Imaging

Left Ventricular Concentric Remodeling Is Associated With Decreased Global and Regional Systolic Function

The Multi-Ethnic Study of Atherosclerosis

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Background—The transition from compensatory concentric remodeling to myocardial failure is not completely understood in humans. To investigate determinants of incipient myocardial dysfunction, we examined the association between concentric remodeling and regional LV function in asymptomatic participants of the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods and Results—Myocardial tagged MRI was performed. Regional myocardial function expressed as peak systolic midwall circumferential strain (Ecc) was analyzed in 441 consecutive studies by HARP, a harmonic phase tool. Peak Ecc was correlated with the extent of concentric remodeling determined by the ratio of left ventricular mass to end-diastolic volume (M/V ratio). In men, a gradual decline in peak global Ecc was seen with increasing M/V ratio (test for trend, $P<0.001$). Among women, however, Ecc tended to be lower only in the fifth compared with the first quintile of M/V ratio ($P=0.1$). The association of lower Ecc with increasing M/V ratio was regionally heterogeneous but was particularly prominent in the LAD region in men (test for trend, $P<0.001$) and in women (test for trend, $P=0.02$). In the right coronary and left circumflex artery territories, these associations were less marked in both genders.

Conclusions—In this cross-sectional study of asymptomatic individuals, concentric left ventricular remodeling was related to decreased regional systolic function. The reduction in regional function, which was more pronounced in the left anterior descending coronary artery territory, may reflect the local transition from compensatory remodeling to myocardial dysfunction. **(*Circulation*. 2005;112:&NA;-.)**

Key Words: hypertrophy ■ magnetic resonance imaging ■ remodeling ■ systole

Left ventricular (LV) remodeling and hypertrophy are associated with the development of congestive heart failure (CHF) and an increased incidence of other major cardiovascular events, including sudden death.[1–4] LV remodeling may be produced by various physiological and pathological mechanisms. Under pressure overload, remodeling is primarily concentric because of the addition of myocyte sarcomeres in parallel.[5] Therefore, LV wall thickness increases to a greater extent than the volume of the LV cavity; as a result, the ratio of LV mass to end-diastolic volume (M/V ratio) increases. Conversely, disorders that cause volume overload are usually associated with eccentric remodeling and entail a proportional increase in mass and volume. LV hypertrophy, however, is defined as an absolute increase in LV mass and may develop in parallel or subsequent to the remodeling process.[5]

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Concentric remodeling is commonly conceptualized as an adaptive response to increased cardiac afterload caused by conditions such as hypertension and aortic stenosis. This adaptation is known to be finite in extent and eventually may lead to myocardial dysfunction and CHF. The transition from compensatory remodeling to regional and global LV dysfunction has been studied experimentally in animal models but never in a large clinical or epidemiological study.

This study investigates the relationship between concentric remodeling and regional LV dysfunction in a multiethnic population without a history of clinical heart disease. Study participants were individuals enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA).[6]

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In this cross-sectional study, quantitative analysis of myocardial MR tagged images was used to study regional myocardial function in a subset of MESA participants.[7] The hypothesis was that increased concentric remodeling is associated with regional impairment of systolic function. This decline in regional function may presage the eventual development of global LV dysfunction and heart failure.

Methods

Study Population

The characteristics of subjects enrolled in MESA have been described elsewhere.[6] In short, the goal of MESA is to investigate the mechanisms associated with the development and progression of subclinical cardiovascular disease. This study enrolled 6814 men and women 45 to 85 years of age from different ethnic origins (non-Hispanic white, black, Hispanic, and Chinese). Individuals with known cardiovascular disease were excluded. Cardiac MRI was performed as a part of the MESA baseline examination. In this ancillary study, participants were randomly selected to undergo tagged MRI studies in 6 centers (Wake Forest University, Winston Salem, NC; Columbia University, New York, NY; Johns Hopkins University, Baltimore, Md; University of Minnesota, Minneapolis; Northwestern University, Chicago, Ill; and UCLA, Los Angeles, Calif). The study protocol was approved by the institutional review boards in each participating center, and informed consent was obtained from each participant.

