Original Article

Age- and Sex-Based Reference Limits and Clinical Correlates of Myocardial Strain and Synchrony

The Framingham Heart Study

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Background—There is rapidly growing interest in applying measures of myocardial strain and synchrony in clinical investigations and in practice; data are limited regarding their reference ranges in healthy individuals.

Methods and Results—We performed speckle-tracking–based echocardiographic measures of left ventricular myocardial strain and synchrony in healthy adults (n=739, mean age 63 years, 64% women) without cardiovascular disease. Reference values were estimated using quantile regression. Age- and sex-based upper (97.5th quantile) limits were: −14.4% to −17.1% (women) and −14.4 to −15.2% (men) for longitudinal strain; −22.3% to −24.7% (women) and −17.9% to −23.7% (men) for circumferential strain; 121 to 165 ms (women) and 143 to 230 ms (men) for longitudinal segmental synchrony (SD of regional time-to-peak strains); and 200 to 222 ms (women) and 216 to 303 ms (men) for transverse segmental synchrony. In multivariable analyses, women had ≈1.7% greater longitudinal strain, ≈2.2% greater transverse strain, and ≈3.2% greater circumferential strain (P<0.0001 for all) compared with men. Older age and higher diastolic blood pressure, even within the normal range, were associated with worse transverse segmental synchrony (P<0.001). Overall, covariates contributed to ≤12% of the variation in myocardial strain or synchrony in this healthy sample.

Conclusions—We estimated age- and sex-specific reference limits for measures of left ventricular strain and synchrony in a healthy community-based sample, wherein clinical covariates contributed to only a modest proportion of the variation. These data may facilitate the interpretation of left ventricular strain-based measures obtained in future clinical research and practice. **(*Circ Cardiovasc Imaging*. 2013;6:692-699.)**

Key Words: echocardiography ■ left ventricular function ■ reference values

Traditional methods for noninvasively assessing left ventricular (LV) function are based on estimates of LV ejection fraction (EF). However, it is well recognized that EF has limited sensitivity for characterizing abnormalities in cardiac function that can develop in individuals with or without symptoms of cardiac failure.[1] Indeed, as many as half of the patients with clinical heart failure present with a normal EF.[2,3] Thus, in an effort to better characterize LV function, several imaging techniques have been developed during the past 2 decades. In 1988, Zerhouni et al[4] introduced a cardiac magnetic resonance–based tissue tagging method for quantifying myocardial tissue deformation. Since then, numerous cardiac magnetic resonance studies have demonstrated the use of cardiac magnetic resonance–based measures of LV deformation (ie, myocardial tissue strains) for quantifying cardiac dysfunction in a variety of preclinical and disease states, with a primary focus on circumferential strains measured in the short axis.[5] More recently, speckle-tracking–based echocardiography has emerged as an accessible, as well as valid and reproducible, method for quantifying cardiac tissue deformation in multiple planes, including longitudinal strains measured in the long axis.[3,6–8] Speckle-tracking–based measures of LV strain now have been used to perform detailed assessments of LV function in numerous clinical and experimental studies.[9–11] Furthermore, echocardiographic measures of LV myocardial strain and segmental synchrony have been shown to add prognostic information on top of EF in a variety of clinical settings, including asymptomatic cardiomyopathy and overt heart failure.[9,12–18]

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Clinical Perspective on p 699

Although speckle-tracking echocardiography represents a versatile method for phenotyping cardiac function with potentially broad applications,[1,3] there are few data regarding the reference values for these measures in a rigorously characterized, healthy population.[19–23] Such information is critical for interpreting strain measures obtained in both the research and the clinical settings. Because common cardiovascular risk factors have been associated with measures of LV strain and synchrony in selected populations,[24–26] it is also important to determine the factors that influence normal values in a relatively healthy reference sample. Therefore, we performed echocardiographic speckle-tracking–based measurements of LV strain and synchrony in a well-characterized reference sample of healthy men and women in the community with the following aims: (1) to establish reference limits for advanced measures of LV function; (2) to assess the relationships of age and sex on these reference limits; and (3) to examine the clinical correlates of advanced LV myocardial measures in a relatively healthy sample of ambulatory adults.

