previous MI.[12] Data from the Cardiovascular Health Study (CHS) also demonstrated that higher LVM and wall thickness predict HF incidence.[13,14] In the latter investigation, Gardin et al[14] also reported increased risk for HF in participants with LV hypertrophy patterns, but the sample was modest in size and elderly, and the analyses were limited by very few HF events (n = 23). Similarly, a recent investigation from the Multi-Ethnic Study of Atherosclerosis (MESA) reported associations between cardiac magnetic resonance imaging−derived LVM and concentricity index and incident coronary heart disease, stroke, and HF.[15] However, previous investigations were limited by low rates of HF events,[14,16] were confined to specific subgroups (based on age,[17] hypertension status,[18] MI status,[16] etc.), and did not specifically address the their relationship of hypertrophy patterns to HF risk but rather focused on the relations of these patterns to overall cardiovascular outcomes and death.[14,15,17−23]

One interpretation of these findings is that elevated LVM on the basis of increased LV internal dimensions (the substrate for eccentric LV hypertrophy) is more strongly associated with HF risk relative to elevated LVM because of increased wall thickness (evident in concentric hypertrophy) or compared with greater wall thickness alone (with normal LVM, as in concentric remodeling). According to the Laplace law, the tension in the LV wall is directly proportional to transmural pressure and chamber radius and inversely proportional to wall thickness. A greater amount of tension must be developed in the wall of a dilated left ventricle to generate the same amount of forward flow compared with a normal left ventricle, requiring that wall thickness increase in proportion to the increased chamber diameter. Because LV wall thickness (an adaptive response to reduce wall stress) does not increase in proportion to LV dilation in eccentric hypertrophy (but does so in concentric hypertrophy),[24] this hypertrophy pattern is likely associated with greater LV wall stress, which may contribute to a greater propensity for overt HF overall.

An alternative interpretation is that a dilated LV hypertrophy pattern confers higher HF risk because of associated changes in LV shape (i.e., increased sphericity). Evidence from experimental and clinical studies also is consistent with the premise that reduction of LV sphericity (the pattern noted in eccentric hypertrophy) ameliorates LV systolic function.[25,26] Experimental evidence[27] and observations in humans[28] suggest that concentric hypertrophy is associated with abnormal diastolic function, and abnormalities of active relaxation, passive stiffness, or both have been shown to be key correlates of HFPEF.[29,30] These observations serve to explain the association between concentric hypertrophy and HFPEF. Thus eccentric hypertrophy and concentric hypertrophy predict HF occurrence but differ with respect to the magnitude of risk, the type of incident HF, and pathophysiologic mechanisms.

Our choice of baseline examinations limited us to the use of M-mode echocardiography, the available imaging technology at that time. Our investigation is therefore limited by a lack of adjustment for LV wall motion abnormalities, baseline LV ejection fraction, and indices of baseline LV

diastolic function. Because valve disease was assessed on the basis of physical examination, it is possible that participants with clinically important valve disease but without significant murmurs were misclassified in our investigation. Although we accounted for intervening MI, confounding of our results by occult coronary disease is possible. Our study sample was composed of middle-aged white subjects, so our results may not be generalizable to other ethnicities or age groups.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2013.09.028.

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