MRI Protocol

Images were acquired by 1.5-T MR scanners (SIGNA LX and CVi, GE Electric Medical Systems, and Somatom Vision and Sonata, Siemens Medical Solutions). Dedicated phase-array coils were used for signal reception. After the standard protocol was completed, 3 tagged short-axis slices were obtained. All images were obtained by ECG-triggered segmented *k*-space fast gradient-echo (SPGR or FLASH) pulse sequence during breathholds (12 to 18 seconds). Parallel stripe tags were prescribed in 2 orthogonal orientations (0° and 90°) using identical pulse sequence with additional spatial modulation of magnetization encoding gradients. All MRI studies were submitted to the core MESA MRI Reading Center at Johns Hopkins Hospital where all the analyses were performed.

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Parameters for tagged images were as follows: field of view, 40 cm; slice thickness, 8 to 10 mm; repetition time, 6 ms (range, 3.5 to 7.2 ms); echo time, 3.0 ms (range, 2.0 to 4.2 ms); flip angle, 12°; matrix size, 256×96 to 140; phase-encoding views per segment, 4 to 9; and tag spacing, 7 mm. With these parameters, 19 to 27 phases per cycle were acquired, yielding a temporal resolution of 40 ms (range, 20 to 41 ms).

LV mass, LV end-diastolic volume, and ejection fraction (EF) were determined for each study with a commercially available software package (MASS, version 4.2, Medis). Septal and posterior wall thicknesses (midlevel slice at end diastole) were measured with the same software.

Harmonic Phase Analysis

Tagged short-axis slices were analyzed by HARP, a harmonic phase tool (Diagnosoft, Inc). HARP is a new method that enables fast determination of myocardial strain.[8,9] Peak systolic circumferential strain (Ecc) was determined for 12 segments, 3 slices, and 3 layers in each study. To evaluate regional myocardial function, we used peak midwall systolic Ecc (expressed as a percentage). Ecc values are normally negative during systole because they express circumferential shortening. Less negative Ecc indicates a diminished regional LV function.

An tool developed in-house was used to evaluate regional strains according to the coronary artery perfusion areas (left anterior descending [LAD], left circumflex [LCx], and right coronary artery [RCA] perfusion territories). The different regions were assigned to coronary territories according to recently published standards.[10] Peak "global" systolic strain was defined as the peak midwall Ecc averaged across all segments; peak regional strain was defined by the corresponding coronary region. Both regional and global peak systolic circumferential strains were evaluated in relation to LV mass and M/V ratio.

Peak global and regional systolic circumferential strains from 441 consecutive studies performed between September 2001 and September 2002 (229 men, 212 women; mean age, 65.3±9.2 years) were analyzed by HARP and MASS.

Statistical Analysis

Data are presented as mean±SD. Study participants were grouped into sex-specific quintiles according to M/V ratios and LV mass. Demographic characteristics, cardiovascular risk factors, and systolic function across the different groups were compared by use of Student *t* test or χ^2 when appropriate. Comparisons between men and women were made with the Student *t* test or the χ^2 test. The Mann-Whitney *U* test was used to test variables with skewed distribution (coronary calcium scores). One-way ANOVA was used to study the strains across quintiles. When results suggested differences, pairwise differences were assessed by Scheffé's post hoc test.

To understand the association of strains and LV M/V ratio, we sought to determine whether there is a nonlinear component for the overall study population. This issue was tested by adding in a hierarchal fashion a quadratic, cubic, and higher-degree polynomial. The *t* statistics on strains were 2.5 ($P=0.01$), 2.01 ($P=0.02$), and 1.77 ($P=0.09$) for LAD, RCA, and LCx for the quadratic term, respectively, so the hypothesis of linearity was rejected against the quadratic alternative. Addition of a cubic term was not associated with a statistically significant change in the model. Second, as an a priori hypothesis, we tested whether the M/V ratio effect on strains (both the linear and quadratic terms) varies by gender. To do so, we built a single model and incorporated interaction terms to test whether the M/V linear effects and quadratic M/V effects differ between genders. M/V-gender interaction terms (linear and quadratic) were statistically significant. As a result, men and women were analyzed separately. When genders were analyzed separately, in all regions, addition of a quadratic term did not change the model assessing association between strains and M/V ratio in men, indicating a linear relationship. In contrast, the presence of a quadratic term was statistically significant in all regions in women, and the hypothesis of linearity was rejected against the quadratic alternative at the 1% significance level in all regions. Because of significant gender interaction and a different M/V regional strain pattern in men and women, sex-specific quintiles were chosen to present the data.