Methods

Study Sample

The Framingham Offspring Study began in 1971 with recruitment of 5124 men and women who were the offspring of the original cohort and their spouses. Design and selection criteria have been detailed.[27,28] All participants (N=3021) who attended the eighth examination cycle (2005–2008) were eligible for this investigation. Individuals were excluded for the following reasons in hierarchical order: prevalent hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure [DBP] ≥90 mm Hg or taking antihypertensive therapy; n=1923), obesity (body mass index ≥30 kg/m^2; n=225), diabetes mellitus (fasting glucose ≥126 mg/dL or use of hypoglycemic medications; n=23), prevalent cardiovascular disease (coronary heart disease, stroke, or heart failure; n=13), history of atrial fibrillation (n=9), valvular heart disease (grade 3/6 systolic murmur or any diastolic murmur on examination; n=12), renal insufficiency (estimated glomerular filtration rate ≤60 mL/min using the modified diet in renal disease formula; n=56), missing echocardiographic measures of myocardial deformation (n=12), or <45 years or ≥85 years of age (n=9). The resulting healthy reference sample comprised 739 individuals. The Institutional Review Board of Boston University Medical Campus approved the study protocols, and all participants provided written informed consent at the examination.

Clinical Assessment

During the eighth examination cycle of the Framingham Offspring Study, each participant provided a detailed medical history and underwent anthropometry, a physical examination targeted at the cardiovascular system, and phlebotomy for collecting fasting blood samples. Blood pressure was measured using a standard mercury column sphygmomanometer in the left arm of each participant (after being seated for 5 minutes); the examining physician recorded values to the nearest even number, and the mean of 2 separate readings was used for all analyses.

Echocardiographic Measures of Myocardial Deformation

In addition to the clinical assessment, participants underwent routine M-mode, 2-dimensional (2D), and pulse-wave Doppler echocardiography. All images were digitally acquired using an HP Sonos 5500 Ultrasound Machine (Philips Healthcare, Andover, MA) and stored in Digital Imaging and Communications in Medicine (DICOM) format, with frame rates of 41±6 frames per second. Using an off-line image analysis program (2D Cardiac Performance Analysis v1.1, TomTec Imaging Systems, Unterschleissheim, Germany), previously validated[6–8] speckle-tracking–based analyses of LV myocardial deformation were performed according to a standardized protocol. Longitudinal and transverse LV strains were measured in the apical 4-chamber and 2-chamber views; circumferential and radial strains were measured in the midventricular parasternal short-axis view. Interobserver coefficients of variation were calculated for all measures of global peak strain, and these values ranged from 3.0% to 9.7%; intraobserver coefficients of variation ranged from 3.5% to 10.0%.

The primary measurements of LV myocardial deformation included global systolic longitudinal strain (average of peak longitudinal strain measured in 12 regions in the apical views), global systolic transverse strain (average of peak transverse strains measured in 12 regions in the apical views), midventricular average systolic circumferential strain (average of peak circumferential strain measured in 6 regions in the parasternal view), midventricular average systolic radial strain (average of peak radial strain measured in 6 regions in the parasternal view), transverse segmental synchrony (SD of time-to-peak systolic transverse strains measured in 12 regions in the apical views),[14] and longitudinal segmental synchrony (SD of time-to-peak systolic longitudinal strains measured in 12 regions in the apical views).[29–31] Measures of transverse strain and segmental synchrony refer to measurements performed in the radial plane from images acquired in the longitudinal axis. The 6 myocardial segments, from which peak systolic strain measurements were averaged to calculate midventricular average circumferential strain, included the following regions: midanteroseptal, midanterior, midanterolateral, midinferolateral, midinferior, and midinferoseptal.[12]

Statistical Analyses

To develop reference limits for each measure of myocardial deformation, the total study sample was divided into subgroups based on sex and 10-year age groups. Because measures of myocardial deformation vary by sex and age,[20,22] we estimated 2.5th, 50th, and 97.5th quantile thresholds in men and women separately within each age group. We estimated these reference limits using quantile regression[32,33] because empirical estimates are known to vary substantially in small- to moderate-sized samples. Accordingly, linear quantile regression (SAS PROC QUANTREG),[34] sex-specific and age-adjusted, was used to estimate the 2.5th, 50th, and 97.5th quantiles for each myocardial measure. In men and women separately, we reported the estimated 2.5th, 50th, and 97.5th quantile values for the middle age within each 10-year age group.

