Correlates of Echocardiographic Indices of Cardiac Remodeling Over the Adult Life Course

Longitudinal Observations From the Framingham Heart Study

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Background—The heart progressively remodels over the life course, yet longitudinal data characterizing such remodeling in the community are limited.

Methods and Results—Using multilevel modeling, we analyzed up to 4 serial echocardiographic observations obtained over a 16-year period in 4062 Framingham Heart Study participants (mean age 45 years, 54% women; 11 485 person-observations). We related left ventricular (LV) wall thickness, LV systolic and diastolic dimensions, and fractional shortening to age, sex, body mass index, blood pressure (including antihypertensive medication use), smoking, and diabetes mellitus (separate analyses for each echocardiographic measure). With advancing age, LV dimensions decreased, whereas fractional shortening and LV wall thickness increased concomitantly. Male sex, body mass index, and blood pressure indices/hypertension treatment were significantly related to both greater LV dimensions and LV wall thickness. The effect of age on cardiac remodeling was influenced by key covariates ($P<0.05$ for all interactions): Women and individuals with diabetes mellitus experienced greater age-associated increases in LV wall thickness; presence of diabetes or a higher blood pressure was associated with a lesser decrease in LV diastolic dimensions with increasing age; and antihypertensive medication use was a marker of an attenuated increase in fractional shortening with aging.

Conclusions—Cardiac remodeling over the adult life course is characterized by a distinct pattern of increasing LV wall thickness, decreasing LV dimensions, and increasing fractional shortening with advancing age. Overall, female sex, greater blood pressure load, and presence of diabetes mellitus serve to attenuate this remodeling pattern. These observations suggest a mechanism for the preponderance of women with hypertension and individuals with diabetes among patients with diastolic heart failure. **(*Circulation*. 2010;122:570-578.)**

Key Words: aging ■ cardiac remodeling, ventricular ■ heart failure

The human heart undergoes dynamic, incremental alterations in structure and function over the life course, a phenomenon referred to as cardiac remodeling. These alterations are associated with changes in the cellular and extracellular composition of myocardial tissue, processes that can involve cardiomyocyte hypertrophy, apoptosis, and regeneration.[1–3] The morphology of this progressive cardiac remodeling may be characterized by changes in multiple measurable echocardiographic dimensions. Accordingly, several cross-sectional studies suggest that the cardiac remodeling that occurs with advancing age involves increasing left ventricular (LV) wall thickness and may also involve decreasing LV cavity diameter in the setting of globally preserved or even increased systolic function.[4–7] Although common patterns of cardiac remodeling might be attributed to aging-related processes, they are associated with adverse clinical consequences.[8] In fact, such remodeling may contribute to the higher incidence of heart failure in older adults, particularly heart failure that presents with a normal ejection fraction.[6,9] Therefore, prospective investigation of LV remodeling over the life course could elucidate the evolution of alterations in cardiac structure and function that antedate symptomatic myocardial dysfunction by years to decades.

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Clinical Perspective on p 578

We have previously described the tracking of LV mass over the adult life course, highlighted the age-associated increase in cardiac mass, and underscored the adverse impact of cardiovascular risk factors (notably obesity, hypertension, and diabetes mellitus) on such increases in LV mass with aging.[10] However, LV mass is a composite variable that only indirectly reflects variation in the multiple components of LV morphology, including LV internal dimensions and wall thickness. As such, tracking of LV mass may not adequately capture distinctive patterns of LV remodeling that may be the consequence of disparate trajectories of changes in LV wall thickness (LVWT) versus LV dimensions. In the present investigation, we evaluated the longitudinal tracking of LVWT, diastolic and systolic dimensions (LVDD and LVDS, respectively), and endocardial fractional shortening (FS), a measure of pump function, over the adult life course in a large, community-based sample. Specifically, we used multilevel modeling to estimate growth curves that tracked change in several indices of LV morphology, as captured by serial and routine echocardiograms performed over an extended follow-up period of up to 16 years. We also analyzed the degree to which these morphological alterations were associated with traditional risk factors, many of which have been reported as possible determinants of LV remodeling in cross-sectional studies.[5,11]

Methods

Study Sample

In 1971, the Framingham Offspring Study began with the enrollment of 5124 individuals who were the children of the Original cohort of the Framingham Heart Study, as well as the spouses of the children.[11] Routine examinations of the Offspring cohort are performed approximately every 4 years and include a medical history focused on the incidence of new-onset cardiovascular events since the previous examination, a targeted physical examination that includes anthropometry and blood pressure measurements according to a standardized protocol, and phlebotomy to obtain specimens used for the laboratory assessment of cardiovascular risk factors. Attendees at Offspring cohort examination cycles 2 (1979–1982), 4 (1987–1990), 5 (1991–1995), and 6 (1996–1998) underwent routine transthoracic echocardiography. Of the 4556 unique attendees (15 216 observations) at these examinations, we excluded individuals who were <25 or ≥ 75 years old at the time of their examination (n=12; 344 observations) and those with prevalent or incident myocardial infarction or heart failure (n=269; 763 observations), which are conditions that can affect LV measurements based on M-mode echocardiography. We also excluded observations if participants had atrial fibrillation or valvular disease (n=22; 312 observations), were missing clinical covariates for analyses (n=7; 58 observations), were missing echocardiographic measurements (n=183; 2251 observations), or had outlier values for these measurements (n=1; 3 observations). Thus, 4062 unique individuals providing 11 485 observations were included in the analyses that involved longitudinal tracking of LV indices.

