Association of Concentric Left Ventricular Hypertrophy With Subsequent Change in Left Ventricular End-Diastolic Volume

The Dallas Heart Study

BACKGROUND: In the conventional paradigm of the progression of left ventricular hypertrophy, a thick-walled left ventricle (LV) ultimately transitions to a dilated cardiomyopathy. There are scant data in humans demonstrating whether this transition occurs commonly without an interval myocardial infarction.

METHODS AND RESULTS: Participants (n=1282) from the Dallas Heart Study underwent serial cardiac magnetic resonance ≈7 years apart. Those with interval cardiovascular events and a dilated LV (increased LV end-diastolic volume [EDV] indexed to body surface area) at baseline were excluded. Multivariable linear regression models tested the association of concentric hypertrophy (increased LV mass and LV mass/volume$^{0.67}$) with change in LVEDV. The study cohort had a median age of 44 years, 57% women, 43% black, and 11% (n=142) baseline concentric hypertrophy. The change in LVEDV in those with versus without concentric hypertrophy was 1 mL (−9 to 12) versus −2 mL (−11 to 7), respectively, $P<0.01$. In multivariable linear regression models, concentric hypertrophy was associated with larger follow-up LVEDV ($P\leq0.01$). The progression to a dilated LV was uncommon (2%, n=25).

CONCLUSIONS: In the absence of interval myocardial infarction, concentric hypertrophy was associated with a small, but significantly greater, increase in LVEDV after 7-year follow-up. However, the degree of LV enlargement was minimal, and few participants developed a dilated LV. These data suggest that if concentric hypertrophy does progress to a dilated cardiomyopathy, such a transition would occur over a much longer timeframe (eg, decades) and may be less common than previously thought.

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WHAT IS NEW?

- There are scant data in humans demonstrating whether concentric hypertrophy commonly transitions to a dilated cardiomyopathy without an interval myocardial infarction.
- We evaluated the association of concentric hypertrophy with change in left ventricular end-diastolic volume among 1282 participants of the Dallas Heart Study.
- In the absence of interval myocardial infarction, concentric hypertrophy was associated with minimal left ventricular enlargement after 7-year follow-up, and few participants developed a dilated left ventricle.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Our findings highlight that the progression of concentric hypertrophy to a dilated cardiomyopathy would require a much longer time frame (eg, decades) and also raise the possibility that in the absence of interval myocardial infarction, such a transition may occur infrequently in humans.

In the conventional paradigm of the natural history of left ventricular hypertrophy (LVH), the left ventricle (LV) first develops concentric hypertrophy (wall thickening) before transitioning to a dilated cardiomyopathy, manifested by LV dilation, thin LV walls, and a reduced ejection fraction (EF).[1,2] This transition has been described in some experimental animal models including the spontaneously hypertensive rat[3] or after transverse aortic constriction in rats and mice,[4,5] although it has not consistently been observed in larger mammal models.[6–8] In humans, this transition has been reported in patients with aortic stenosis although the cause is considered multifactorial,[9–11] in a small subset of those with hypertrophic cardiomyopathy,[12–14] and is well established after interval myocardial infarction.[15–19] Outside of these particular circumstances, there remain scant data in humans demonstrating whether this transition to a dilated cardiomyopathy is a common pathway.

Several longitudinal echocardiographic studies of patients with concentric LVH have reported that progression to eccentric LVH[15,17,20,21] or development of low EF[16,18,22] is uncommon, especially in the absence of interval myocardial infarction. However, these studies were limited because they defined eccentric hypertrophy by the absence of an increase in relative wall thickness, rather than by LV dilation.[23] In addition, previous studies did not use cardiac magnetic resonance (CMR), a more accurate measure of cardiac structure including LV volume.[24,25] Further, the majority of the studies were performed in predominantly nonblack cohorts, despite the prevalence of concentric LVH being highest among black individuals.[26–28]

In the present study, we sought to determine in a multiethnic population whether baseline concentric LVH and left ventricular wall thickening were associated with changes in LV volume over time, as assessed by serial CMR, in the absence of interval myocardial infarction.