Within the healthy reference sample, we also used stepwise multivariable linear regression analyses to assess the association of each myocardial measure with the following clinical covariates: age, sex, body mass index, systolic blood pressure, DBP, total/high-density lipoprotein cholesterol ratio, fasting glucose, and heart rate. In separate models for each myocardial measure, stepwise regression was used to associate the myocardial measure with covariates having $P<0.10$ in individuals models. Continuous covariates were standardized (mean=0, SD=1) to facilitate the comparison of effect sizes. Because of right-skewed distributions, values of transverse and longitudinal synchrony were natural log transformed.

A $P<0.10$ was the criterion for the covariates to enter and remain in stepwise regression models. Given the number of strain measures (6) and clinical traits (7) analyzed, we used a Bonferroni-corrected P value threshold of 0.001 (=0.05/42) for the analyses of clinical correlates; because select clinical traits are known to be at least modestly correlated with one another (eg, age, systolic blood pressure, and DBP), this correction was considered conservative.

Conventional echocardiographic LV traits may reflect variation in hemodynamic load that is not completely captured by blood pressure. Thus, in secondary analyses, we analyzed the association of conventional echocardiographic LV traits with strain measures in models adjusting for age, sex, and any additional significant clinical

correlates that were identified in the main analyses described above. These conventional LV traits analyzed included LV wall thickness (the sum of septal and posterior wall thickness), LV end-diastolic diameter, LV relative wall thickness, calculated LV mass,[35] calculated LV end-diastolic volume,[36] and LV mass/volume ratio. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Characteristics of our healthy reference sample are shown in Table 1. The mean age was 63±8 years, and 64% were women. Mean body mass index was 24.8±2.9 kg/m^2, and systolic blood pressure was 119±11 mm Hg (data for pooled sexes).

Sex-Specific and Age-Adjusted Results: Reference Limits

We estimated the reference limits for each of the primary measures of LV myocardial deformation in men and women between 45 and 84 years of age. Upper (97.5th quantile), median (50th quantile), and lower (2.5th quantile) reference limits are presented by 10-year age intervals separately for men and women in Table 2 and the Figure.

Longitudinal strain values were lower, representing better contractile function, in women compared with those in men at the ages examined, with similar trends observed for transverse strain. With respect to circumferential strain, the upper reference limit was higher with older mean age in women, whereas the lower reference limit was lower with higher mean age in men. For radial strain, there was a widening of the upper and lower reference limits with age in both sexes although this pattern appeared more pronounced in men than in women.

For measures of synchrony, the median and lower reference limits were similar between the sexes and did not substantially vary with age. However, the upper limit of longitudinal segmental synchrony was higher (worsened) with age in men but lower (better) with age in women. The upper limit of transverse segmental synchrony was higher with age in both sexes, where men had higher (worse) upper limit reference values across all age groups.

Table 1. Characteristics of the Reference Sample

Characteristics	Men (N=263)	Women (N=476)
Age, y	62.4±8.1	63.5±7.8
Body mass index, kg/m^2	25.8±2.5	24.2±2.9
Systolic blood pressure, mm Hg	121±9	118±11
Diastolic blood pressure, mm Hg	75±7	71±8
Total cholesterol, mg/dL	189±33	204±33
HDL cholesterol, mg/dL	54±13	69±17
Total/HDL cholesterol ratio	3.7±1.0	3.1±0.9
Fasting glucose, mg/dL	101±8	96±8
Heart rate, bpm	60±10	63±10
Longitudinal strain, %	−20.2±2.7	−22.0±3.2
Transverse strain, %	28.4±6.0	30.6±6.9
Circumferential strain, %	−30.4±4.7	−32.8±5.3
Radial strain, %	43.7±16.2	45.7±15.5
Longitudinal segmental synchrony, ms	52 (41, 69)	49 (38, 63)
Transverse segmental synchrony, ms	85 (63, 128)	84 (58, 116)

Values are mean±SD or median (25th, 75th percentiles). HDL indicates high-density lipoprotein.