The study protocols for Offspring examinations were approved by the Institutional Review Board at the Boston University Medical Center, and all attendees at the examinations provided written informed consent.

Echocardiographic Measures

Study participants underwent standardized routine transthoracic echocardiography, as detailed elsewhere.[10] The equipment used to obtain echocardiographic measures differed across examination cycles: Hoffrel 201 ultrasound receiver (with Aerotech transducer; Hoffrel Instruments, Norwalk, Conn) at cycle 2; Hewlett-Packard (model 77020AC; Hewlett-Packard, Palo Alto, Calif) ultrasound machine at cycles 4 and 5; and Hewlett-Packard Sonos 1000 machine at cycle 6. All echocardiograms were evaluated by an experienced technician or cardiologist using a standardized reading protocol. End-diastolic LV septal wall thickness, posterior wall thickness, and LV diameter at the end of diastole (LVDD) and systole (LVDS) were obtained by use of a leading-edge technique and averaging of M-mode measurements from at least 3 cardiac cycles.[12] Total LVWT was calculated as the sum of septal wall thickness and posterior wall thickness. FS was calculated according to the following formula: $FS=[(LVDD-LVDS)/LVDD]\times 100$. Relative wall thickness, a commonly used measure of LV hypertrophy, was calculated as LVWT divided by LVDD. For secondary analyses, LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were derived from M-mode measures by the Teichholz method,[12] and LV ejection fraction was defined as $([LVEDV-LVESV]/LVEDV)\times 100$.

Statistical Analyses

Estimation of Individual Growth Curves for LV Indices

Multilevel statistical modeling allows the analysis of data that vary at multiple levels. It is applicable to longitudinal data for which repeated measurements are obtained on different occasions (level 1) within the same individual (level 2). The models allow for estimation of the overall pattern of change over time and also for the impact of risk factors on the temporal pattern. Compared with traditional regression models, this analytic approach has the advantage of accommodating participants with missing data at some of the serial examinations and facilitates analyses with the maximum number of observations in a longitudinal investigation.[13] Results of formal testing indicated that the relationship between the echocardiographic variables and covariates was similar for participants with data collected at all examination cycles and participants who may have had missing values at later examination cycles (data not shown).

We estimated growth curves for each morphological index of LV remodeling (LVWT, LVDD, LVDS, and FS) using multilevel statistical modeling (SAS PROC MIXED, with an unstructured correlation matrix). Growth curves were also estimated for relative wall thickness, a variable derived from measures of both LVWT and LVDD. We used forward direct entry to analyze the associations of each LV index with common clinical covariates that have been related to measures of LV remodeling in cross-sectional studies: Age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), antihypertensive treatment, smoking status, and diabetes mellitus. In analyses in which the relation of the LV measure with SBP and DBP was discordant, we additionally examined the association of the same LV measure with the difference between SBP and DBP, which is also known as the pulse pressure. Examination cycle was included as a covariate in all analyses to account for variation in LV indices across examinations due to variation in the echocardiographic instrumentation used. Random intercepts and random effects of age were fitted for all models to reflect different starting values and different relationships with age for each LV index measured in each participant.

We also examined the quadratic effect of age, which was not found to reach statistical significance. We fit a series of clinically prespecified models, with direct entry of candidate variables. Biologically plausible statistical interactions between age, sex, and other clinical risk factors were also investigated. Separate growth curves were graphically displayed for men and women to demonstrate the tracking of LV indices over time.

Association of Clinical Risk Status With Longitudinal Tracking of LV Structure and Function

To clarify the association of the overall burden of clinical risk factors on patterns of longitudinal tracking, we additionally estimated sex-specific associations stratified by "high" versus "low" risk factor

status: High risk factor status was defined as having hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg or taking antihypertensive treatment), obesity (BMI ≥30 kg/m^2), or diabetes mellitus (fasting glucose ≥126 mg/dL or taking medication for diabetes); low risk factor status was defined as not having hypertension, not being obese, and not having diabetes mellitus. The covariates used to define high versus low risk factor status (ie, hypertension, obesity, and diabetes mellitus) were selected on the basis of their significant associations with LV measures in the final regression models. To graphically illustrate the effect of risk factor burden on longitudinal tracking of LV measures, we plotted the mean value of each LV measure versus age for men and women in the high and low risk factor groups separately (where values were adjusted for specific combinations of risk factors according to their statistical significance in the final regression model produced for each LV measure). Median values of SBP and DBP among groups with and without hypertension were used in the regression equation to determine the graphically depicted mean outcome values for individuals with and without hypertension, respectively.