METHODS

Study Population

The DHS (Dallas Heart study) is a multiethnic, population-based, cohort study of Dallas County adults in which deliberate oversampling of blacks was performed, as previously described.[29] In brief, the initial phase occurred between 2000 and 2002, at which time collection of demographics, medical history, and blood and urine samples, as well as detailed imaging studies, including CMR (n=2803), were performed. The second phase of the DHS occurred between 2007 and 2009 and consisted of repeated collection of participant information and follow-up imaging, including CMR. Both baseline and follow-up CMR were performed in 1386 participants (Figure). Baseline characteristics of those who did or did not have a follow-up CMR are shown in Table I in the Data Supplement. Written informed consent was provided by all participants, and the University of Texas Southwestern Institutional Review Board approved the study. For this analysis, we excluded participants with a dilated LV at baseline, defined by LV end-diastolic volume indexed to body surface area (LVEDV/BSA) >97.5th percentile of a normal subpopulation[30] (82.8 mL/m^2 for men and 80.3 mL/m^2 for women). We also excluded those who developed cardiovascular disease (CVD), defined as myocardial infarction, coronary bypass surgery, percutaneous intervention, stroke, or heart failure, between phase 1 and 2, resulting in a final cohort of 1282 participants (Figure).

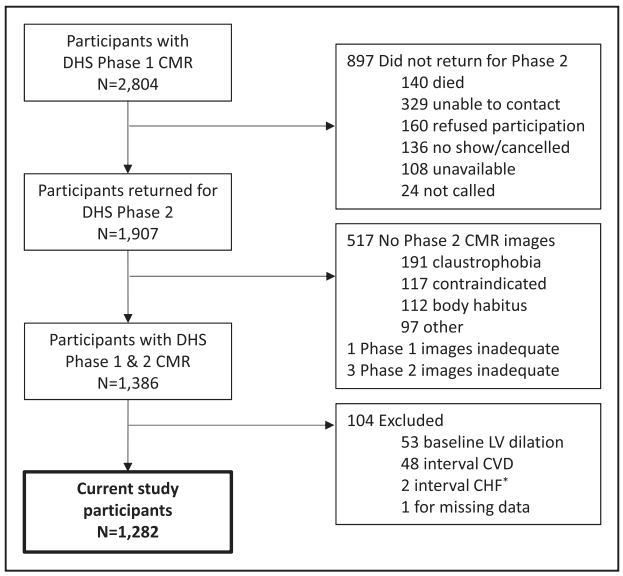

Figure. Study population.
*Neither participant developed a dilated left ventricle at follow-up. CHF indicates congestive heart failure; CMR, cardiac magnetic resonance; CVD, cardiovascular disease; and DHS, Dallas Heart Study.

Cardiac Magnetic Resonance

The details of CMR for DHS phase 1 have been described previously.[30,31] Briefly, in phase 1 of DHS, short-axis, breath-hold, prospective electrocardiographic gated turbo field echo cine images were obtained from 2 comparable 1.5-T systems (Philips Medical Systems, Best, The Netherlands).

Follow-up imaging (phase 2) was performed a median of 7 years after baseline imaging. In phase 2, CMR was obtained using a 3-T system (Achieva; Philips Medical Systems, Best, The Netherlands). The 2-chamber and 4-chamber views were acquired using balanced field echo sequence and used to plan the short-axis images. Cine images were obtained spanning the cardiac apex through the base of the LV as a series of 9 to 13 short-axis slices (additional parameters include 6-mm slice thickness and 4-mm slice gap). Images were acquired during 15 to 20 second end-expiratory breath-holds using prospective electrocardiographic gated turbo field echo sequence.