Multiple linear regressions were used to assess the independent association of increasing levels of sex-specific quintiles of M/V ratios with strains in all regions. These quintiles were modeled as ordinal variables to assess trend. Potential confounding factors—including age, gender, ethnicity, body mass index (BMI), and systolic and diastolic blood pressures (SBP and DBP, respectively), presence or absence of diabetes mellitus, and drug treatment for hypertension—were introduced simultaneously in the regression model. STATA Statistical Software, release 7.0 (Stata Corp, Inc), was used for the analyses. Values of $P<0.05$ were considered statistically significant.

Reproducibility of HARP

Twenty-four studies were analyzed twice by 3 reviewers. Intraclass correlation coefficients (*R*) for interobserver and intraobserver agreement for peak systolic midwall Ecc were 0.81 and 0.84, respectively, revealing excellent agreement.

Results

Demographic and hemodynamic data from the 441 MESA participants included in this analysis are shown by gender (Table 1) and by sex-specific quintiles of M/V ratio (Table 2).

AQ: 3

T1 T2

TABLE 1. Demographic and Hemodynamic Parameters in Men Compared With Women

Characteristic	Men (n=229)	Women (n=212)	*P*
Age, y	64±10	66±8	0.02
Ethnicity, %*			
White	30.7	32.0	
Black	27.8	23.1	
Hispanic	27.8	28.0	
Asian American	13.7	16.9	0.63
BMI, kg/m^2	26.9±4.1	28.0±5.2	0.01
BSA, m^2	1.9±0.2	1.7±0.2	<0.001
SBP, mm Hg	127±19	131±24	0.03
DBP, mm Hg	75±9	69±11	<0.001
Mean BP, mm Hg	92±11	90±14	0.16
HTN, %†	35.5	47.6	0.01
Treated for HTN, %	29.4	43.9	0.002
Diabetes mellitus, %	10.1	11.3	0.68
LV mass, g	168±42	122±29	<0.001
Septal width, mm	10.5±2.1	9.1±1.8	<0.001
Posterior wall width, mm	10.7±2.9	8.7±2.2	<0.001
M/V ratio, g/mL	1.3±0.2	1.1±0.3	<0.001
LVEDV, mL	134±34	109±25	<0.001
LVESV, mL	46±17	31±13	<0.001
EF, %	66±8	72±7	<0.001
Stroke volume, mL	88±22	78±17	<0.001

BSA indicates body surface area; HTN, hypertension; LVEDV, LV end-diastolic volume; and LVESV, LV end-systolic volume. Significance levels (*P*) for the differences in men vs women are shown.

*Ethnicity indicates the ethnic distribution of the study participants for each gender.

†Hypertension is defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or treatment for hypertension. Percentage (of the total study population) is shown where indicated.

Compared with men, women were more likely to be older, to have a higher BMI and SBP, and to have a lower body surface area and DBP (Table 1).

Approximately one third of the men and half of the women had a history of hypertension. Mean LV mass, M/V ratio, LV end-diastolic and end-systolic volumes, and stroke volume were higher in men compared with women ($P<0.001$), whereas mean EF was significantly lower ($P<0.001$). Finally, both septal and posterior wall widths were greater in men than women ($P<0.001$).

Age was not significantly different across sex-specific quintiles of M/V ratio, whereas the ethnic distribution differed significantly in men across quintiles ($P=0.002$; Table 2). SBP tended to be higher in women with increasing M/V ratio except for the fifth quintile (test for trend, $P<0.01$), whereas no association of DBP with increasing M/V ratio was evident in both women and men.

The percentage of women with hypertension and those treated for hypertension and the prevalence of diabetes mellitus were higher with increasing levels of M/V ratio in women, whereas no such association was evident in men. In both genders, decreases in stroke volume and LV end-diastolic volume were evident with increasing M/V ratio.

Coronary Calcification

The coronary artery calcium score was 99.4±273.7 in women and 232.9±424.2 in men (median, 0 and 31.8, respectively; $P<0.0001$). Adjusted coronary artery calcium score in the LAD territory was higher than in the LCx and the RCA territories (mean coronary artery calcium scores, 83.8, 35.8, and 46.5, respectively; $P<0.001$).