Secondary Analyses

In secondary analyses, we repeated all multivariable analyses after excluding individuals with type 1 diabetes mellitus, given its predisposition for premature LV remodeling and dysfunction.[14] To clarify the independent effects of obesity and diabetes, which often coexist, we compared the relation of BMI to LV indices in multivariable models with and without adjustment for diabetes. Because parameters of LV geometry, particularly LVWT and LVDD, are influenced by body size, we also repeated multivariable analyses of LVWT and LVDD using models that adjusted for height and weight (instead of BMI). Multilevel regression analyses were additionally performed with volumetric assessments of cavity size, derived from direct M-mode measurements by the Teichholz method,[12] including LVEDV, LVESV, and LV ejection fraction.

All analyses were performed with SAS version 9.2, and a 2-tailed *P*-value of <0.05 was considered significant. S-PLUS and Excel were used to create the graphical displays.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The baseline characteristics of the study sample are shown in Table 1.

Table 1. Clinical and Echocardiographic Characteristics of the Study Samples Used to Characterize Clinical Correlates of Longitudinal Tracking of LV Remodeling Indices*

	Men (n=1851)	Women (n=2211)
Clinical characteristics		
Age, y	45±10	45±10
BMI, kg/m^2	26.9±3.7	25.0±5.0
SBP, mm Hg	126±16	119±17
DBP pressure, mm Hg	81±9	75±9
Pulse pressure, mm Hg	45±11	44±12
Antihypertensive treatment, %	10.0	8.9
Hypertension, %	27.8	18.5
Smoking, %	40.1	34.9
Diabetes mellitus, %	5.8	3.3
Echocardiographic characteristics		
LVWT, mm	19.4±2.5	16.8±2.3
LVDD, mm	51.1±3.8	46.2±3.5
LVDS, mm	33.0±3.6	28.9±3.3
FS, %	35.9±3.6	37.8±3.8

*Sample characteristics were obtained at the first attended examination cycle.

Patterns of Longitudinal Change in LV Structure and Function: Unadjusted

In both sexes, LVWT increased progressively and both LVDD and LVDS decreased, whereas FS increased with advancing age (Figure 1).

Multivariable Clinical Correlates of Longitudinal Tracking of LV Structure and Function

LV Wall Thickness

Over the 16-year observation period, several clinical factors were positively related to progressively increasing LVWT: Age, male sex, BMI, SBP, DBP, antihypertensive treatment, and diabetes mellitus (Table 2). We observed statistically significant interactions of age with sex ($P<0.0001$), BMI ($P=0.021$), and diabetes mellitus ($P=0.018$). Women had a greater increase in LVWT with advancing age relative to men (Figure 1 and Table 2), as did participants with diabetes compared with those without diabetes mellitus (Table 2). Notably, LVWT increased more among individuals with higher versus lower BMI. Similar to findings for LVWT, progressively increasing relative wall thickness was associated with age, BMI, DBP, antihypertensive treatment, and diabetes mellitus, as well as smoking (online-only Data Supplement Table I). As with LVWT, women had a greater increase in relative wall thickness with age relative to men (online-only Data Supplement Figure I).

LV Internal Dimensions

Correlates of long-term tracking were similar for LVDD and LVDS, with positive associations being observed with BMI and inverse relations with age (Tables 3 and 4). Blood pressure measures were associated with LV diastolic dimensions (Table 3). Of note, LVDD was associated positively with SBP but inversely with DBP, with the coefficients being opposite in direction and of a similar magnitude, which suggests a potential pulse-pressure effect. Accordingly, longitudinal tracking of LVDD was positively related with pulse pressure (Table 3 footnote).

The association of age with both LVDD and LVDS varied with diabetes status, such that LV diameter decreased more in people without diabetes mellitus than in participants with diabetes mellitus (Tables 3 and 4). For LVDD, there was an interaction between sex and BMI ($P=0.03$) with a negative coefficient, which indicates that the association of BMI with LVDD was of larger magnitude in women than in men (Table 3). For LVDS, the interaction between age and antihypertensive treatment was also statistically significant ($P=0.02$); the age-associated decrease in LVDS was attenuated in individuals undergoing antihypertensive treatment.

Fractional Shortening

Longitudinal correlates of FS included age, sex, SBP, DBP, and antihypertensive treatment (Table 5). Notably, FS increased progressively with advancing age, and FS values were consistently higher in women than in men (Figure 1; Table 5). As with LVDD, FS was associated positively with