An accreditation phantom was imaged on the 1.5-T and 3-T systems, allowing baseline and follow-up mass and volume measurements to be normalized to this control. QMass software (Medis Medical Imaging Systems, Leiden, The Netherlands; version 6.2.3) was used to analyze the data. Endocardial and epicardial borders at end diastole and end systole were traced manually in each short-axis image. Papillary muscles were delineated independently of the left ventricular wall and included in the myocardial LV mass and excluded from the LV volume. Measurements from each slice were summed by the method of disks (Simpson rule). LV mass was determined by the difference between the end-diastolic endocardial and epicardial contour multiplied by the specific gravity of myocardium (1.05 g/mL). LV wall thickness (LVWT) was determined using the short-axis images, with the most apical and basal slices excluded from the calculation. The center of mass was determined for each slice, and 60 chords were drawn from that point to the epicardial borders. The intersection of the chord with the endocardial border was noted. The distance between the intersection point and the epicardial border was the wall thickness for that particular chord. The wall thickness for each slice was the average over the chords, and the overall LVWT was the average over the slices.

All baseline and follow-up, turbo field echo images were read by analysts based on a standardized protocol for tracing end-systolic and end-diastolic endomyocardial and epicardial borders. They analyzed participant studies only after satisfactory completion of a training set of images taken from phase 1 and phase 2, with measurements within 10% of established values for LVEDV, LV end-systolic volume, LV EF, and LV mass, which were reviewed by an experienced level-2 trained CMR physician. In addition, a level-2 CMR physician over-read a random sample of 10% of the studies as well as the outliers (<5th percentile and >95th percentile) for LV mass and LVEDV at baseline and follow-up. In addition, outliers (<5th percentile and >95th percentile) in the change in LV mass and LVEDV were over-read by a level-2 CMR physician. The intraobserver correlation coefficients were 0.94 for LVEDV, 0.90 for LV end-systolic volume, and 0.82 for LV mass. The interobserver correlation coefficients were 0.91 for LVEDV, 0.84 for LV end-systolic volume, and 0.86 for LV mass.

Definitions

All phase 1 studies were reinterpreted using the updated software to match the method used for reading phase 2 imaging, resulting in revised baseline LV measurements. As such, we redefined thresholds at >97.5th percentile of the previously described healthy subpopulation[30] for increased LV mass (LVH, 38.1 g/m$^{2.7}$ for men and 34.1 g/m$^{2.7}$ for women based on LV mass indexed to height$^{2.7}$), increased LVEDV/BSA (82.8 mL/m^2 for men and 80.3 mL/m^2 for women), and increased LV mass/LVEDV$^{0.67}$ (7.2 g/mL$^{0.67}$ for men and 5.8 g/mL$^{0.67}$ for women). As previously described, concentric hypertrophy was defined as having increased LV mass and increased LV mass/volume$^{0.67}$.[23] Because we excluded participants with LV dilation at baseline, concentric hypertrophy in this study excluded those who had concomitant LV dilation. Finally, given that we are using LV mass/volume$^{0.67}$ reported as g/mL$^{0.67}$ (ie, we did not convert mass in grams to milliliters), we have elected to report mass/volume as g/mL for consistency.

NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels were measured at both phase 1 and phase 2 of DHS, as previously described.[32]

Statistical Analysis

We compared characteristics among those with baseline concentric hypertrophy and those without using the χ^2 test for dichotomous variables and Wilcoxon rank-sum test for continuous variables. Unadjusted and multivariable linear regression models were used to assess the association of concentric hypertrophy and baseline LVWT with change in LVEDV and LVEDV/BSA. Change in LVEDV (or LVEDV/BSA) was modeled using phase 2 LVEDV (or LVEDV/BSA) as the dependent variable with adjustment for phase 1 LVEDV (or LVEDV/BSA). Continuous parameters were reported as standardized estimates representing 1 SD change in baseline LVWT and 1 SD change in LVEDV. Model 1 includes adjustment for age, sex, race, systolic blood pressure, use of antihypertension medications, diabetes mellitus, CVD, and LV EF. Model 2 includes the adjustments from model 1 in addition to change in weight, change in systolic blood pressure between phase 1 and 2, use of antihypertension medications at phase 2, and development of diabetes mellitus at phase 2. The parameters of height, weight, and change in weight were included in the models involving LVEDV but not LVEDV/BSA.

