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Prevalence, Clinical Characteristics, and Outcomes Associated with Eccentric versus Concentric Left Ventricular Hypertrophy In Heart Failure with Preserved Ejection Fraction

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Abstract

While concentric remodeling (CR) and concentric hypertrophy (CH) are common forms of left ventricular (LV) remodeling in heart failure with preserved ejection fraction (HFpEF), eccentric hypertrophy (EH) can also occur in these patients. However, clinical characteristics and outcomes of EH have not been well described in HFpEF. We prospectively studied 402 patients with HFpEF, divided into 4 groups based on LV structure: normal geometry (no LV hypertrophy [LVH] and relative wall thickness [RWT] < 0.42); CR (no LVH and RWT > 0.42); CH (LVH and RWT > 0.42); and EH (LVH and RWT < 0.42). We compared clinical, laboratory, echocardiographic, invasive hemodynamic, and outcome data among groups. Of 402 patients, 48 (12%) had EH. Compared to CH, patients with EH had lower systolic blood pressure and less renal impairment despite similar rates of hypertension. After adjustment for covariates, EH was associated with reduced LV contractility compared to CH (lower LVEF [β-coefficient = −3.2; 95% confidence interval (CI) −5.4, −1.1%] and ratio of systolic blood pressure to end-systolic volume [β-coefficient = −1.0; 95% CI −1.5, −0.5 mmHg/ml]). EH was also associated with increased LV compliance compared to CH (LV end-diastolic volume at an idealized LV end-diastolic pressure of 20 mmHg [EDV_{20}] β-coefficient = 14.2;95% CI 9.4, 19.1 ml). Despite these differences, EH and CH had similarly elevated cardiac filling pressures and equivalent adverse outcomes. In conclusion, the presence of EH denotes a distinct subset of HFpEF that is pathophysiologically similar to HF with reduced EF (HFrEF), and may benefit from HFrEF therapy.

Keywords

heart failure with preserved ejection fraction; left ventricular hypertrophy; cardiac remodeling; echocardiography; outcomes

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INTRODUCTION

Left ventricular (LV) structure in heart failure with preserved ejection fraction (HFpEF) has been classically defined as a small, thick ventricle. Contemporary studies show that most patients with HFpEF have a normal sized LV.[5,6] Indeed, concentric remodeling (CR) and concentric hypertrophy (CH) have been demonstrated to be the most common LV structural abnormalities observed in HFpEF.[7] A smaller subset of HFpEF patients demonstrate eccentric hypertrophy (EH);[8]however, EH has not been well described in the setting of HFpEF. We sought to define HFpEF based on LV geometry, with a focus on the subset of patients with EH. We hypothesized that this group, while less prevalent, represents a unique pathophysiologic subset of HFpEF patients who may benefit from tailored therapy, which may include medications typically used to treat patients with heart failure and reduced ejection fraction (HFrEF).

METHODS

Between March 2008 and May 2011, consecutive patients were prospectively enrolled from the outpatient clinic of the Northwestern University HFpEF Program as part of a systematic observational study of HFpEF (ClinicalTrials.gov identifier #NCT01030991), as described previously.[9] All patients were recruited after hospitalization for HF. Patients were initially identified by an automated daily query of the inpatient electronic medical record at Northwestern Memorial Hospital. The list of patients generated was screened daily, and only those patients with an LV ejection fraction (EF) > 50% and who met Framingham criteria for HF[10] were offered post-discharge follow-up in a specialized HFpEF outpatient program. The HF diagnosis was confirmed in the post-hospitalization, outpatient HFpEF clinic. Based on previously published criteria, in addition to the presence of symptomatic HF and EF > 50%, we required evidence of either significant diastolic dysfunction (grade 2 or 3) on echocardiography or evidence of elevated LV filling pressures on invasive hemodynamic testing. Patients with greater than moderate valvular disease, prior cardiac transplantation, prior LVEF < 40%, LV end-diastolic volume (EDV)>97 ml/m^2or diagnosis of constrictive pericarditis were excluded. For the present analysis, patients with known sources of extracardiac volume overload or high output HF were also excluded. All study participants gave written, informed consent, and the institutional review board at Northwestern University approved the study.

We collected the following data in all study participants: demographics, race/ethnicity, New York Heart Association (NYHA) functional class, comorbidities (as defined in Table 1), medications, vital signs, body-mass index, and laboratory data, including serum sodium, blood urea nitrogen, creatinine, hemoglobin, and B-type natriuretic peptide (BNP).

All study participants underwent comprehensive 2-dimensional echocardiography with Doppler and tissue Doppler imaging (TDI) using commercially available ultrasound systems with harmonic imaging (Philips iE33 or 7500, Philips Medical Systems, Andover, MA; or Vivid 7, GE Healthcare, General Electric Corp., Waukesha, WI). Cardiac structure and function were quantified as recommended by the American Society of Echocardiography. [13] Relative wall thickness (RWT) was calculated as 2*(posterior wall thickness)/LV end-diastolic dimension. LV hypertrophy (LVH) was defined as LV mass indexed to height$^{2.7}$>44g/$m^{2.7}$ in women and >48g/$m^{2.7}$ in men. Normal geometry was classified as RWT<0.42 and no LVH; CR was defined as RWT>0.42 and no LV hypertrophy; CH was defined as RWT>0.42 and LVH; and EH was defined as RWT<0.42 and LVH.[13] All measurements were made by experienced research sonographer (blinded to clinical data and outcomes) using ProSolv 4.0 software (ProSolv CardioVascular; Indianapolis, IN) and verified by a board-certified echocardiographer.