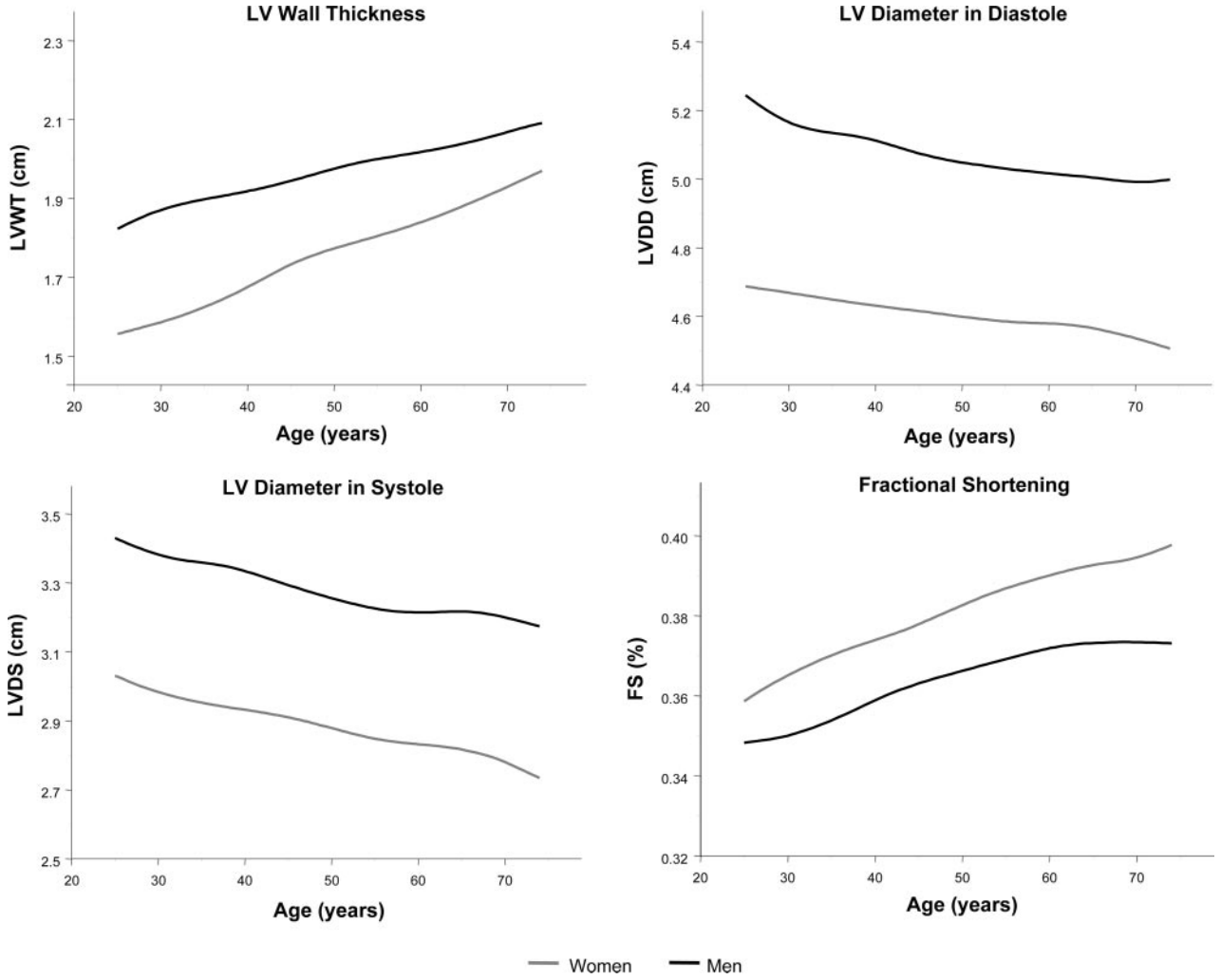

Figure 1. Unadjusted LVWT, LVDD, LVDS, and FS with increasing age for men and women.

SBP and negatively with DBP. Models that incorporated pulse pressure confirmed a positive relation with pulse pressure (Table 5 footnote). Although overall tracking of FS was positively related to antihypertensive treatment, there was a statistically significant interaction between age and antihypertensive treatment ($P=0.008$), which suggests that FS increased less in individuals who were being treated for hypertension than in those not being treated (Table 5).

Association of Clinical Risk Status With Longitudinal Tracking of LV Structure and Function

Consistent with the age interactions described above, longitudinal tracking of LV measures was not the same in individuals with hypertension, obesity, or diabetes as in individuals without these risk factors (Figure 2; online-only Data Supplement Figure II). Both women and men in the higher clinical risk group demonstrated greater increases in LVWT and relative wall thickness with advancing age than their lower-risk counterparts. Whereas LV dimensions decreased over time in the low-risk group, LVDD decreased to a much lesser extent and LVDS even increased slightly in the high-risk group. Accordingly, FS did not increase as much in high-risk as in low-risk individuals with aging.

Secondary Analyses

In analyses that excluded individuals with type 1 diabetes mellitus (n=3; 8 observations), results remained unchanged (data not shown). The association of BMI with indices of LV remodeling was similar in multivariable models with and without adjustment for diabetes (data not shown) and as reflected by results in the total sample. In multivariable analyses of LVWT and LVDD that included adjustment for height and weight as clinical covariates (instead of BMI), the direction and magnitude of associations between clinical covariates and LV structural indices were similar to those in analyses that adjusted for BMI (online-only Data Supplement Tables II and III). In analyses of derived volumetric measures, the clinical covariates associated with longitudinal tracking of LVEDV were similar to those associated with LVDD; similarly, the clinical correlates of LVESV were comparable to those of LVDS, as were those of LV ejection fraction to FS (online-only Data Supplement Tables IV through VI).