Multivariable-Adjusted Results: Clinical Correlates

The clinical correlates of the myocardial measures that were assessed in our healthy reference sample are shown in Table 3. Based on estimates of the adjusted R^2 calculated for each model, the common clinical variables analyzed (age, sex, body mass index, blood pressure, fasting glucose, and lipids) accounted for only a modest percentage of the variability in myocardial measures: 12.0% for longitudinal strain, 3.3% for transverse strain, 9.8% for circumferential strain, 1.9% for radial strain, 4.0% for longitudinal segmental synchrony, and 4.1% for transverse segmental synchrony. The estimated coefficients shown in Table 3 represent the amount by which the expected (average) strain value would change, given the presence versus absence of a corresponding covariate (for a categorical variable) or given a change in the corresponding covariate by 1 SD (for a continuous variable).

For measures of LV strain, most variation was attributable to sex. In multivariable-adjusted analyses, women had ≈1.7% lower (better) longitudinal strain (P<0.0001), ≈2.2% higher (better) transverse strain (P<0.0001), and ≈3.2% lower (better) circumferential strain (P<0.0001) compared with men. Higher heart rate was significantly associated with higher (worse) longitudinal and circumferential strains (P<0.0001) and lower (worse) radial strain (P=0.0004). In this healthy sample, observed associations of myocardial strain with age and fasting glucose did not meet the Bonferroni-corrected threshold of statistical significance. With respect to synchrony, higher values of longitudinal and transverse segmental synchrony (ie, worse synchrony or more dyssynchrony) were significantly associated with older age (Table 3). Higher DBP was also associated with worse transverse segmental synchrony (P<0.0001).

Secondary Analyses: Conventional Echocardiographic Correlates

The conventional echocardiographic LV traits assessed in the study sample are shown in Table I in the online-only Data Supplement. In multivariable-adjusted analyses, increased LV mass was associated with higher (worse) longitudinal synchrony (P=0.0006). The remaining conventional LV traits were not significantly associated with strain-based measures (Table II in the online-only Data Supplement).

Discussion

The present study establishes reference limits for LV myocardial strain and synchrony measures in a healthy sample of middle-aged to older men and women. We also identified factors that contribute to interindividual variation in measures of myocardial deformation in this reference sample. Overall, these reference limits may facilitate the interpretation of LV myocardial strain and synchrony data obtained in research or in clinical settings.

Several previous investigations have proposed reference limits for speckle-tracking–based measures of LV function. These prior studies have included predominantly younger or middle-aged samples,[19–23] with a focus on measures of LV strain, and none have formulated reference limits for LV synchrony. Takigiku et al[21] examined measures of LV strain in