End-systolic elastance (E_{es}) was estimated by the single-beat method.[14,15] The relationship between end-systolic pressure (P_{es}) and end-systolic volume (ESV) was related by the equation: [$P_{es} = E_{es}(ESV - V_0)$]. Using 0.9*(systolic blood pressure) as an estimate of P_{es}, we estimated V_0, the volume-axis intercept, for each patient. We then used the average V_0 and E_{es} to define the end-systolic pressure volume relationship (ESPVR) in the EH and CH groups. We also generated the estimated ESV at an idealized P_{es} of 120 mmHg (ESV_{120}) for each patient as a basis for comparison of ESPVR between groups. The effective arterial elastance (E_a) was estimated using the equation:E_a = 0.9*SBP/stroke volume. The end-diastolic pressure-volume relationship (EDPVR) was also characterized by a single-beat method using the equation:LVEDP = $\alpha(LVEDV)^{\beta}$. The parameters α and β were calculated for each individual based on their LVEDV and LVEDP (as estimated by [11.96 + (lateral E/e' ratio)*0.596]).[20] These parameters were then used to calculate the LVEDV at an idealized LVEDP of 20 mmHg (EDV_{20}) for each patient as a basis for comparison of EDPVR among groups.

Right-sided heart catheterization was performed from either the right internal jugular or right femoral vein approach using standard Seldinger technique under fluoroscopic guidance. Participants underwent recording of invasive hemodynamics using a fluid-filled, 6F pulmonary artery catheter (Edwards Lifesciences, Irvine, CA) and a properly zeroed pressure transducer. Pressure recordings were analyzed off-line using a WITT Hemodynamic Workstation (Philips Medical Systems, Andover, MA) at a 50 mm/s paper speed with adjustment of pressure (mmHg) scale as needed. All hemodynamic pressure measurements were made at end-expiration and in duplicate using a standardized measurement protocol by a physician blinded to all clinical data.

After enrollment, study participants were evaluated in the Northwestern HFpEF Program as clinically indicated but at least every 6 months. At each visit, inter-current hospitalizations were documented, reviewed, and categorized as due to cardiovascular or non-cardiovascular causes. Every 6 months, participants (or their proxy) were contacted to determine vital status with verification of deaths through query of the Social Security Death Index. Enrollment date was defined as the first visit to the outpatient HFpEF clinic. Date of last follow-up was defined as date of death or last HFpEF clinic visit. Follow-up was complete in all patients. The combined outcome included any hospitalization for HF or any cardiovascular cause, or death.

Study participants were divided into 4 groups based on LV geometry (normal, CR, CH, and EH). Clinical characteristics, laboratory data, and echocardiographic parameters were compared between groups. Categorical variables were compared using Chi-squared tests, and continuous variables were compared using ANOVA (or Kruskal-Wallis test, when appropriate). Pairwise group comparisons were made using t-tests (or Wilcoxon rank-sum test, when appropriate). Variables from the univariate analysis that were significantly different between EH and CH groups were compared using multivariable-adjusted linear regression models. Covariates, chosen on the basis of known associations between the variable of interest and LV geometry, included age, sex, African-American race, hypertension, hyperlipidemia, diabetes mellitus, obesity, heart rate, log BNP, GFR, and wall motion abnormality on echocardiography.

Finally, we used Cox proportional-hazards analyses and the log-rank statistic to evaluate the relationship between LV geometry groups and outcomes. Covariates included in multivariable Cox regression models, chosen based on clinical relevance, included age, sex, African American race, hypertension, DM, obesity, and estimated GFR. To correct for multiple testing, false discovery rate (FDR) methods were applied using all calculated p-values. FDR Q-values were calculated using the Benjamini-Hochberg method.[1621] FDR <

5% corresponded to p-values <0.0172, which was therefore used as the threshold for statistical significance. All analyses were performed using Stata 12 (StataCorp, College Station, TX).

RESULTS

We prospectively enrolled 402 consecutive outpatients with HFpEF after hospitalization for HF. The majority of subjects had CH, followed by CR, and similar frequencies of normal geometry and EH (Figure 1).EH, while less frequent than other forms of LV remodeling, was not rare, occurring in 12% of the study cohort. Table 1 displays the clinical and demographic characteristics by LV geometry. Those with normal geometry were significantly younger than those in any other group. Significant differences among the 4 groups, especially in comorbidities, were largely driven by the differences between those with and without LVH.

However, there were significant differences in kidney function and blood pressure between the EH and CH groups. Those with EH had a mean systolic blood pressure (SBP)of 121 mmHg (95% confidence interval [CI]115–127 mmHg), while those with CH had a mean SBP of 129 mmHg (95% CI 127–132 mmHg); P=0.01. Mean diastolic blood pressure was also lower among those with EH compared to CH. Despite the differences in blood pressure, prevalence of hypertension and number of antihypertensive medications were not significantly different between the EH and CH groups. Patients with EH also had lower serum creatinine and higher GFR compared to those with CH, reflecting better renal function in the EH subgroup.