Discussion

Although data from numerous cross-sectional studies have suggested that the human heart remodels over the life course,

Table 2. Clinical Correlates of Longitudinal Tracking of LVWT

Covariates	Coefficient	95% CI
Age (10-y increase)*		
Men, with diabetes mellitus	0.48	0.28–0.67
Men, without diabetes mellitus	0.25	0.18–0.31
Women, with diabetes mellitus	0.75	0.55–0.95
Women, without diabetes mellitus	0.52	0.46–0.58
Male sex†	1.73	1.63–1.82
BMI (5-kg/m^2 increase)†	0.58	0.53–0.63
SBP (10-mm Hg increase)	0.11	0.08–0.15
DBP (10-mm Hg increase)	0.12	0.07–0.18
Antihypertensive treatment	0.28	0.16–0.40
Diabetes mellitus†	0.21	0.00–0.42

CI indicates confidence interval.

The coefficients represent the change in LVWT in millimeters per increase in the continuous covariates (or presence vs absence of categorical covariates). All models also adjusted for examination cycle and significant interaction terms; any nonsignificant covariates were retained in the model if they contributed to a significant interaction term.

*Given the presence of a significant interaction between BMI and age, coefficients are for individuals with a BMI of 25 kg/m^2.

†Given the presence of a significant interaction of age with sex, BMI, and diabetes mellitus, coefficients are for individuals at age 50 years.

and likely in association with certain cardiovascular risk factors, a comprehensive longitudinal assessment of cardiac remodeling in the community has been limited. Lieb and colleagues[10] recently reported on the correlates of longitudinal changes in LV mass in the Framingham cohort. Alterations in LV mass, a composite measure of LV morphology, represent the summation of multiple discrete aspects of LV remodeling, which can demonstrate either concordant or discordant trajectories of change over time. Therefore, in the present investigation, we extend prior work by using serial echocardiographic observations to evaluate longitudinal tracking of the components of LV mass (cavity dimensions and wall thickness) in addition to LV systolic function.

Table 3. Clinical Correlates of Longitudinal Tracking of LVDD

Covariates	Coefficient	95% CI
Age (10-y increase)		
With diabetes mellitus	−0.11	−0.45 to 0.23
Without diabetes mellitus	−0.60	−0.70 to −0.50
Male sex*	4.38	4.17 to 4.58
BMI (5-kg/m^2 increase)		
Men	0.83	0.66 to 1.00
Women	1.05	0.94 to 1.17
SBP (10-mm Hg increase)	0.24	0.17 to 0.30
DBP (10-mm Hg increase)	−0.27	−0.38 to −0.17
Diabetes mellitus†	−0.31	−0.72 to 0.10

CI indicates confidence interval.

The coefficients represent the change in LVDD in millimeters per increase in the continuous covariates (or presence vs absence of categorical covariates). All models also adjusted for examination cycle and significant interaction terms; any nonsignificant covariates were retained in the model if they contributed to a significant interaction term. In a model that included pulse pressure instead of SBP and DBP, the coefficient of millimeter change in LVDD per 10-mm Hg increase in pulse pressure was 0.31 (95% CI 0.21 to 0.40) for men and 0.19 (95% CI 0.12 to 0.27) for women.

*Given the presence of a significant interaction between BMI and sex, coefficients are for individuals with a BMI of 25 kg/m^2.

†Given the presence of a significant interaction between age and diabetes mellitus, coefficients are for individuals at age 50 years.

Table 4. Clinical Correlates of Longitudinal Tracking of LVDS

Covariates	Coefficient	95% CI
Age (10-y increase)		
Diabetes melllitus, undergoing antihypertensive treatment	0.09	−0.27 to 0.46
No diabetes mellitus, undergoing antihypertensive treatment	−0.39	−0.61 to −0.18
Diabetes mellitus, not undergoing antihypertensive treatment	−0.17	−0.51 to 0.18
No diabetes mellitus, not undergoing antihypertensive treatment	−0.66	−0.74 to −0.57
Male sex	3.69	3.51 to 3.88
BMI (5-kg/m^2 increase)	0.67	0.57 to 0.76
Antihypertensive treatment*	−0.18	−0.45 to 0.08
Diabetes mellitus*	−0.02	−0.42 to 0.39

CI indicates confidence interval.

The coefficients represent the change in LVDS in millimeters per increase in the continuous covariates (or presence vs absence of categorical covariates). All models also adjusted for examination cycle and significant interaction terms; any nonsignificant covariates were retained in the model if they contributed to a significant interaction term.

*Given the presence of significant interactions of age with antihypertensive treatment and diabetes mellitus, coefficients are for individuals at age 50 years.