The uncommon progression to a dilated LV precluded the evaluation of incident LV dilation as an end point because of insufficient statistical power. Thus, to assess whether concentric hypertrophy was associated with a categorical change of LVEDV of smaller magnitude, we defined a sex-specific threshold of ΔLVEDV >75th percentile (ΔLVEDV75; 6.5 mL for men and 8.9 mL for women) of a previously described healthy subpopulation (n=239)[30] that returned for repeat imaging. We tested whether NT-proBNP was associated with ΔLVEDV75 in multivariable regression in attempt to assess the potential significance of this degree of ventricular dilation. Multivariable logistic regression was then used to assess the association of concentric hypertrophy and LVWT with this categorical change in LVEDV (ΔLVEDV75). The categorical definition for ΔLVEDV75 was modeled as a dependent variable with adjustment for phase 1 LVEDV. Odds ratios (with confidence intervals) were reported for 1 SD increase in the

continuous parameter of baseline LVWT. Serial adjustment was performed in a manner identical to the linear regression models (described above). In sensitivity analysis, we evaluated these models in a restricted cohort (n=817) after additional exclusion of participants with self-reported history of baseline CVD (defined above) or self-reported use of antihypertensive medications at either phase 1 or phase 2. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Inc, Cary, NC) statistical software. All *P* values are 2-sided with an α of 0.05, and no corrections were made for multiple comparisons.

RESULTS

The primary study cohort included 1282 participants, the mean age was 44 years, 57% were women, and 43% black. Approximately 10% (n=142) of the participants had concentric hypertrophy at baseline. The baseline and follow-up clinical characteristics of participants with and without baseline concentric hypertrophy are shown (Table 1). Presence of concentric hypertrophy was associated with older age, black race, higher weight, hypertension, higher blood pressure, diabetes mellitus, CVD, and higher NT-proBNP levels at follow-up.

The baseline, follow-up, and change in LV structure and function from baseline to follow-up, stratified by baseline concentric hypertrophy, are shown (Table 2). Concentric hypertrophy was associated with increased LVWT, mass/volume$^{0.67}$ (by definition) and LV mass (by definition) at baseline and follow-up, and smaller baseline but not follow-up LVEDV/BSA. The median change in unindexed LVEDV or LVEDV/BSA was significantly greater when comparing those with and without concentric hypertrophy. In contrast, LVWT, LV mass, and LV mass/volume$^{0.67}$ all decreased more in those with concentric hypertrophy though there was no significant difference in the change in LVEF between these 2 groups.

Association of Concentric Hypertrophy and LVWT With Change in LVEDV in Linear Regression

The association of concentric hypertrophy with subsequent change in LVEDV in linear regression analysis is shown (Table 3). In unadjusted linear regression analysis, the baseline presence of concentric hypertrophy was associated with an increase in follow-up LVEDV ($P<0.01$). Similarly, in both adjusted linear regression models, concentric hypertrophy remained associated with an increase in follow-up LVEDV ($P<0.01$), where model 1 included adjustment for baseline risk factors, and model 2 included additional adjustment for changes in these factors over time. In sensitivity analysis restricted to participants not on antihypertensive therapy and without CVD (n=817), concentric hypertrophy remained associated with larger change in LVEDV in linear regression models. Concentric hypertrophy had similar significant associations with change in LV volume in linear regression models when LVEDV/BSA was substituted as the dependent variable (data not shown).

Baseline LV wall thickness was also associated with a larger follow-up LVEDV in both univariable and mul-

Table 1. Baseline and Follow-Up Clinical Characteristics of Those With and Without Baseline Concentric Hypertrophy