Table 2. Quantile Regression Reference Limits By Sex

	Men			Women		
Age Group*, y	2.5th Quantile (95% CI)	50th Quantile (95% CI)	97.5th Quantile (95% CI)	2.5th Quantile (95% CI)	50th Quantile (95% CI)	97.5th Quantile (95% CI)
Longitudinal strain, %						
45–54	−26.1 (−38.2, −15.5)	−20.4 (−27.5, −13)	−15.2 (−25.1, −4.1)	−28.3 (−41, −17.1)	−21.9 (−27.4, −15.9)	−17.1 (−27.5, −5.1)
55–64	−25.4 (−39, −14)	−20.1 (−27.9, −12)	−15 (−25.9, −3)	−28.4 (−42.7, −16.8)	−21.8 (−27.7, −15.3)	−16.2 (−27.4, −2.8)
65–74	−24.6 (−39.7, −12.6)	−19.8 (−28.4, −11.1)	−14.7 (−26.8, −1.9)	−28.6 (−44.3, −16.5)	−21.7 (−28.1, −14.7)	−15.3 (−27.3, −0.5)
75–84	−23.9 (−40.5, −11.1)	−19.5 (−28.8, −10.2)	−14.4 (−27.6, −0.7)	−28.7 (−46, −16.1)	−21.6 (−28.4, −14.1)	−14.4 (−27.2, 1.8)
Transverse strain, %						
45–54	16.1 (−17.6, 49.3)	27.3 (19, 36.3)	42.7 (3.5, 80.9)	18.4 (5.1, 31.5)	29.2 (11.2, 44.7)	43.7 (21.8, 66.7)
55–64	17.7 (−20.5, 52.6)	28.2 (18.9, 37.8)	41.6 (0.5, 84.9)	18.2 (3.8, 32.5)	30 (9.8, 46.5)	43.9 (20.1, 68.8)
65–74	19.2 (−23.3, 55.9)	29 (18.9, 39.3)	40.5 (−2.5, 88.9)	18.1 (2.4, 33.4)	30.8 (8.4, 48.3)	44.1 (18.4, 70.9)
75–84	20.7 (−26.2, 59.1)	29.8 (18.8, 40.8)	39.4 (−5.4, 92.9)	18 (1.1, 34.3)	31.6 (7, 50.1)	44.3 (16.7, 73)
Circumferential strain, %						
45–54	−38.9 (−74.8, −3.2)	−29.9 (−37.4, −21.9)	−23.9 (−53.1, 27.1)	−38.9 (−78.3, −12.5)	−31.4 (−39.2, −24.1)	−22.3 (−38.7, −4.1)
55–64	−39.4 (−78.8, −0.2)	−30.1 (−38.3, −21.3)	−21.9 (−53.7, 32.1)	−42.5 (−84.0, −13.3)	−32.1 (−40.6, −24.2)	−23.1 (−40.6, −2.9)
65–74	−40.0 (−82.8, 2.9)	−30.4 (−39.1, −20.7)	−19.9 (−54.3, 37.1)	−46.1 (−89.7, −14.1)	−32.8 (−41.9, −24.2)	−23.9 (−42.6, −1.8)
75–84	−40.5 (−86.8, 5.9)	−30.7 (−40, −20.1)	−17.9 (−54.9, 42.0)	−49.8 (−95.5, −14.9)	−33.5 (−43.3, −24.2)	−24.7 (−44.5, −0.6)
Radial strain, %						
45–54	21.3 (−21.3, 60.1)	39.6 (16.8, 59.2)	73.8 (−182.9, 334.2)	18.2 (−17.9, 55.4)	46.5 (21.2, 68.5)	74.9 (44.7, 108.9)
55–64	18.2 (−27.4, 61.8)	40.8 (15.2, 61.8)	86.0 (−212.4, 355.5)	19.3 (−22.1, 57.8)	45.2 (17.3, 69.0)	79.1 (46.3, 115.8)
65–74	15.0 (−33.6, 63.4)	42.0 (13.6, 64.3)	98.2 (−241.8, 376.7)	20.5 (−26.3, 60.1)	43.9 (13.4, 69.6)	83.3 (48.0, 122.8)
75–84	11.8 (−39.7, 65.1)	43.3 (12.0, 66.9)	110.4 (−271.3, 398.0)	21.6 (−30.5, 62.5)	42.6 (9.5, 70.1)	87.5 (49.6, 129.7)
Longitudinal segmental synchrony, ms						
45–54	26 (−78, 131)	48 (−7, 106)	143 (−294, 642)	25 (6, 40)	46 (13, 80)	121 (−126, 428)
55–64	25 (−91, 137)	51 (−9, 115)	172 (−302, 712)	24 (4, 41)	48 (12, 86)	136 (−154, 447)
65–74	24 (−103, 142)	54 (−10, 123)	201 (−310, 781)	23 (1, 41)	50 (12, 91)	150 (−182, 467)
75–84	23 (−116, 148)	58 (−11, 131)	230 (−317, 850)	22 (−1, 41)	52 (12, 97)	165 (−210, 486)
Transverse segmental synchrony, ms						
45–54	22 (−106, 151)	73 (7, 139)	216 (−262, 1505)	24 (−34, 73)	69 (−25, 152)	222 (105, 360)
55–64	25 (−115, 164)	82 (9, 153)	245 (−296, 1566)	25 (−37, 80)	80 (−25, 168)	215 (83, 360)
65–74	28 (−125, 178)	90 (11, 167)	274 (−330, 1627)	25 (−40, 88)	92 (−25, 185)	207 (61, 361)
75–84	31 (−135, 192)	99 (13, 182)	303 (−364, 1688)	26 (−42, 96)	103 (−25, 202)	200 (39, 361)

CI indicates confidence interval.

*Age groups included the following number of men and women: 43 and 63 (45–54 y); 133 and 232 (55–64 y); 66 and 134 (65–74 y); and 21 and 46 (75–84 y).