Features of Progressive LV Remodeling: Overview

We observed a distinct pattern of longitudinal tracking of LV structure and function over the adult life course in both sexes. First, LVWT increased steadily with age, which is consistent with the higher frequency of LV hypertrophy seen among older adults in cross-sectional studies.[4] Such an increase in LVWT may result from cardiomyocyte hypertrophy, apopto-

Table 5. Clinical Correlates of Longitudinal Tracking of FS

Covariates	Coefficient	95% CI
Age (10-y increase)		
Undergoing antihypertensive treatment	0.17	−0.12 to 0.46
Not undergoing antihypertensive treatment	0.58	0.47 to 0.69
Male sex	−1.71	−1.92 to −1.50
SBP (10-mm Hg increase)	0.23	0.14 to 0.31
DBP (10-mm Hg increase)	−0.21	−0.35 to −0.07
Antihypertensive treatment*	0.41	0.07 to 0.76

CI indicates confidence interval.

The coefficients represent the change in FS in percent per increase in the continuous covariates (or presence vs absence of categorical covariates). All models also adjusted for examination cycle and significant interaction terms; any nonsignificant covariates were retained in the model if they contributed to a significant interaction term. In a model that included pulse pressure instead of SBP and DBP, the coefficient of percent change in FS per 10-mm Hg increase in pulse pressure was 0.23 ($P<0.0001$).

*Given the presence of a significant age interaction, coefficients are for individuals at age 50 years.

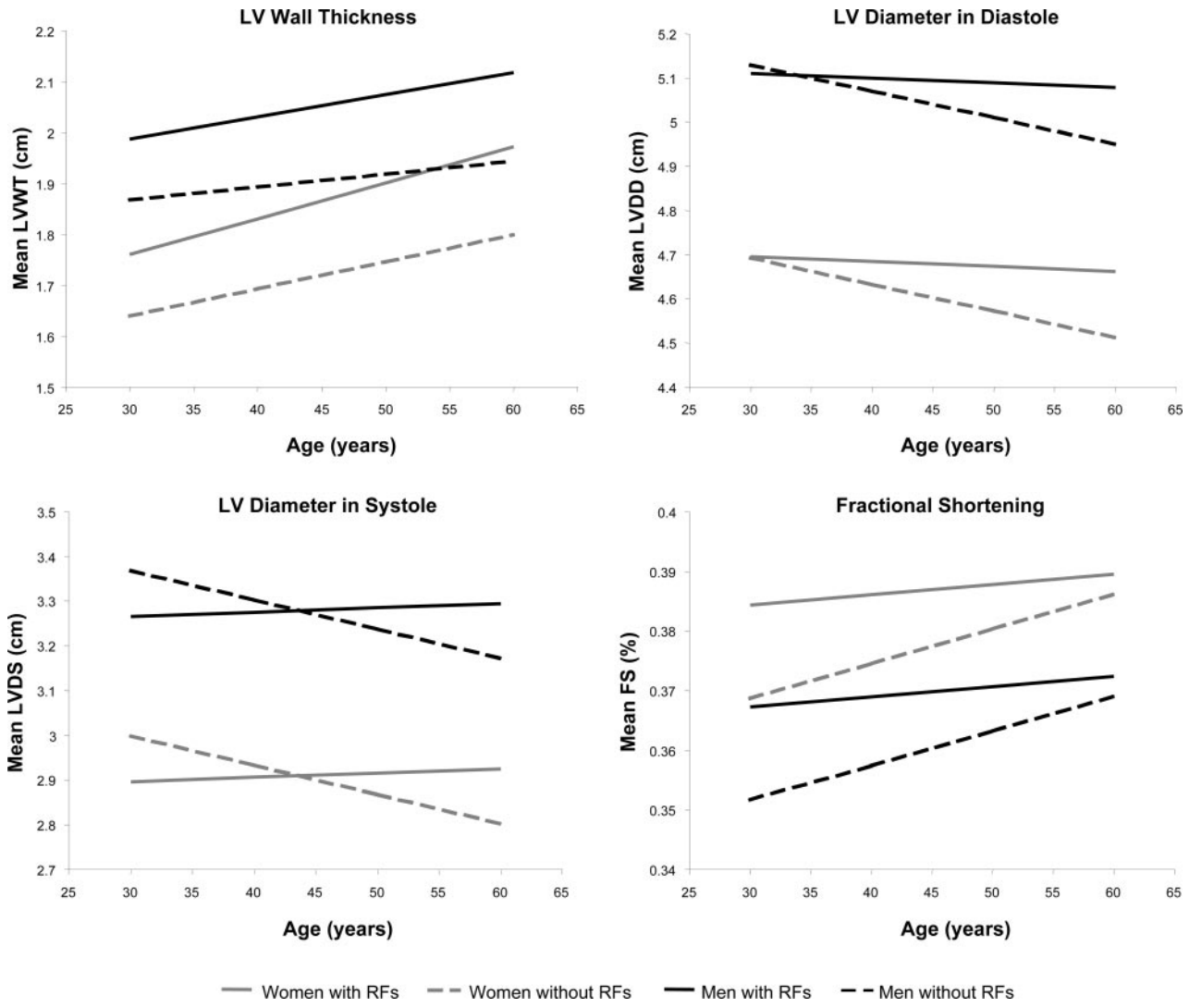

Figure 2. Adjusted mean values of LVWT, LVDD, LVDS, and FS with increasing age for men and women, with and without risk factor burden (ie, hypertension, obesity, and diabetes mellitus).