Characteristic	With Concentric Hypertrophy (n=142)	Without Concentric Hypertrophy (n=1140)	*P* Value	With Concentric Hypertrophy (n=142)	Without Concentric Hypertrophy (n=1140)	*P* Value
	Baseline			Follow-Up		
Age, y	47 (39–53)	44 (36–52)	0.002	54 (46–60)	51 (43–58)	0.002
Male sex, %	29	44	0.0004	29	44	0.0004
Black race, %	76	39	<0.0001	76	39	<0.0001
BSA, m^2	2.0 (1.9–2.2)	1.9 (1.8–2.1)	<0.0001	2.0 (1.9–2.2)	1.9 (1.8–2.1)	<0.0001
Weight, kg	90 (77–105)	79 (68–92)	<0.0001	91 (80–103)	82 (70–94)	<0.0001
Diabetes mellitus, %	17	6	<0.0001	27	11	<0.0001
Hypertension, %	67	22	<0.0001	81	40	<0.0001
SBP, mm Hg	137 (124–147)	121 (112–130)	<0.0001	138 (126–152)	127 (117–138)	<0.0001
DBP, mm Hg	83 (77–91)	77 (71–82)	<0.0001	82 (76–89)	79 (74–85)	0.0001
Antihypertensive medications, %	34	14	<0.0001	67	27	<0.0001
CVD, %	9	3	0.0003	6	2	0.02
eGFR, mL/min per 1.73 m^2	99 (84–114)	96 (84–110)	0.2	91 (75–104)	90 (78–105)	0.7
NT-proBNP, pg/mL	29 (13–75)	27 (12–53)	0.1	55 (26–116)	39 (24–71)	0.001

Values with parenthesis are presented as median (25%–75%). *P* values compare participants with baseline concentric hypertrophy vs those without concentric hypertrophy. BSA indicates body surface area; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; and SBP, systolic blood pressure.

Table 2. Baseline, Follow-Up, and Change in LV Structure and Function in Those With and Without Concentric Hypertrophy

Characteristic	With Concentric Hypertrophy (n=142)	Without Concentric Hypertrophy (n=1140)	*P* Value	With Concentric Hypertrophy (n=142)	Without Concentric Hypertrophy (n=1140)	*P* Value	With Concentric Hypertrophy (n=142)	Without Concentric Hypertrophy (n=1140)	*P* Value
	Baseline			Follow-Up			Change		
LVEDV, mL	114 (100 to 134)	117 (102 to 132)	0.8	117 (98 to 141)	114 (98 to 131)	0.1	1 (–9 to 12)	–2 (–11 to 7)	0.007
LVEDV/BSA, mL/ m^2	56.2 (50.4 to 66.0)	61.8 (54.9 to 68.4)	<0.0001	59.9 (50.1 to 67.2)	58.8 (52.1 to 66.2)	0.7	0.7 (–4.7 to 5.3)	–1.9 (–7.2 to 2.7)	<0.0001
LV mass, g	162 (142 to 191)	121 (99 to 145)	By definition	151 (133 to 183)	120 (94 to 144)	<0.0001	–9 (–21 to 3)	–2 (–9 to 7)	<0.0001
LV mass/height$^{2.7}$, g/$m^{2.7}$	41.4 (38.6 to 45.7)	30.2 (25.9 to 34.1)	By definition	39.2 (35.2 to 43.7)	29.1 (25.2 to 33.4)	<0.0001	–2.8 (–5.4 to 0.1)	–0.7 (–2.7 to 1.7)	<0.0001
Mass/volume, g/mL	1.4 (1.3 to 1.6)	1.1 (0.9 to 1.2)	<0.0001	1.3 (1.2 to 1.5)	1.1 (0.9 to 1.2)	<0.0001	–0.07 (–0.2 to 0.02)	0.01 (–0.09 to 0.10)	<0.0001
Mass/volume$^{0.67}$, g/mL$^{0.67}$	6.9 (6.2 to 7.9)	5.1 (4.4 to 5.8)	By definition	6.4 (5.9 to 7.3)	5.1 (4.4 to 5.9)	<0.0001	–0.5 (–0.9 to 0.1)	0.0 (–0.4 to 0.4)	<0.0001
LVWT, mm	9.4 (8.6 to 10.4)	7.4 (6.4 to 8.3)	<0.0001	9.1 (8.2 to 10.0)	7.3 (6.4 to 8.4)	<0.0001	–0.3 (–0.8 to 0.1)	0.0 (–0.5 to 0.5)	<0.0001
LV EF, %	70 (64 to 74)	68 (65 to 73)	0.2	70 (65 to 75)	70 (65 to 74)	0.2	0.01 (–0.03 to 0.05)	0.01 (–0.03 to 0.04)	1.0
LVESV, mL	35 (28 to 44)	37 (29 to 45)	0.3	33 (25 to 45)	35 (27 to 43)	0.9	0.1 (–6.0 to 5.6)	–1.4 (–6.7 to 3.5)	0.1
LVESV/BSA, mL/m^2	17.5 (13.4 to 21.5)	19.3 (15.6 to 23.2)	0.001	17.2 (12.9 to 21.5)	17.8 (14.3 to 22.0)	0.2	–0.3 (–3.3 to 3.2)	–1.0 (–4.1 to 1.5)	0.01