≈800 hospital employees, their relatives, and volunteer recruits in Japan, with limited clinical information available. Marwick et al[19] studied 242 healthy volunteers recruited through centers in Brisbane, Australia, Aachen, Germany, and Cleveland, OH; this middle-aged study sample (mean age of 51±12 years) included both men and women, and the reported reference limits for LV strain were for pooled sexes.[19] Advantages of our reference sample include its moderate-to-large size and the wide age range (including healthy adults aged >75 years), reflecting the spectrum of individuals most predisposed to cardiovascular risk factor exposure and, in turn, to subclinical abnormalities in cardiac function. Furthermore, all study participants underwent detailed medical evaluations, including physician-administered physical examinations and laboratory testing, allowing the use of rigorous criteria to define a healthy reference sample. In addition, we assessed measures of LV segmental synchrony and strain and performed sex-specific analyses.

In determining reference limits for biological measurements performed in human samples, empirical estimates are conceptually straightforward and are commonly used; however, empirical limits may be influenced by a few outlying values, especially in the setting of small- or moderate-sized samples. Therefore, we used quantile regression models, which are not sensitive to outliers, to estimate reference limits for measures of myocardial deformation.

Reference Limits for Measures of Strain

For measures of longitudinal strain, our median values of −19.5% to −20.4% for men and −21.6% to −21.9% for women are similar to the empirically estimated mean values reported for sex-pooled samples in prior studies.[21,22] Our median estimates also match values of normal longitudinal deformation derived from a mathematical model of dynamic LV geometry that was reported by Dumesnil et al[37] >30 years ago. Importantly, the