Echocardiographic analysis (Table 2) revealed that subjects with EH had larger LV volumes, lower relative wall thickness, and lower LV mass/volume ratio compared to those with CH. Contractile function was worse in EH compared to CH. Patients with EH had lower LVEF, lower SBP/ESV ratio, and higher ESV_{120}, indicative of worse contractility on LV pressure-volume analysis (Figure 2).Patients with EH also demonstrated less arterial stiffening, as E_a and pulse pressure/stroke volume ratio were significantly lower in EH compared to CH.HFpEF patients with EH also had less LV diastolic stiffness (increased LV compliance) compared to patients with CH as shown in Table 2 and Figure 2 with a rightward- and downward-shifted EDPVR curve, as indicated by a larger EDV_{20}. Diastolic relaxation (i.e., e' velocity) was also less impaired in EH compared to CH. However, LV filling pressures (E/e' ratio and PCWP) were similarly elevated in EH and CH (Tables 2 and Table 3). Pulmonary artery systolic pressure was higher in LVH compared to no LVH but was similar in EH and CH groups (Table 3). Rates (and severity) of mitral regurgitation did not vary between groups, and no patient had greater than mild aortic regurgitation.

Clinical characteristics that were significantly different between EH and CH groups on univariate analysis were analyzed further using multivariable-adjusted linear regression models (Table 4). After adjustment for covariates, SBP, diastolic blood pressure, LVEF, SBP/ESV ratio, and E_a remained significantly lower while GFR, ESV_{120}, EDV_{20}, and stroke volume remained significantly higher in EH compared to CH.

Over a mean follow-up time of 12.2±8.5 months, there was no significant difference in the number of hospitalizations, death, or combined outcomes between subjects with EH and CH(Table 5). There were also no significant differences in the Cox-proportional hazard ratios (HRs) between these groups. The difference between EH and CH groups after multivariable adjustment was not significant (P = 0.24). Figure 3shows the Kaplan-Meier curves for the combined outcome of HF hospitalization, cardiovascular hospitalization, and death. Outcomes did differ by presence or absence of LV hypertrophy; those with LV

hypertrophy (EH or CH) had worse outcomes compared to those without LV hypertrophy (Figure 3, log-rank P=0.0005).

DISCUSSION

In a prospective study of LV geometry in 402 subjects with HFpEF, we found that a non-trivial proportion of these individuals (12%) have EH. Study participants with HFpEF who had EH represent a unique subset with lower blood pressure, better kidney function, and higher LV compliance, but lower contractility, compared to individuals with CH. These differences were not attenuated by multivariable adjustment. LV filling pressures and outcomes were nonetheless similar in patients with EH and CH, underscoring the continued unmet need for therapies for patients with HFpEF who have either type of LVH. To our knowledge this is the most comprehensive analysis of characteristics of EH in HFpEF to date.

The frequency of EH in HFpEF in our study is similar to the16% prevalence found in the Olmsted County HFpEF cohort. Despite having lower BP, those with EH had similar rates of hypertension as those with CR or CH. Only subjects with normal geometry, who were significantly younger, had less prevalent hypertension. Since those with EH were not taking more or significantly different antihypertensive medications compared to CH, our results may suggest that patients with EH have greater responses to anti-hypertensive medication. Results from the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study demonstrated that treatment with losartan or atenolol induced conversion from CH to EH in 34% of individuals with hypertension and baseline CH, while only 3% converted from EH to CH. [22] Therefore, the presence of EH in HFpEF may represent a differential response to anti-hypertensive medications compared to those with CH or CR.

Echocardiographic analysis in our study found that when compared to other types of LV geometry in HFpEF, patients with EH have characteristics that are similar to HFrEF, despite a preserved EF. In our study, patients with EH demonstrated lower EF, lower SBP/ESV ratio, and a greater ESV_{120} compared to those with CH. Taken together, these data suggest worse contractility in the EH group. EH patients also demonstrated better diastolic function compared to CH patients, with increased LV compliance (larger EDV_{20}) and better, but still abnormal, LV relaxation. However, lateral e' tissue velocity was not different between groups after adjustment for covariates. Figure 2, which summarizes the pressure-volume relationships of the 2 groups, demonstrates that patients with EH have larger ventricles with worse systolic function and better diastolic function. The pressure-volume loop in EH is more like that of a patient with HFrEF compared to the classic model of HFpEF. Additionally, E_a in EH was lower than in CH, suggesting less arterial stiffening, a difference also found when comparing HFpEF with HFrEF.[17,2]

Despite differences in ventricular and vascular structure and function, patients with EH had similarly elevated cardiac filling pressures and similar adverse outcomes when compared to those with CH. The similarity in left atrial size, LV filling pressures (i.e., E/e' ratio and PCWP), and outcomes in HFpEF patients with EH and CH underscores the need to develop therapies for HFpEF patients with EH. Although EH is only represented in 12–16% of HFpEF patients, given the high overall prevalence of HFpEF, an estimated 360,000 to 480,000 patients in the United States have both HFpEF and EH.[18,19] Given the pathophysiologic profile of patients with HFpEF who have EH, it is possible that these patients may benefit from therapies proven to be effective in HFrEF. These therapies have thus far failed in HFpEF,[20–25] but future HFpEF clinical trials may benefit from *a priori* stratification by type of LV remodeling to determine whether there are differential treatment responses among groups.