Values are presented as median (25% to 75%). Change was calculated as phase 2 measurement–phase 1 measurement. BSA indicates body surface area; CMR, cardiac magnetic resonance; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricular; and LVWT, left ventricular wall thickness.

tivariable linear regression models (*P*<0.001 for all). In sensitivity analysis restricted to participants not on antihypertensive therapy and without CVD, baseline LVWT remained associated with an increase in LVEDV modeled as a continuous parameter (*P*<0.001 for all). LVWT had similar significant associations with change in LV volume when LVEDV/BSA was substituted as the dependent variable (data not shown).

Association of Concentric Hypertrophy and LVWT With ΔLVEDV75

The progression to a dilated LV was uncommon in our study population (2%, n=25), both in those with (4/142, 3%) or without (21/1,140, 2%) baseline concentric hypertrophy. Thus, we defined ΔLVEDV75, a categorical definition of a change in LVEDV >75th percentile of a healthy subpopulation to test whether baseline concentric hypertrophy was associated with a smaller magnitude of LV enlargement. In an effort to determine the significance of ΔLVEDV75, we evaluated the association of NT-proBNP with this end point. Higher follow-up NT-proBNP levels were associated with ΔLVEDV75 after adjustment for baseline NT-proBNP (odds ratio 1.6 [1.3–1.9]; *P*<0.0001).

ΔLVEDV75 was more common in those with versus without baseline concentric hypertrophy (35% versus 22%; *P*=0.002). Both in univariable and multivariable logistic regression models, baseline concentric hypertrophy was associated with ΔLVEDV75 (*P*<0.01; Table 4). Similarly, baseline LVWT was associated with ΔLVEDV75 in both univariable and multivariable logistic regression models (*P*<0.001 for all). In sensitivity analysis restricted to participants not on antihypertensive therapy and without CVD, both baseline concentric hypertrophy and LVWT remained associated with ΔLVEDV75.

DISCUSSION

An important unresolved question is whether concentric hypertrophy is a common precursor to dilated cardiomyopathy, the latter manifest as a dilated LV with thinned walls and a reduced EF. Herein, we demonstrate for the first time to our knowledge that concentric hypertrophy was an independent risk factor for a small, but significant, increase in LV volume, whether assessed as a continuous or categorical variable. However, we found that the progression from concentric hypertrophy to a dilated LV over 7 years was uncommon (2%).

Previous echocardiographic longitudinal studies have assessed the natural history of concentric hypertrophy.[15–18,20–22] Progression from concentric LVH to eccentric LVH occurred in 19% of subjects after 4 years[17]

Table 3. Association of Concentric Hypertrophy and LVWT With Change in LVEDV in Linear Regression Models

	Concentric Hypertrophy		LVWT	
	β*	*P* Value	β*	*P* Value
Primary cohort				
Unadjusted	3.8	0.004	0.13	<0.0001
Model 1†	3.9	0.006	0.09	<0.0001
Model 2‡	4.1	0.004	0.09	<0.0001
Restricted cohort§				
Unadjusted	8.3	0.0002	0.14	<0.0001
Model 1†	6.4	0.005	0.11	<0.0001
Model 2‡	6.7	0.003	0.11	<0.0001

The association of baseline LVWT and concentric hypertrophy with change in LVEDV as a continuous parameter was tested in linear regression models in which phase 2 LVEDV was the dependent variable and phase 1 LVEDV was an independent variable. CVD indicates cardiovascular disease; EDV, end-diastolic volume; EF, ejection fraction; LV, left ventricle; and LVWT, LV wall thickness.