Ejection Fraction

Figure 1A shows that EF was significantly higher in women than men ($P<0.05$) across sex-specific quintiles of LV mass. In men, a gradually lower EF with increasing LV mass was noted (test for trend, $P<0.001$); in women, lower EF was seen only in the uppermost quartile of LV mass (fifth versus first quintile, $P=0.015$). A gradual decrease in EF with increasing M/V ratio was seen in men (test for trend, $P<0.01$; Figure 1B), whereas in women, EF remained unchanged despite an increasing M/V ratio. F1 AQ: 4

Peak Ecc in Relation to M/V Ratio

M/V-gender interaction terms (linear and quadratic) were statistically significant (all $P<0.005$), suggesting that the relationship between M/V ratio and strains is significantly modified by gender. As a result, men and women were analyzed separately.

Figure 2 demonstrates peak circumferential shortening averaged across all regions according to sex-specific M/V ratio quintiles. We observed gradually lower (absolute) values of peak Ecc with increasing M/V ratio in men. Peak Ecc values in the first and the fifth quintiles were −15.7±3.9% and −13.2±3.4% (test for trend, $P<0.001$). In women, Ecc tended to increase from the first to fourth quintile (Ecc in the fourth versus the first, $P=0.02$); in the fifth quintile of M/V ratio, however, peak Ecc tended to be lower compared with the first quintile ($P=0.1$). F2

Regional Circumferential Strains and Their Relation to M/V Ratio

In both genders, the highest (absolute) values of regional peak systolic strains were observed in the LCx territory, and peak systolic Ecc was higher in the LAD territory than in the RCA territory. In men, peak systolic Ecc in the LAD, RCA, and LCx territories were −16.5±3.7%, −13.1±3.9%, and −18.9±4.3%, respectively (Ecc in different regions, $P<0.01$). In women, peak systolic strains in the corresponding regions were −17.6±4.0%, −13.9±4.1%, and 18.7±5.1% (Ecc in different regions, $P<0.01$). AQ: 5

In men, lower (absolute) Ecc with increasing M/V ratio was seen in all regions (Figure 3A). This decline was gradual and more marked in the LAD and RCA regions (test for trend in both regions, $P<0.001$). In the LCx territory, a smaller yet significant decrease was also evident (test for trend, $P=0.01$). F3

In the LAD territory in women (Figure 3B), Ecc (absolute value) in the fourth quintile tended to be higher than in the first 3 quintiles of M/V ratio (fourth versus first quintile,

TABLE 2. Demographic and Hemodynamic Parameters Within Sex-Specific Quintiles of LV M/V Ratio

	Quintile									
	Men					Women				
	1	2	3	4	5	1	2	3	4	5
n	46	46	46	46	45	43	42	43	42	42
Age, y	64±10	63±10	65±11	63 ±10	66±8	66±8	64±9	67±9	67±9	68±7
Ethnicity, %*										
White	22.2	12.5	16.7	20.8	27.8	21.5	16.9	20.0	16.9	24.6
Black	9.6	13.5	23.1	23.1	30.8	10.2	15.3	22.0	27.1	25.4
Hispanic	17.5	28.6	20.6	20.6	12.7	22.0	25.4	20.3	17.0	15.3
Asian American	36.8	26.3	21.1	15.8	0	34.5	24.1	17.2	17.2	6.9
BMI, kg/m^2	25.8±3.6	26.2±4.3	27.8±4.1	27.2±4.3	27.5±3.8‡	26.0±4.5	27.7±4.9	29.0±5.6	27.6±5.2	29.7±5.2
BSA, m^2	1.9±0.2	1.9±0.2	2.0±0.2	1.9±0.2	2.0±0.2‡	1.6±0.1	1.7±0.2	1.7±0.2	1.7±0.2	1.7±0.2
SBP, mm Hg	135±23	133±18	137±21	139±17	140±18	137±19	133±18	145±19	147±26	139±20§
DBP, mm Hg	77±11	78±9	78±9	82±12	81 ±12	74±11	73±10	76±12	76±14	74±14
Mean BP, mm Hg	97±14	97±9	97±10	100±11	100±12	94±12	92±12	100±15	100±17	97±15‡
Hypertension, %†	23.5	17.3	17.3	18.5	23.5	13.9	13.9	24.8	24.8	22.8‡
Treated for HTN, %	20.9	19.4	17.9	17.9	23.9	15.1	11.8	25.8	24.7	22.6‡
Diabetes mellitus, %	15.2	10.9	6.5	10.9	6.8	0	4.8	9.3	16.7	26.2‖
LV mass, g	150±38	156±37	170±41	173±42	190±44‖	99±20	117±26	125±23	131±23	139±35‖
Septal thickness, mm	9.2±1.6	9.7±1.6	10.4±1.8	11.1±1.7	12.5±2.0‖	7.8±1.3	8.2±1.0	9.2±1.4	9.5±1.4	11.0±2.1‖
Posterior wall thickness, mm	9.1±1.9	9.5±2.2	9.8±2.4	11.7±2.5	13.6±3.2‖	7.1±1.4	7.7±1.5	9.1±2.3	9.3±1.8	10.5±2.1‖
M/V ratio, g/mL	0.87–1.07	1.07–1.18	1.18–1.29	1.29–1.43	1.44–2.13	0.71–0.95	0.95–1.04	1.05–1.17	1.17–1.27	1.27–2.57
LVEDV, mL	150±36	138±33	138±34	127±31	118±29‖	115±25	117±27	113±21	107±19	93±28‖
LVESV, mL	49±18	46±18	46±15	47±18	44±18	34±14	34±13	32±12	28±11	28±13
EF, %	68±7	67±7	67±6	64±9	64±8§	71±6	72±7	72±7	74±7	70±8
Stroke volume, mL	101±22	92±19	92±22	80±20	75±18‖	81±16	83±17	81±14	79±14	65±19‖