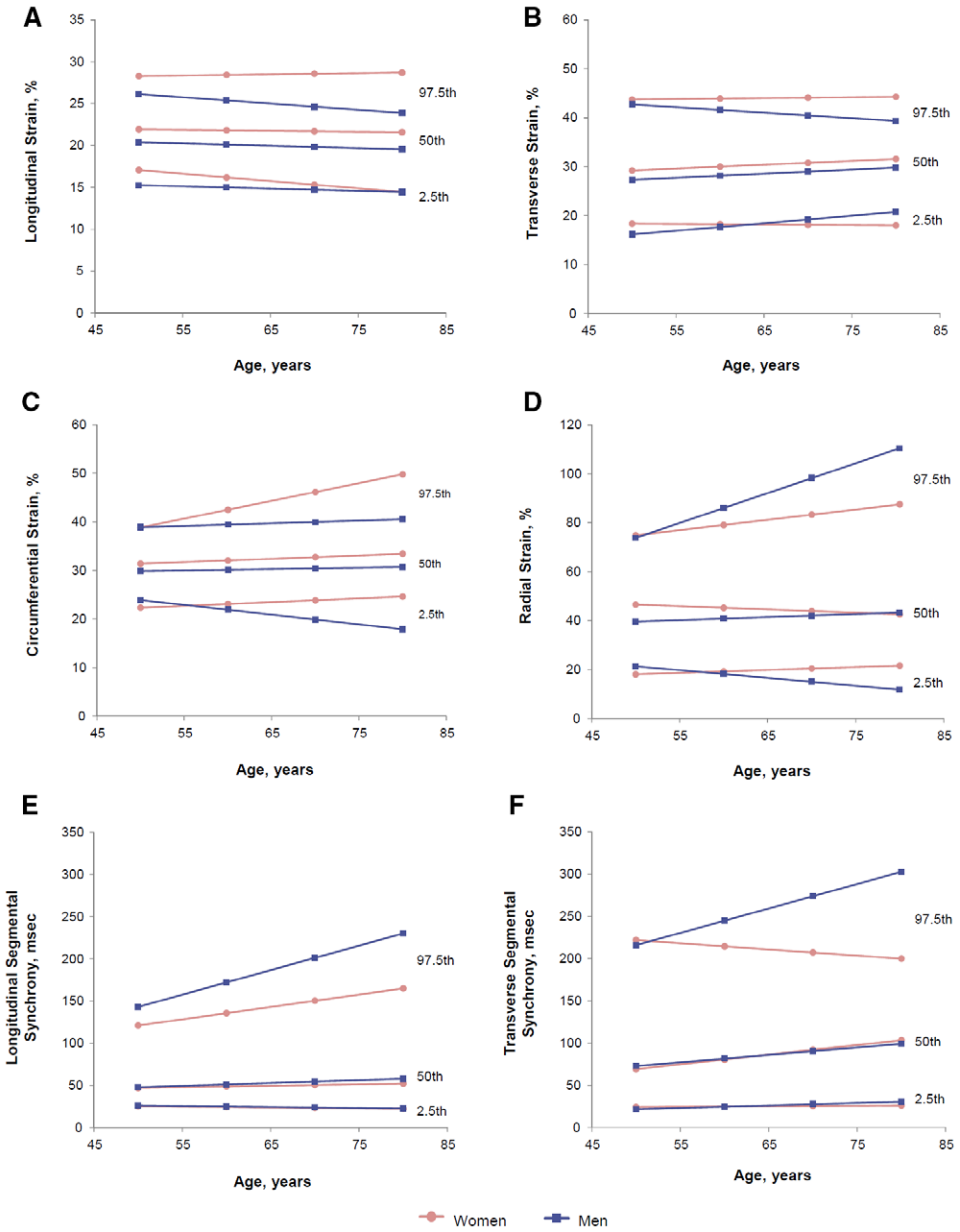

Figure. Quantile regression reference limits in men and women are shown for each of the primary measures of myocardial deformation and synchrony: global longitudinal strain (**A**), global transverse strain (**B**), midventricular average circumferential strain (**C**), midventricular average radial strain (**D**), longitudinal segmental synchrony (**E**), and transverse segmental synchrony (**F**).

upper limits of longitudinal strain (−14.4% to −15.2% for men and −14.4% to −17.1% for women in our sample), representing reduced (worse) longitudinal myocardial shortening, are consistent with abnormal values of longitudinal strain that have been associated with adverse outcomes in previous reports.[9,15,18] Although circumferential, transverse, and radial strains have been less well studied, our data suggest sex-specific reference limits that are also within the range of previously reported sex-pooled empirical estimates.[21,22] Because empirical estimates are sensitive to outliers within a given study sample, our estimates based on quantile regression offer a set of relatively robust reference limits for interpreting measurements of myocardial deformation obtained in ambulatory cohorts.

Our data underscore the fact that values of LV strain observed in healthy individuals are, in large part, a function of sex, even when adjusting for age and blood pressure. All reference limits for longitudinal strain, representing longitudinal deformation of the innermost myocardial (endocardial) fibers, were lower (better) in women compared with those in men. Similar trends were seen for LV circumferential and transverse strain. Although similar sex-based differences in longitudinal strain have been reported in many prior speckle-tracking–based studies,[20–22] the underlying mechanisms remain unclear. It is likely, however, that increased shortening of longitudinal and circumferential fibers contributes to higher EFs seen in women compared with that in men, particularly in the setting of smaller LV cavity sizes.[38] Indeed, prior population-based studies have consistently demonstrated higher EFs in women compared with those in men across the age spectrum.[39] In this context, our findings underscore the need for additional studies to examine the

Table 3. Multivariable-Adjusted Results: Clinical Correlates of Strain-Based Measures in the Reference Sample

	Longitudinal Strain, %		Transverse Strain, %		Circumferential Strain, %		Radial Strain, %		Log Longitudinal Segmental Synchrony, ms		Log Transverse Segmental Synchrony, ms	
Variable	Estimate* (SE)	*P* Value	Estimate* (SE)	*P* Value	Estimate* (SE)	*P* Value	Estimate* (SE)	*P* Value	Estimate* (SE)	*P* Value	Estimate* (SE)	*P* Value
Age	…		0.58 (0.26)	0.023	−0.38 (0.20)	0.052	…		0.06 (0.02)	0.0008	0.12 (0.02)	<0.0001
Female	−1.74 (0.26)	<0.0001	2.24 (0.53)	<0.0001	−3.22 (0.43)	<0.0001	2.89 (1.28)	0.024	−0.07 (0.04)	0.050	…	
Body mass index	…		…		…		…		0.05 (0.02)	0.007	…	
Systolic blood pressure	…		…		…		…		…		−0.07 (0.03)	0.007
Diastolic blood pressure	0.23 (0.12)	0.052	…		…		…		…		0.10 (0.03)	<0.0001
Total/HDL cholesterol	0.23 (0.13)	0.062	…		…		…		…		…	
Fasting glucose	…		…		−0.59 (0.21)	0.004	…		…		…	
Heart rate	0.66 (0.12)	<0.0001	…		1.16 (0.20)	<0.0001	−2.25 (0.63)	0.0004	−0.05 (0.02)	0.009	−0.06 (0.02)	0.003

HDL indicates high-density lipoprotein.