From our data we cannot determine what led patients to develop EH rather than other types of LV remodeling. EH is classically thought to result from volume overload states.[26,27] We excluded patients with obvious causes of high-output heart failure or extracardiac sources of volume overload. Valvular heart disease (i.e., mitral or aortic regurgitation) is another possible cause of EH, but valvular heart disease greater than moderate in severity was an exclusion criteria for our study, and rates of mitral regurgitation did not differ between the EH and CH groups. Another potential limitation of our study is the recruitment of all patients from a single academic medical center. However, Northwestern Memorial Hospital serves a large, diverse urban environment. While our cohort was younger than epidemiologic and registry studies of HFpEF, rates of comorbidities were similar, and our study sample was more racially diverse; this may better represent the broader population of HFpEF patients compared to other contemporary HFpEF studies. Finally, our study design only included those HFpEF patients who had recently been hospitalized for HF; however, post-hospitalization patients are at the highest risk for adverse outcomes, and have the most urgent need for effective therapies.[19]

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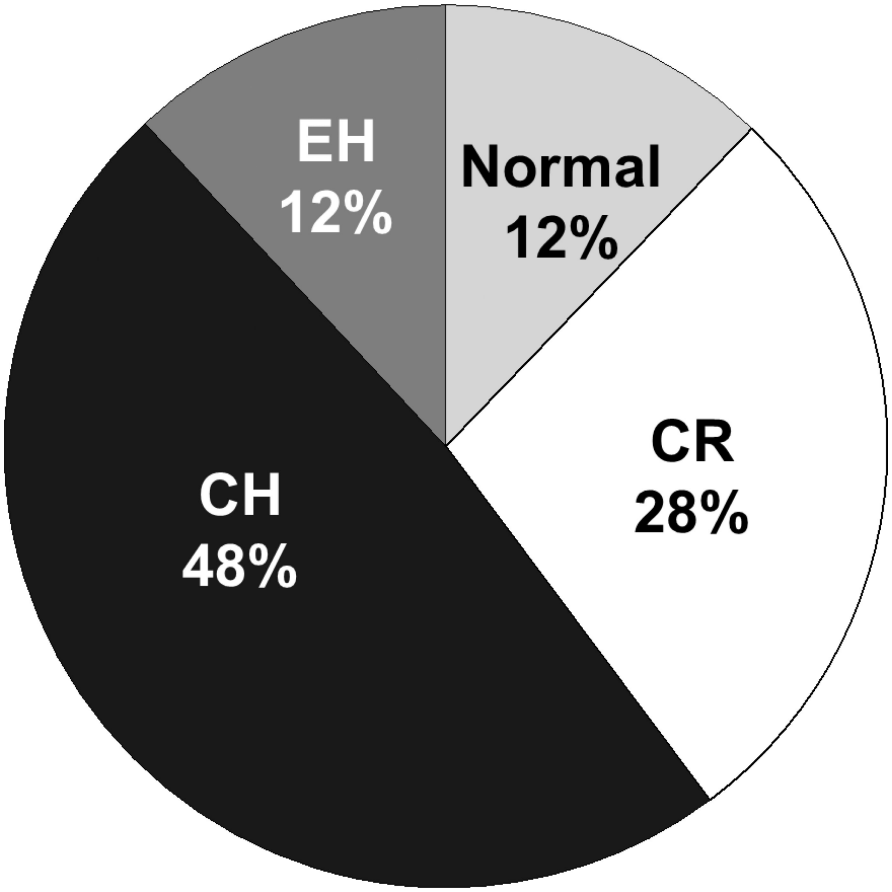

Figure 1. Distribution of Left Ventricular Geometries in Heart Failure with Preserved Ejection Fraction

Left ventricular hypertrophy was defined as left ventricular mass/height$^{2.7}$>44g/m$^{2.7}$ in women and >48 g/m$^{2.7}$ in men. Concentric geometry defined as RWT > 0.42.CR = concentric remodeling; CH = concentric hypertrophy; EH = eccentric hypertrophy.