Abbreviations as in Table 1.

*Distribution of participants from specific ethnicities within sex-specific quartiles is shown. For men, $P=0.002$; for women, $P=0.23$.

†Hypertension is defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or treatment for hypertension. Values indicate the percentage of hypertensive individuals of the total study population. There is a progressively higher percentage of hypertensive women for each increasing quintile of concentric remodeling measured as the M/V ratio ($P=0.014$); in men, no significant differences were evident. ANOVA was used to test differences of continuous variables. χ^2 was used to test for differences in categorical variables.

‡$P<0.05$; §$P<0.01$; ‖$P\leq0.001$, test for trend (for each gender separately).

$P<0.01$), whereas the lowest circumferential strains were seen in the top quintile (fifth quintile versus first quintile, $P=0.02$). A similar pattern was seen in the LCx territory, although the differences were less marked.

T3 Table 3 provides the adjusted mean change in systolic strain (regression coefficients) derived from multiple linear regression analyses with increasing quintiles and the first quintile of sex-specific M/V ratio as the reference group for men and women. This analysis was performed after multivariate adjustment for age, ethnicity, BMI, SBP, DBP, treatment for hypertension, diabetes mellitus, and regional coronary artery calcium scores. These results underscore the pattern seen in women of an initial increase in strains between the first and fourth quintiles and thereafter a reduction in Ecc in the top quintile; in men, however, there is a pattern of gradual reduction in Ecc (absolute) with increasing M/V ratio (a positive slope). A similar pattern was noted when the same M/V ratio intervals were used to define quintiles in both genders (data not shown). There were no significant relationships between LV strains and calcium score in men or in women.

Finally, the relationship between regional LV function and LV wall thickness was studied. The association between septal thickness and regional LV function was not statistically significant, although a similar trend was noted in men compared with the M/V–regional function relationship. In women, no significant relationship was observed. Similarly, the relationships between posterior wall thickness and regional LV function were not significant (data not shown).

Discussion

We found that an increasing degree of concentric remodeling in men, expressed by the M/V ratio, is associated with a decline in LV systolic function evaluated by midwall circumferential strain. This reduction was heterogeneous and was most marked and consistent in the LAD territory. In women, the relationship between concentric remodeling and function is more complex, with a gradual increase in function for the first 3 quartiles and evidence of dysfunction thereafter.

LV hypertrophy is a prevalent condition associated with an increased risk of all-cause mortality and major cardiovascular