*The parameter estimates are reported as a standardized β coefficient representing 1 SD change in the independent variable of LVWT and 1 SD change in LVEDV. The parameter estimate is reported as a raw β coefficient for the categorical independent variable of concentric hypertrophy.

†Model 1 included adjustment for age, sex, race, systolic blood pressure, antihypertension medications, diabetes mellitus, CVD, and LV EF.

‡Model 2 includes model 1 with added adjustment for change in weight, change in systolic blood pressure, incident hypertension medications, and incident diabetes mellitus.

§Restricted cohort (n=817) included additional exclusion of self-report of antihypertensive therapy at baseline or at follow-up and baseline CVD in addition to exclusions of primary analysis (interval CVD and baseline dilation).

Table 4. Association of Concentric Hypertrophy and LVWT With Change in LVEDV in Logistic Regression Models

	Concentric Hypertrophy		LVWT	
	Odds Ratio	*P* Value	Odds Ratio*	*P* Value
Primary cohort				
Unadjusted	1.9 (1.3–2.7)	0.001	1.8 (1.6–2.1)	<0.0001
Model 1†	2.0 (1.3–3.2)	0.003	1.7 (1.4–2.0)	<0.0001
Model 2‡	2.0 (1.3–3.2)	0.003	1.6 (1.3–2.0)	<0.0001
Restricted cohort§				
Unadjusted	2.4 (1.3–4.6)	0.007	1.9 (1.6–2.3)	<0.0001
Model 1†	2.1 (1.0–4.4)	0.04	1.8 (1.4–2.4)	<0.0001
Model 2‡	2.1 (1.0–4.4)	0.05	1.8 (1.4–2.4)	<0.0001

The association of baseline LVWT and concentric hypertrophy with change in LVEDV as a categorical parameter was tested in logistic regression models in which categorical change in LVEDV (>75% of healthy normal subpopulation) was the dependent variable with adjustment for phase 1 LVEDV. CVD indicates cardiovascular disease; EDV, end-diastolic volume; EF, ejection fraction; LV, left ventricle; and LVWT, LV wall thickness.

*Odds ratios are reported for 1 SD increase in phase 1 LVWT.

†Model 1 included adjustment for age, sex, race, systolic blood pressure, antihypertension medications, diabetes mellitus, CVD, and LV EF.

‡Model 2 included model 1 with added adjustment for change in weight, change in systolic blood pressure, incident hypertension medications, and incident diabetes mellitus.

§Restricted cohort (n=817) included additional exclusion of self-report of antihypertensive therapy at baseline or at follow-up and baseline CVD in addition to exclusions of primary analysis (interval CVD and baseline dilation).

and 25% after 7 years,[15] but it was not reported how often those who transitioned to eccentric LVH had a dilated LV at follow-up. In the CHS (Cardiovascular Health Study), increased LV mass was associated with subsequent reduction in LVEF after 5-year follow-up, although it was baseline eccentric and not concentric hypertrophy that was associated with incident reduced LVEF.[22] In 2 longitudinal analyses of clinical echocardiographic databases, the progression from concentric LVH and a normal LVEF to a low LVEF, as may occur in a dilated cardiomyopathy, was infrequent especially in the absence of an interval myocardial infarction (8% after ≈3 years and 13% after 7.5 years).[16,18]

The current study substantially extends these previous studies. Using detailed phenotypic assessment based on CMR, we were able to demonstrate differences in the natural history of subjects with versus without baseline concentric hypertrophy after 7 years of follow-up. Specifically, those with versus without baseline concentric hypertrophy had a larger decrease in LV mass, LVWT, and LV mass/volume$^{0.67}$, and a larger increase in LV volume during follow-up, consistent with a reduction in the magnitude of concentric remodeling among the former group. Of note, despite this reduction, the median LVWT and LV mass/volume$^{0.67}$ remained elevated at follow-up. Further, although those with concentric hypertrophy rarely (2%) progressed to a dilated LV after 7-year follow-up, baseline markers of concentric hypertrophy (LV mass/volume$^{0.67}$ and LVWT) were associated with a more subtle degree of LV enlargement during this timeframe in multivariable regression models (Tables 3 and 4). These associations were robust to whether LV enlargement was defined using continuous or categorical assessments of changes in LVEDV. They were also consistent in sensitivity analyses excluding subjects with history of CVD at baseline or those taking antihypertensive medications, an important analysis given the described effect of medical therapy on LVH regression.[20,21] Another strength of our study was that our study cohort had a broad representation of blacks, an important group to study given their predilection to hypertensive heart failure.[33]