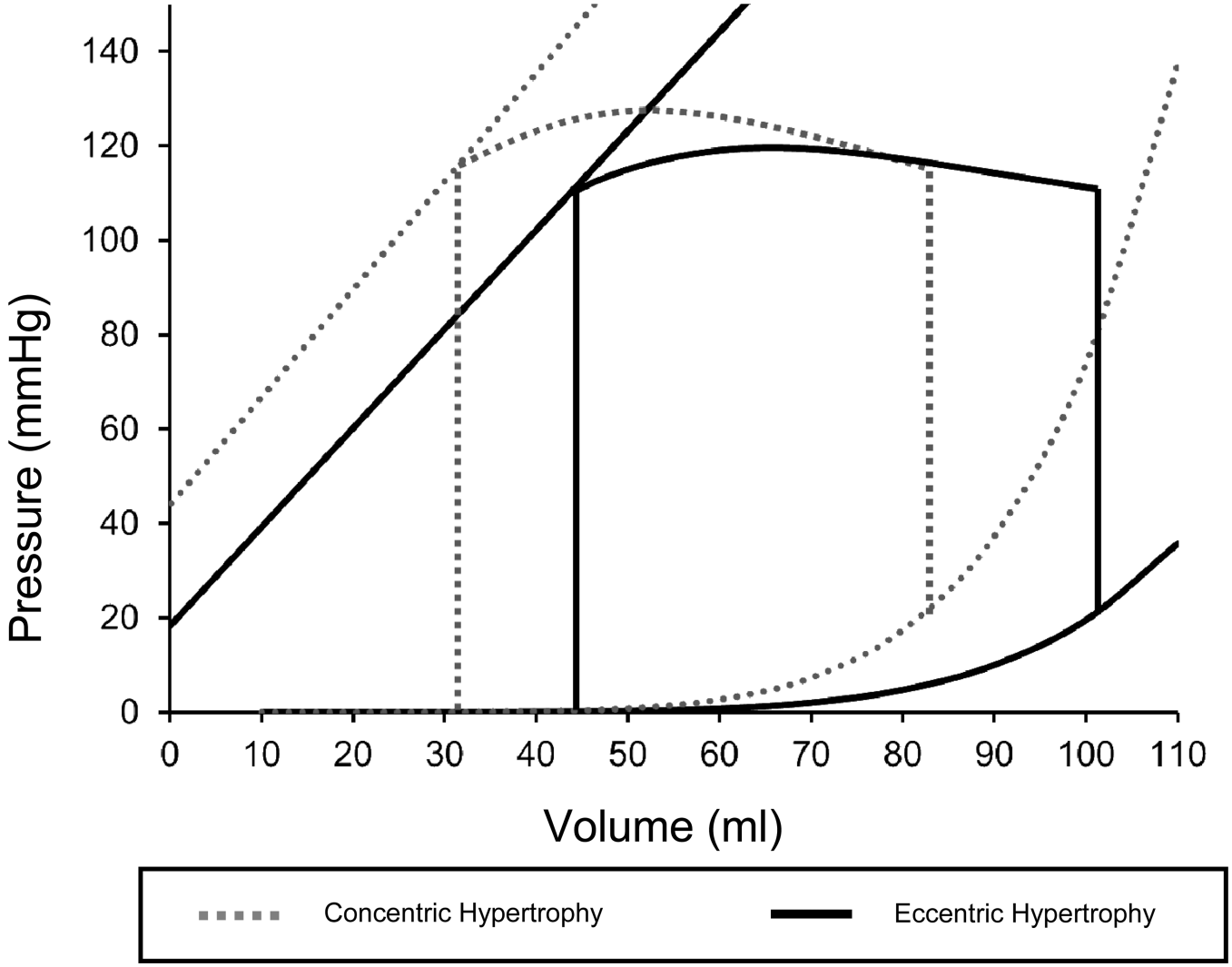

Figure 2. Pressure-Volume Relationships in Heart Failure with Preserved Ejection Fraction: Eccentric Hypertrophy versus Concentric Hypertrophy

Patients with eccentric hypertrophy have downward and rightward shifted end-systolic and end-diastolic pressure volume relationships, as indicated by larger ESV_{120} and EDV_{20} values.