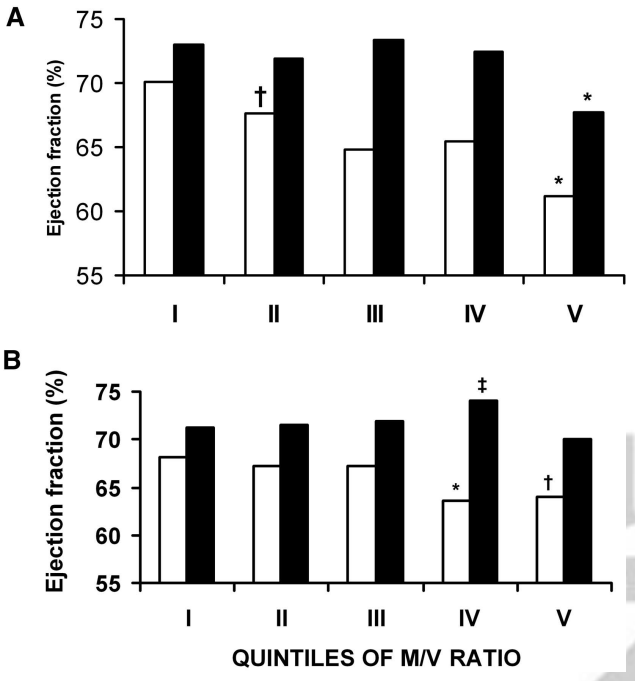

Figure 1. A, EF (%) in different sex-specific quintiles of LV mass. $P<0.001$, EF in men vs women. B, EF in different sex-specific quintiles of M/V ratio (indicating degree of concentric LV hypertrophy). White bars indicate LV mass or M/V ratio in men; black bars, similar variables in women. *$P<0.001$, †$P<0.05$, ‡$P=0.06$ vs first quintile.

events.[1–4] Importantly, in a recently published study, it has been shown that increased baseline LV mass was an independent risk factor for the development of depressed EF 5 years later in elderly individuals enrolled in the Cardiovascular Health Study.[11] Thus, both systolic and diastolic myocardial function is impaired by LV hypertrophy.[11–13]

Previous prospective studies have shown that concentric remodeling in hypertensive patients is associated with adverse cardiovascular events, including myocardial infarction, CHF, and increased mortality, despite normal absolute LV

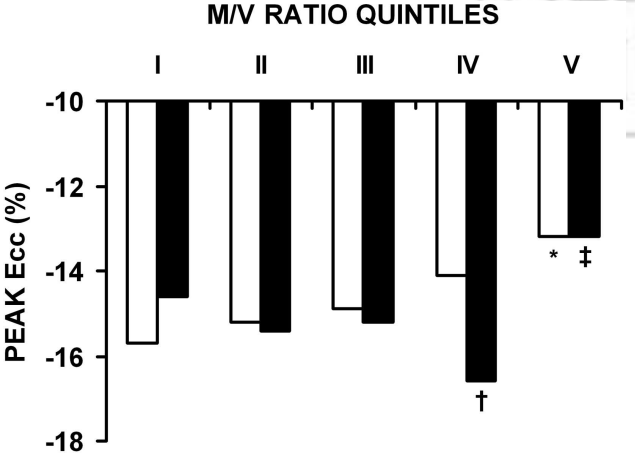

Figure 2. Peak Ecc in different sex-specific quintiles of M/V ratio in men and women. White bars indicate M/V ratio in men; black bars, M/V ratio in women. For men, *$P<0.001$ vs first quintile. For women, †$P<0.05$, ‡$P=0.1$ vs first quintile.

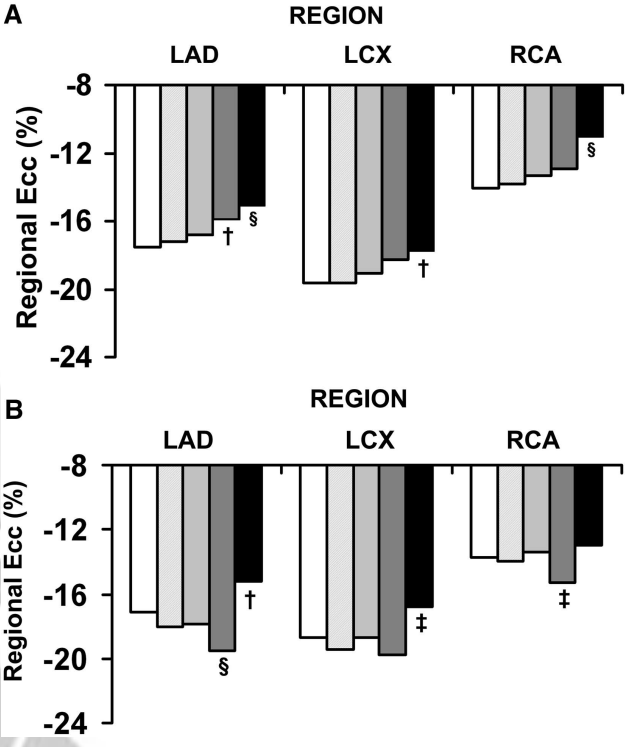

Figure 3. A, Peak regional Ecc in men in different quintiles of M/V ratio. B, Peak regional Ecc in women in different quintiles of M/V ratio. White bars indicate lowest M/V quintile; black bars, highest quintile; and light, medium, and dark gray bars, second, third, and fourth quintiles, respectively. §$P<0.01$, †$P<0.05$, ‡$P<0.1$ vs first quintile.