Although LV dilation has been shown to be a risk factor for the development of heart failure,[34–36] the clinical significance of the association of baseline concentric hypertrophy with change in LV volume in the current study is uncertain, given the small magnitude of LV enlargement and because few participants transitioned to a dilated LV. Concentric hypertrophy was associated with ΔLVEDV75, and ΔLVEDV75 was associated with higher NT-proBNP levels. Given the association of NT-proBNP with adverse outcomes,[37–39] these data suggest that ΔLVEDV75 is a meaningful end point, although additional follow-up is needed to test this hypothesis. Nevertheless, given the small magnitude of LV enlarge-

ment evident over 7 years in this study, these data suggest that if concentric hypertrophy does progress to a dilated cardiomyopathy, such a transition would occur over a much longer time frame (eg, decades) and may be less common than previously thought.

Limitations

We recognize the potential for selection bias among those who returned for DHS phase 2 CMR, noting that subjects who did versus did not undergo follow-up CMR imaging had significantly lower body mass index and prevalence of diabetes mellitus, hypertension, and baseline CVD (Table I in the Data Supplement). Thus, the reported frequency of transition to an overly dilated phenotype may be an underestimate, if those traits are risk factors for this transition. However, such selection bias would have biased the primary analysis of this study (testing an association of concentric hypertrophy with subsequent ventricular dilation) toward the null. CMR was performed on different systems during phase 1 and 2 of our study, although we expended considerable effort on calibration to account for these differences.

We also recognize that regression to the mean may have occurred in this longitudinal study, perhaps explaining the decrease in LVWT over time in those with baseline concentric hypertrophy. However, we note that there was no significant difference in baseline LVEDV between those with and without concentric hypertrophy (Table 1), suggesting that regression to the mean is unlikely to explain the association of concentric hypertrophy with subsequent change in LVEDV. Finally, because of the large number of statistical comparisons, the type I error rate may be inflated above the nominal 5% per-test rate.

Conclusions

Concentric hypertrophy and greater LVWT were associated with a small, but significant increase in LVEDV after 7-year follow-up, even in the absence of interval myocardial infarction. However, the degree of LV enlargement over 7 years was minimal, and few participants developed a dilated LV. Together, these data suggest that a much longer time frame (eg, decades) would be required for the transition from concentric hypertrophy to a dilated cardiomyopathy and also raises the possibility that in the absence of interval myocardial infarction, such a transition may occur infrequently in humans.

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DISCLOSURES

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FOOTNOTES

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Association of Concentric Left Ventricular Hypertrophy With Subsequent Change in Left Ventricular End-Diastolic Volume: The Dallas Heart Study

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SUPPLEMENTAL MATERIAL

Supplemental Table S1: Baseline characteristics of those who underwent Phase 1 & 2 CMR compared with those with only Phase 1 CMR.

Variable	Participants with Phase 1 & Phase 2 CMR (n=1,386)	Participants with Phase 1 CMR only (n=1,417)	p-value
Age (yr)	44 (37, 52)	43 (36, 52)	0.6
Male	603 (43)	660 (47)	0.1
Black Race	616 (44)	760 (54)	<0.0001
BMI (kg/m^2)	28.2 (24.6, 32.5)	30.2 (25.8, 35.7)	<0.0001
Diabetes	112 (8)	195 (14)	<0.0001
Hypertension	388 (28)	534 (38)	<0.0001
Baseline SBP (mmHg)	123 (113, 133)	126 (115, 138)	<0.0001
Baseline CVD	56 (4)	139 (10)	<0.0001

Values are median (25%, 75%) or n (%).

CMR = cardiac magnetic resonance; BMI = body mass index; SBP = systolic blood pressure;

CVD = cardiovascular disease