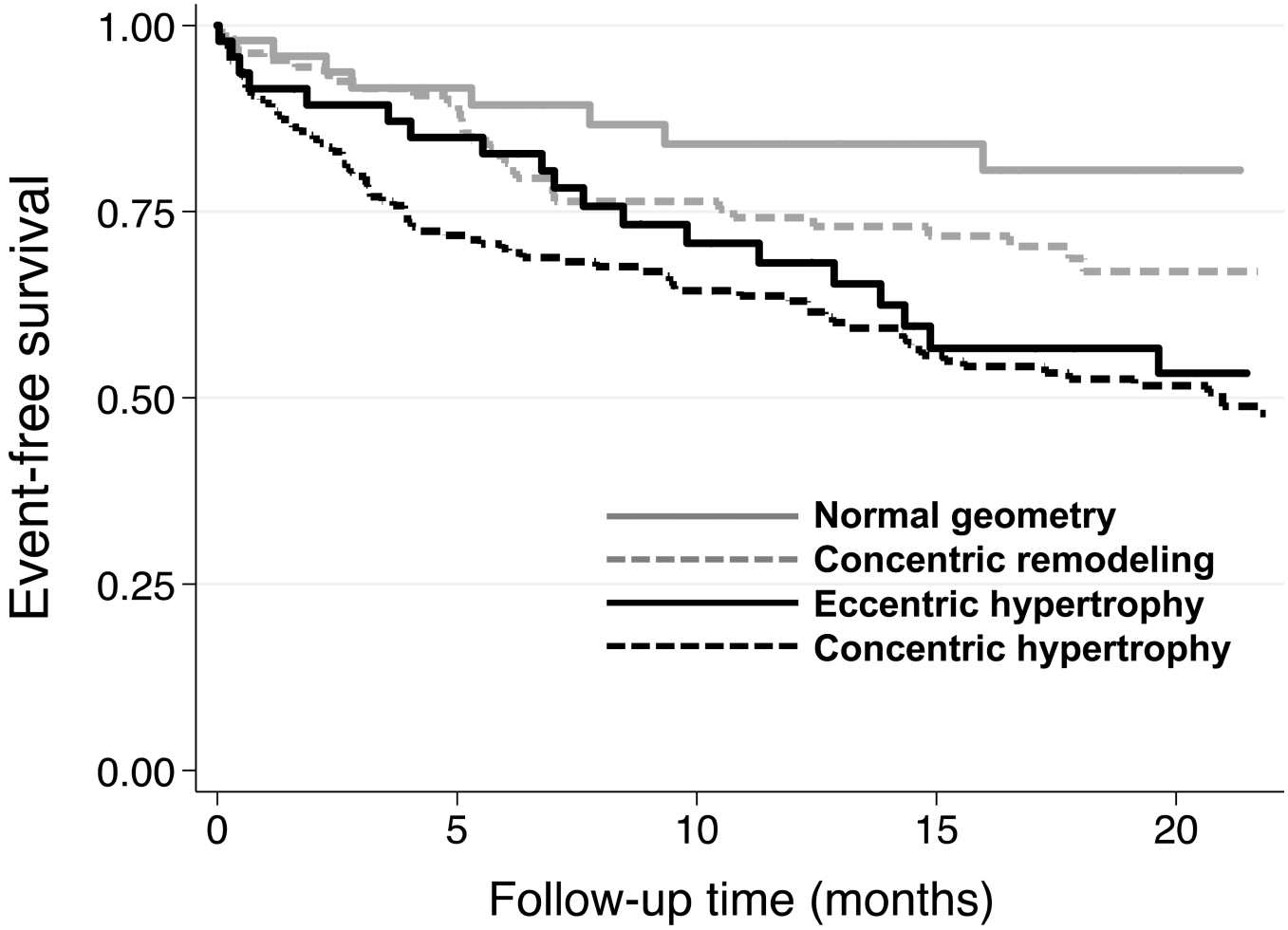

Figure 3. Kaplan-Meier Survival Curves for the Combined Outcome of Heart Failure Hospitalization, Cardiovascular Hospitalization, or Death, Stratified by Left Ventricular Geometry Group

Patients with eccentric hypertrophy had outcomes that were similar to patients with concentric hypertrophy (Log-rank P=0.33).Patients with left ventricular hypertrophy (either eccentric or concentric hypertrophy) had worse outcomes compared to those without left ventricular hypertrophy (Log-rank P=0.0005).

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Table 1

Clinical Characteristics by Left Ventricular Geometry Group

Clinical characteristic	Normal geometry (N=49)	Concentric remodeling (N=111)	Concentric hypertrophy (N=194)	Eccentric hypertrophy (N=48)	p-value*
Age (years)	56±13.2	67±12.1	66±12.3	62±13.9	<0.001**
Female	29 (59%)	55 (50%)	132 (68%)	35 (73%)	0.005**
Race					
White	34 (69%)	60 (54%)	87 (45%)	28 (58%)	0.01
Black	10 (20%)	41 (37%)	85 (44%)	18 (38%)	0.03**
Other	5 (10%)	10 (9%)	22 (11%)	2 (4%)	0.50
New York Heart Association functional class					
I	14 (29%)	16 (14%)	16 (8%)	4 (8%)	0.001**
II	24 (49%)	49 (44%)	68 (35%)	16 (33%)	0.16
III	9 (18%)	45 (41%)	103 (53%)	26 (54%)	<0.001**
IV	2 (4%)	1 (1%)	6 (3%)	1 (2%)	0.57
Coronary artery disease¶	8 (16%)	36 (32%)	79 (41%)	15 (31%)	0.01
Hypertension‡	25 (51%)	84 (76%)	163 (84%)	37 (77%)	<0.001**
Hyperlipidemia§	18 (37%)	63 (57%)	108 (56%)	28 (58%)	0.08
Diabetes mellitus	6 (12%)	30 (27%)	73 (38%)	19 (40%)	0.003**
Chronic kidney disease /	5 (10%)	35 (32%)	75 (39%)	14 (29%)	0.002**
Smoker	18 (37%)	48 (43%)	78 (40%)	19 (40%)	0.88
Atrial fibrillation	14 (29%)	27 (24%)	55 (28%)	14 (29%)	0.87
Obesity#	19 (39%)	44 (40%)	114 (59%)	33 (69%)	<0.001**
Chronic obstructive pulmonary disease	8 (16%)	29 (26%)	40 (21%)	11 (23%)	0.52
Heart rate (beats per minute)	71±14.7	71±14	71±13.6	68±13.3	0.62
Systolic blood pressure (mmHg)	118±16	121±17	129±22	121±19†	<0.001**
Diastolic blood pressure (mmHg)	70±10	70±10	71±13	67±13	0.23
Pulse pressure (mmHg)	49±13	51±15	59±18	54±19	<0.001**
Body mass index (kg/m^2)	28±6.5	29±6.7	34±9.6	3 6± 11.1	<0.001**

Clinical characteristic	Normal geometry (N=49)	Concentric remodeling (N=111)	Concentric hypertrophy (N=194)	Eccentric hypertrophy (N=48)	p-value*
Serum sodium (mEq/l)	139±2.1	138±3.1	138±2.8	138±3.2	0.75
Blood urea nitrogen (mg/dl)	17.7±11.2	24.9± 18.1	26.6±17	22±11.5	0.006
Serum creatinine (mg/dl)	1.01±0.4	1.41±1.2	1.85±1.8	1.29±0.9†	<0.001
Estimated glomerular filtration rate (ml/min/1.73m^2)	76±26.8	60±26.3	52±25.5	64±29.2†	<0.001**
Fasting glucose (mg/dl)	99±20	125±66	121±54	121±52	0.05
Hemoglobin (g/dl)	12.0±1.8	12.1±1.9	11.8±1.8	11.6±2.1	0.46
B-type natriuretic peptide (pg/ml)	131 (54–245)	230 (59–402)	278 (101–664)	261 (94–473)	<0.001**
Number of antihypertensive medications	2.0±1.1	2.3±1.5	3.0±1.4	2.7±1.3	<0.001**
Medications					
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	27 (55%)	51 (46%)	113 (58%)	30 (63%)	0.13
β-blocker	29 (59%)	69 (62%)	138 (71%)	32 (67%)	0.26
Calcium channel blocker	6 (12%)	27 (24%)	77 (40%)	15 (31%)	<0.001**
Nitrate	0 (0%)	13 (12%)	39 (20%)	6 (13%)	0.003**
Loop diuretic	29 (59%)	54 (49%)	124 (64%)	27 (56%)	0.08
Thiazide diuretic	6 (12%)	26 (23%)	50 (26%)	12 (25%)	0.25
Statin	17 (35%)	54 (49%)	98 (51%)	28 (58%)	0.12
Aspirin	17 (35%)	57 (51%)	91 (47%)	21 (44%)	0.27