mass, underscoring the importance of this type of remodeling relative to remodeling associated with proportional increases in LV mass and volume. In those studies, the presence of depressed midwall fractional shortening conferred a substantial risk for the development of CHF.[2,14–17]

A progressive reduction in midwall circumferential shortening in patients with increasing degrees of LV hypertrophy has been demonstrated previously by echocardiography and tagged MRI.[18,19] This reduction in midwall circumferential and longitudinal shortening was manifest despite normal EF and unchanged endocardial stress-shortening relationship.[19] These results were interpreted as demonstrating that the development of concentric hypertrophy tends to preserve LV pumping function despite a decrease in myocardial function. Our study extends the relationship between circumferential shortening and concentric LV remodeling to demonstrate for the first time that the decline in function is regionally heterogeneous and is especially manifest in the LAD territory. Nonetheless, a lesser decrease in midwall Ecc was also observed in the RCA and to a greater extent in the LCx regions for participants of both genders.

The reasons underlying the heterogeneous reduction in circumferential strain with concentric LV remodeling are not known. Several potential mechanisms merit discussion. First, the anterior wall is flatter; ie, its radius of curvature is larger than for other regions of the LV.[20] Therefore, the stress imposed on the anterior wall may be higher, especially in states of increased afterload (eg, hypertension). Second,

TABLE 3. Adjusted Mean Differences of Ecc Derived From Multivariable Linear Regression Model and Mean Change in Ecc Across Quintiles of the M/V Ratio Analyzed by Gender

Comparison of M/V Ratio Quintiles	LAD		LCx		RCA	
	Men	Women	Men	Women	Men	Women
2 vs 1	0.11 (−1.42–1.64)	−0.95 (−2.70–0.79)	−0.44 (−2.27–1.40)	−0.16 (−2.39–2.07)	0.20 (−1.48–0.87)	−0.35 (−2.17–1.47)
3 vs 1	0.33 (−1.2–1.87)	−1.13 (−2.91–0.64)	0.17 (−1.66–2.00)	0.45 (−1.80–2.70)	0.36 (−1.30–2.03)	0.144 (−1.70–1.99)
4 vs 1	1.15 (−0.39–2.70)	−2.34† (−4.15–0.53)	0.77 (−1.10–2.64)	−0.01 (−2.32–2.30)	1.00 (−0.69–2.71)	−1.33 (−3.21–0.56)
5 vs 1	2.10‡ (0.55–3.66)	1.5 (−0.39–3.43)	1.74* (−1.33–3.61)	2.82† (0.42–5.23)	2.65§ (0.96–4.34)	0.75 (−1.22–2.71)

Values in parentheses are 95% CIs. Probability values indicate the significance levels of the regression coefficients for changes in M/V ratio in each gender. Estimates are adjusted for age, ethnicity, BMI, SBP, DBP, presence of diabetes mellitus, drug therapy for hypertension, and coronary artery calcium scores in the corresponding regions.

Significance level of each individual regression coefficient: *$P<0.1$; †$P<0.05$; ‡$P<0.01$; §$P<0.005$.

atherosclerosis may be more prominent in the LAD as opposed to the RCA and LCx territories in people, like the MESA participants, with no history of clinical heart disease. However, there was no significant relationship between calcium score and LV function. Moreover, M/V ratio–regional strain relationships did not change after adjustment for coronary scores as marker of subclinical atherosclerosis. Third, other pathological processes possibly related to local activation of signal transduction pathways such as fibrosis, apoptosis, or both may be enhanced in specific regions of the LV.[21]

SBP and DBP are major determinants of afterload and myocardial function. The magnitude of LV hypertrophy increases with higher blood pressure.[22] The present study demonstrates that SBP tended to be increased with concentric remodeling only in women. It was also noted that the relationship between increased concentricity and reduced LV function persisted after adjustment for SBP, DBP, and therapy for hypertension (Table 3). Therefore, the association of increased concentricity with reduced LV function extends beyond the mere presence of hypertension.