sis with replacement fibrosis, or both.[1,2] Second, we observed progressive, steady declines in both LVDS and LVDD with increasing age, which suggests an overall decrease in LV cavity size concurrent with the increase in LVWT. These findings provide confirmatory longitudinal evidence of previously reported cross-sectional trends[5] and provide key information on the longitudinal time course of such changes. Smaller LV volumes in older individuals could contribute to the lower hemodynamic tolerance for a preload challenge seen in older than in younger adults.[15] Finally, we observed a progressive increase in FS with advancing age, which may be attributable to a greater decline in LVDS than LVDD. This finding is similar to the results of cross-sectional studies[7,16] and may reflect a compensatory increase in myocardial contractility to maintain cardiac output in the face of decreasing LV volumes.

Interactions of Risk Factors With Age and the Impact on LV Remodeling

The association of age with measures of LV remodeling varied by sex and the presence of major clinical risk factors, including hypertension, obesity, and diabetes mellitus. Although previous cross-sectional and autopsy studies have suggested that age-related LV remodeling differs between men and women,[2,16,17] prior data on the impact of clinical risk factors have been scant.

Sex Differences in Cardiac Remodeling

Overall, men had greater LVWT than women at baseline and over the life course, but women experienced a greater age-associated increase in LVWT, as noted above. The latter finding is consistent with the sexual dimorphism seen in a longitudinal analysis of LV mass, as reported recently by Lieb and colleagues.[10] Accumulating evidence suggests that estrogens play an important role in LV remodeling, particularly because functional estrogen receptors have been shown to reside in the myocardium of both men and women[18]; estrogen binding to these receptors can result in a variety of genomic and nongenomic effects that influence metabolic, vascular, and intracellular pathways.[19] Accordingly, the sex-related findings in the present study may be related to the postmenopausal withdrawal of estrogen exerting either direct

or indirect effects on myocardial remodeling.[19,20] Additionally, an augmented pulsatile load in older women may induce a more pronounced cardiac remodeling response.[21] Furthermore, LV hypertrophic remodeling has been noted to be more pronounced in women than in men in pressure overload states,[22] potentially owing to differential gene expression of extracellular matrix components[23]; sex-biased gene expression may similarly influence age-associated changes in LVWT.[19]

Impact of BMI

As with male sex, higher BMI was also directly associated with greater LVWT and larger LV dimensions over the long term. These findings are consistent with cross-sectional and autopsy studies that have indicated that obesity is associated with concentric and eccentric hypertrophy.[24–26] Although obesity is typically associated with eccentric LV remodeling, concurrent LVWT may be an earlier manifestation of remodeling, possibly related to hemodynamic, inflammatory, and neurohormonal effects of adiposity that are additive to the effects of coexistent hypertension.[24–26] The association of BMI with LVDD was of greater magnitude in women than in men. Prior cross-sectional studies have observed similar relations of BMI to LV cavity size in both men and women.[26,27] With respect to the longitudinal effects of BMI on alterations in cardiac structure, it is possible that hormonal or other sex-based differences contribute to absolute increases in BMI having a relatively greater impact on LV remodeling in women than in men. Overall, the association of BMI with measures of cardiac structure is consistent with cross-sectional reports and may be related to mechanical, paracrine, and/or systemic effects of adiposity on LV remodeling.[28] In addition, higher BMI may be associated with larger cardiac chamber dimensions due to the direct correlation of body size with total body volume.[29,30] Notably, there was no significant association of BMI with systolic function, as reflected by FS.

Relations of Blood Pressure

Of note, the associations of blood pressure measures to LV measures were not completely concordant with the effects of aging on these measures. Higher blood pressure indices and the use of antihypertensive treatment (a marker of greater severity and chronicity of blood pressure elevation) were associated with greater LVWT, which is similar to the aging effects on LVWT and not unlike the longitudinal effects of blood pressure on LV mass.[10] Higher pulse pressure and use of antihypertensive treatment correlated with greater LVDD and lower LVDS, respectively. Also, individuals undergoing antihypertensive treatment experienced a lesser decrease in LVDS with age and a lesser increase in FS, which is consistent with the hypothesis that LV midwall contractility declines progressively (before there is a detectable reduction in endocardial contractility) in the setting of chronic hypertension.[31] Thus, although arterial stiffening is often considered a hallmark of cardiovascular aging,[32] the present data suggest that elevated pulsatile load is associated with longitudinal effects on LV dimensions that are opposite in direction to the independent effects of age per se. Although hypertension is recognized as primarily being associated with concentric remodeling, prior studies have also reported eccentric hypertrophy coexisting with concentric remodeling in a large proportion of individuals with hypertension.[33,34] The extent to which concentric versus eccentric hypertrophy develops in the setting of hypertension may depend on factors specific to the type and chronicity of hemodynamic load on the LV.[33]