*p value by analysis of variance among groups (or Kruskal-Wallis test for right-skewed variables)

†p-value < 0.05 and remains significant after correction using false discovery rate < 5% for comparison of eccentric hypertrophy vs. concentric hypertrophy

**p-value < 0.05 and remains significant after correction using false discovery rate < 5% for comparison of left ventricular hypertrophy vs. no left ventricular hypertrophy

¶Presence of physician-documented history of coronary artery disease, known coronary stenosis >50%, history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or abnormal stress test results consistent with myocardial ischemia.

‡Systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, physician-documented history of hypertension, or current use of antihypertensive medications.

§Physician-documented history of hyperlipidemia or current use of lipid-lowering medications.

/Estimated glomerular filtration rate < 60 ml/min/1.73 m^2.

#Body-mass index >30 kg/m^2

Table 2

Echocardiographic Characteristics by Left Ventricular Geometry Group

Echocardiographic parameter	Normal geometry (N=49)	Concentric remodeling (N=111)	Concentric hypertrophy (N=194)	Eccentric hypertrophy (N=48)	p-value*
Left ventricular end-systolic volume index (ml/m^2)	17±5	15±4	16±6	21±9†	<0.001**
Left ventricular end-diastolic volume index (ml/m^2)	42±10	38±8	40±11	48±15†	<0.001**
Relative wall thickness	0.38±0.03	0.50±0.07	0.59±0.17	0.38±0.03†	<0.001**
Left ventricular mass index (g/m^{27})	36±6	37±6	64±19	56±10†	<0.001**
Left ventricular mass/volume ratio (g/ml)	1.9±0.4	2.2±0.5	3.2±1.2	2.3±0.5†	<0.001**
Left ventricular ejection fraction (%)	60±5	62±6	62±7	58±6†	<0.001
Stroke volume (ml)	50±16	46±12	50±15	56±17†	<0.001**
Cardiac index (L/min/m^2)	1.7±0.5	1.6±0.5	1.7±0.5	1.9±0.7	0.12
End-systolic volume $_{120}$ (ml)	40±13	34±13	35±16	52±22†	<0.001**
Systolic blood pressure/end systolic volume ratio	3.5±1.3	4.3±1.6	4.2±1.7	2.9±1.4†	<0.001
Effective arterial elastance (mmHg/ml)	2.3±0.8	2.6±0.7	2.5±0.8	2.1±0.7†	0.004
Pulse pressure/stroke volume ratio (mmHg/ml)	1.06±0.41	1.18±0.45	1.24±0.48	1.06±0.53	0.02
End-diastolic volume$_{20}$ (ml)	86±28	75±20	82±25	101±32†	<0.001**
Left atrial volume index (ml/m^2)	33±12	32±17	35±14	35±11	0.30
E/A ratio	1.5±0.6	1.3±0.6	1.3±0.8	1.5±0.8	0.23
E deceleration time (ms)	220±57	227±56	236±77	224±53	0.38
Isovolumic relaxation time (ms)	84±20	85±20	91±23	87±26	0.07
Septal e' tissue velocity (cm/s)	8.4±3.5	7.6±2.9	6.4±2.2	7.1±2.4	<0.001**
Lateral e' tissue velocity (cm/s)	11.2±4.8	10.0±4.0	8.4±3.2	9.7±4.0	<0.001**
Average E/e' ratio	12.6±7.1	13.4±7.3	16.9±9.0	14.9±6.7	<0.001**
Tricuspid annular plane systolic excursion (cm)	2.30±0.71	1.89±0.64	1.97±0.61	2.06±0.54	0.002
Mitral Regurgitation					
None	26 (53%)	70 (63%)	109 (56%)	23 (48%)	0.31
Mild	13 (27%)	29 (26%)	55 (28%)	16 (33%)	0.82
Moderate	10 (20%)	11 (10%)	29 (15%)	8 (17%)	0.32

*
p value by analysis of variance;

†
p-value < 0.05 and remains significant after correction using false discovery rate < 5% for comparison of eccentric hypertrophy vs. concentric hypertrophy;

**
p-value < 0.05 for left ventricular hypertrophy compared to no left ventricular hypertrophy (and remains significant after false-discover rate correction)

Table 3

Invasive Hemodynamics by Left Ventricular Geometry Group (N=217)