We noted a gender interaction in the relationship between concentric remodeling and LV dysfunction. In men, a progressive decline in Ecc was noted, whereas in women, there was an initial improvement in function up to the fourth quintile, followed by the lowest regional function associated with the most severe degree of concentric remodeling. Gender-related discrepancies could be caused by several mechanisms. Indeed, in the present study, compared with women, men had increased end-systolic and end-diastolic LV volumes, higher DBP levels, and greater LV mass, whereas women had higher SBP levels (Table 1). Previous studies have shown gender-specific differences in LV remodeling and development of CHF as a result of pressure and volume overload. These changes were accompanied by gender-specific differences in gene expression.[23–26] The ability to quantify regional myocardial function by MRI tagging in this study and the findings from previous studies suggest that there is indeed a gender difference in adaptation to chronic states of increased afterload (as opposed to volume overload) and that only women develop LV dysfunction in the more advanced stages of LV overload, as documented in our study. The initial improvement in regional LV function seen in women may also indicate that there may be a degree of M/V ratio that enhances myocardial function. This threshold may be different in men and women. Although this "optimal" ratio may be reached in men in the first quartile, after which there is a gradual decrease in regional LV function, it might have been reached later in women. Such differences could be related to LV architecture, neurohumoral factors, or different sensitivities to preload/ afterload. These important interrelationships should be confirmed in the longitudinal follow-up of the MESA population.

The relationship between regional LV function and wall width relationship was weaker than M/V ratio. This finding might reflect the fact that these measures represent 2 different aspects of remodeling (width reflects the extent of LV hypertrophy; M/V ratio reflects concentricity). In addition, wall thickness is limited by the fact that it is a localized, 1D measurement and might not be perpendicular to the LV wall.[27]

Finally, in the present study, the LV EF was significantly lower in men than women, in contrast to the Framingham study in which gender differences in EF were not seen.[28] This difference probably reflects dissimilarities in demographic characteristics or methodology between the 2 studies.

Methodological Considerations

Our study includes 441 subjects, making it one of the largest MRI tagging studies of quantitative regional myocardial function. Cardiac MRI is a robust method for the assessment of LV volumes and mass with a high degree of accuracy and reproducibility.[29] HARP is a new tool capable of fast, reliable determination of global and regional LV function.[8] Although there are well-known limitations of MRI tagging and regional function assessment by HARP, this tool enables the analysis of large MRI data sets in a reasonable period of time. Aside from its size, MESA entails a heterogeneous population composed of 4 different ethnicities. In previous studies, most participants were white.[2,3] This could also account for some of the differences reported from different prospective studies. This study is based on cross-sectional analyses. Therefore, cause-and-effect relationships cannot be established, and only a longitudinal study will be able to address this important subject. Clearly, it is possible that contractile myocardial impairment might have caused increased dia-

stolic and systolic wall stress that would, in turn, have activated different neurohormonal mechanisms such as adrenergic, renin-angiotensin, or other mechanisms that could lead to LV hypertrophy. Conversely, this association might reflect the result of compensatory responses to increased mechanical stress that have caused concentric remodeling, but eventually, changes in the myocyte phenotype and intracellular Ca^{2+} handling and increases in apoptosis and fibrosis may lead to myocardial dysfunction.[5,30] Participants from different age groups were selected as volunteers within MESA and thus may not represent a random sample of the population at large. The relatively small number of individuals in each subgroup (ie, ethnic groups, individuals with hypertension, or those with diabetes mellitus) limited our ability to detect distinctive patterns of LV function–concentric remodeling relationships in each subgroup. Hence, it was not possible to asses this association in different ethnic subgroups.

Segmentation to the 3 major coronary territories is based on a model recommended by the societies for echocardiography, nuclear imaging, and MRI.[10] This segmentation is not devoid of limitations because of the variability of coronary supply to the different segments, especially to the apex. In addition, right or left dominance is not taken into consideration. Because MESA participants did not undergo coronary catheterization, their dominance status could not be ascertained.

Finally, the results of the present study should be interpreted in light of the design of MESA. In this study, individuals with symptoms or a history of cardiovascular disease were excluded. Thus, patients with the most pronounced extent of remodeling response to volume/pressure overload might have been excluded, given the fact that those people are more prone to develop symptomatic heart failure. This limitation may account for the gender differences observed in our study.

In conclusion, this study documents a gradual reduction in global and regional myocardial function with increasing magnitudes of LV concentric remodeling. In both genders, this decline was regionally heterogeneous and more pronounced in the anterior wall of the LV. It may reflect the transition from compensatory remodeling to incipient myocardial failure.

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