Impact of Diabetes Mellitus

The impact of diabetes mellitus on longitudinal LV remodeling was similarly discordant in terms of directionality of relations compared with that of aging. Consistent with cross-sectional reports,[35,36] the presence of diabetes was associated with greater LVWT but also a greater age-associated increase in wall thickness. The presence of diabetes, however, was associated with lesser age-related decrements in both LVDD and LVDS with age. Nevertheless, there was no statistically significant relation of diabetes with longitudinal tracking of LV systolic function, as reflected by FS.

Taken together, several specific risk factors were associated with longitudinal changes in LV structure and function that were different in directionality from the effects of aging itself. This trend was most evident with respect to LV cavity dimensions, which decreased progressively with aging but were actually increased with higher blood pressure and were less likely to decrease with age in the setting of diabetes or hypertension treatment. Interestingly, these same risk factors have been reported in association with the presence of heart failure with preserved ejection fraction, a type of heart failure that occurs predominantly in later life.[37–39] Furthermore, individuals with heart failure with preserved ejection fraction are more likely to have greater LV end-diastolic volume than individuals of similar age range but without heart failure.[37,38] Therefore, aging alone may be associated with a specific pattern of progressive LV remodeling that is altered by early and chronic exposure to certain risk factors; such alterations in the typical course of LV remodeling may, in turn, contribute to the risk for overt heart failure in older age.

Study Limitations and Strengths

Several limitations of the present investigation merit consideration. The change in echocardiographic instrumentation across examinations raises issues relative to comparability of serial measurements. For this reason, we adjusted for the examination cycle as a covariate in all of our analyses. In addition, the Framingham laboratory maintained a limited number of readers over serial echocardiographic examinations, and studies were subject to rigorous quality control with respect to image acquisition and adherence to the measurements protocol. As part of the quality control process at the sixth examination cycle, intrareader and interreader correlations were assessed for LVDD ($r>0.97$ and $r>0.96$) and FS ($r>0.90$ and $r>0.72$) but not for LVWT or LVDS. Any differences in LV remodeling indices across examination cycles are likely to have resulted in random misclassification and therefore likely to bias the present findings toward the null (ie, result in a lack of associations). Doppler-based echocardiographic measures can provide important information about alterations in diastolic function, as well as volume and pressure load, that likely occur in the setting of cardiac

remodeling; however, Doppler-derived measures were unavailable at the Framingham examination cycles that were included in the present study. Lastly, the present study sample included predominantly middle-aged to elderly individuals of European ancestry; thus, the generalizability of our findings to other age and racial/ethnic groups is unknown.

Notwithstanding these limitations, the present study had several strengths. The present investigation included a large sample derived from a community-based cohort with close follow-up for 2 decades. This longitudinal design allowed the use of a multilevel modeling analysis, which facilitates the evaluation of serial echocardiographic measures and the analysis of progressive long-term alterations in LV remodeling indices.

Conclusions

Cardiac remodeling over the life course may be characterized by a distinct pattern of progressive changes in the structure and function of the LV. These changes include LV wall thickening, shrinking cavity dimensions, and increased FS. The presence of certain risk factors in midlife, including hypertension and diabetes mellitus, can serve to alter this typical pattern of LV remodeling. Further research is needed to investigate how such alterations in the course of LV remodeling may contribute to the risk for common cardiovascular diseases, particularly heart failure, in later life.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The human heart undergoes dynamic, incremental alterations in structure and function over the lifespan, a phenomenon referred to as cardiac remodeling. Examination of the course and correlates of cardiac remodeling in aging adults is critical for elucidating the pathways by which older age predisposes to cardiac dysfunction, particularly heart failure, in the setting of a preserved ejection fraction. Using longitudinal data collected from participants in the Framingham Offspring Study (up to 4 serial echocardiographic observations per individual, totaling 11 485 observations) and multilevel statistical modeling, we observed that left ventricular (LV) cavity dimensions (end-systolic more than end-diastolic) decreased with advancing age, whereas LV wall thickness and fractional shortening increased. Women and individuals with diabetes mellitus experienced greater age-associated increases in LV wall thickness. However, the presence of diabetes or a higher blood pressure level was associated with a lesser decrease in LV dimensions with older age. Similarly, treatment with antihypertensive medication was a marker of an attenuated increase in fractional shortening with aging. Together, these findings indicate that cardiac remodeling over the adult life course is characterized by a distinct pattern of increasing LV wall thickness, decreasing LV dimensions, and increasing fractional shortening with advancing age. Notably, female sex, greater blood pressure load, and presence of diabetes serve to attenuate this remodeling pattern. Overall, these observations suggest a mechanism by which women with hypertension and individuals with diabetes may be particularly predisposed to heart failure with a preserved ejection fraction in later life.