Invasive hemodynamic parameter	Normal geometry (N=27)	Concentric remodeling (N=62)	Concentric hypertrophy (N=101)	Eccentric hypertrophy (N=27)	p-value*
Right atrial pressure (mmHg)	15±7	13±6	14±7	13±6	0.31
Pulmonary artery systolic pressure (mmHg)	48±14	45±13	56±20	54±15	<0.001**
Pulmonary artery diastolic pressure (mmHg)	26±8	22±7	27±10	27±9	0.005
Mean pulmonary artery pressure (mmHg)	34±10	30±8	36±12	36±10	0.006
Pulmonary capillary wedge pressure (mmHg)	23±8	21±7	24±10	24±9	0.06
Cardiac index (L/min/m^2)	3.0±0.8	2.7±0.8	3.0±1.1	3.2±1.4	0.06
Pulmonary vascular resistance (Wood units)	1.7±1.3	1.9±1	2.0±1.6	2.2±2.1	0.60

*p value by analysis of variance between groups;

**p-value < 0.05 and remains significant after correction using false discovery rate < 5% for left ventricular hypertrophy compared to no left ventricular hypertrophy. There were no statistically significant differences between the eccentric and concentric hypertrophy groups

Table 4

Differences in Clinical Characteristics and Echocardiographic Parameters between Eccentric Hypertrophy and Concentric Hypertrophy Groups after Multivariable-Adjusted Linear Regression Analysis

Clinical characteristic	β-Coefficient for comparison of EH vs. CH	p-value
Systolic blood pressure (mmHg)	−8.3 (−14.9, −1.8)	0.01
Diastolic blood pressure (mmHg)	−5.3 (−9.1, −1.5)	0.01
Serum creatinine (mg/dl) *	−0.6 (−1.0, −0.2)	0.01
Estimated glomerular filtration rate (ml/min/1.73 m^2) *	12.3 (4.7, 20.0)	0.002
Echocardiographic parameter		
Ejection fraction (%)	−3.2 (−5.4, −1.1)	<0.001
Stroke volume (ml)	4.9 (0.5, 9.3)	0.03 †
End-systolic $volume_{120}$ (ml)	15.7 (8.4, 23.0)	<0.001
Systolic blood pressure/end systolic volume ratio (mmHg/ml)	−1.0 (−1.5, −0.5)	<0.001
E_a, arterial elastance (mmHg/ml)	−0.3 (−0.5, −0.1)	0.01
Pulse pressure/stroke volume ratio (mmHg/ml)	−0.1 (−0.3, 0.0)	0.10
End-diastolic $volume_{20}$ (ml)	14.2 (9.4, 19.1)	<0.001
Lateral e' velocity (cm/s)	0.8 (−0.4, 2.0)	0.19

Model adjusted for age, sex, African-American race, hypertension, hyperlipidemia, diabetes mellitus, obesity, heart rate, log B-type natriuretic peptide, presence of wall motion abnormality on echocardiography, and estimated glomerular filtration rate (except as noted)

* Estimated glomerular filtration rate omitted from model

† No longer significant after adjustment for multiple comparisons using the false discovery rate method

Table 5

Association of Left Ventricular Geometry with Adverse Outcomes on Cox-Proportional Hazards Analysis

	Normal geometry (N=49)	Concentric remodeling (N=111)	Concentric hypertrophy (N=194)	Eccentric hypertrophy (N=48)	p-value*
Outcome					
Heart failure hospitalization	3 (6%)	20 (18%)	64 (33%)	15 (31%)	<0.001
Cardiovascular hospitalization	6 (12%)	28 (25%)	86 (44%)	18 (38%)	<0.001
Death	3 (8%)	14 (14%)	28 (17%)	3 (8%)	0.340
Combined endpoint	8 (16%)	36 (32%)	101 (52%)	20 (42%)	<0.001
Unadjusted HR (95% CI)					
Heart failure hospitalization	1.00	3.10 (0.92–10.40)	6.00 (1.88–19.1)	5.27 (1.51–18.3)	0.002**
Cardiovascular hospitalization	1.00	2.19 (0.91–5.29)	4.20 (1.83–9.62)	3.09 (1.22–7.84)	<0.001**
Death	1.00	1.78 (0.60–5.29)	2.12 (0.75–5.98)	0.73 (0.16–3.28)	0.192
Combined endpoint	1.00	2.09 (0.97–4.50)	3.71 (1.80–7.62)	2.59 (1.14–5.93)	<0.001**
Adjusted HR (95% CI)†					
Heart failure hospitalization	1.00	2.31 (0.67–8.00)	4.03 (1.22–13.3)	3.64 (1.01–13.1)	0.035**
Cardiovascular hospitalization	1.00	1.54 (0.62–3.82)	2.73 (1.15–6.46)	2.34 (0.90–6.11)	0.017**
Death	1.00	1.28 (0.41–3.99)	1.76 (0.59–5.19)	0.85 (0.19–3.93)	0.452
Combined endpoint	1.00	1.51 (0.68–3.32)	2.54 (1.20–5.40)	2.02 (0.86–4.77)	0.012**

*P-value represents difference across all 4 groups (there were no significant differences between the eccentric and hypertrophy groups);

†Adjusted for age, sex, African American race, estimated glomerular filtration rate, hypertension, diabetes mellitus, and obesity;

**p-value < 0.05 and remains significant after correction using false discovery rate < 5% for comparison of left ventricular hypertrophy to no left ventricular hypertrophy HR = hazard ratio; CI = confidence interval