*Estimated change in strain measure per SD change in continuous covariates: 1 SD is equivalent to 8 y of age, 3 kg/m^2 for body mass index, 11 mm Hg for systolic blood pressure, 8 mm Hg for diastolic blood pressure, 10 bpm for heart rate, 8.6 mg/dL for fasting glucose, and 0.98 for total/HDL cholesterol ratio.

neurohormonal[40] or other biological factors that could explain sex-related differences in myocardial mechanical function.

Heart rate was also a significant correlate of myocardial strain in our healthy sample. Higher resting heart rate was associated with less longitudinal and circumferential shortening, as well as less wall thickening in the radial plane. Small clinical studies have observed that as heart rate increases progressively with dobutamine infusion, myocardial strain initially increases and then decreases.[41] Experimental models of dobutamine- or pacing-induced tachycardia show similar findings and indicate that the decrease in peak strain, reflecting the magnitude of myocardial deformation, is coupled with an increase in strain rate, representing the time taken to achieve maximal deformation.[42,43] Our data in a healthy cohort of ambulatory adults suggest that higher heart rates, even at rest, are associated with a lesser magnitude of myocardial deformation; if such decrements in mechanical function are matched by increased temporal efficiency, the combination may contribute to an overall preservation of ventricular performance and output in our study sample.

Although estimated limits of circumferential and radial strain values seemed to vary with increasing age in both sexes, age was not significantly associated with strain measures after multivariable adjustment for clinical covariates and accounted for multiple testing. Therefore, apparent age-related variation in myocardial strain is likely attributable to age-related correlates, such as increased heart rate. The potential role of age-related risk factors was also suggested by nonsignificant associations of DBP and total/high-density lipoprotein cholesterol with longitudinal strain. In the Multiethnic Study of Atherosclerosis,[44] investigators observed that coronary artery calcium was associated with regional decrements in LV circumferential strain, assessed using cardiac magnetic resonance tissue tagging, in people without prevalent cardiovascular disease. Thus, measurable variation in LV strain could represent cardiac dysfunction that occurs early in the progression from risk factors to atherosclerotic coronary disease, even in the absence of symptoms.

Reference Limits for Measures of Synchrony

Segmental synchrony of myocardial contraction is thought to reflect the overall efficiency of myocardial performance. Methods for quantifying segmental synchrony of the LV have evolved substantially during the past decade. More recently, clinical studies have indicated superior use in calculating the SD of time-to-peak longitudinal or transverse strain (across ≥12 regions) as a measure of dyssynchronous LV function,[14,29–31] even in the absence of clearly defined normal values. Because prior studies have predominantly focused on the use of synchrony measures in patients with overt LV dysfunction or heart failure, especially those being considered for cardiac resynchronization therapy, there have been little data regarding normal values in individuals without manifest cardiac disease. In our healthy sample, reference limits for longitudinal and transverse synchrony, based on quantile regression of strain measurements, suggest that values in excess of 121 to 230 ms (longitudinal) and 216 to 303 ms (transverse) represent significantly reduced segmental synchrony of LV function. These values are comparable with time-to-peak SD values reported in association with the presence versus absence of heart failure symptoms in individuals with diastolic dysfunction[45] and with the incidence of death or nonfatal heart failure events in patients with overt LV dysfunction and chronic heart failure.[14] We also observed that upper limits of transverse synchrony were higher with increased age in men but lower with increased age in women; in contrast,

the upper limits of longitudinal synchrony were higher with age in both sexes. These trends may be related to the age- and sex-related variations in LV mechanical function that are represented by LV circumferential and radial strain. Notably, variation in transverse synchrony was associated with elevated blood pressure in our nonhypertensive sample. Similarly, in secondary analyses, longitudinal synchrony was associated with higher increments of LV mass in our healthy sample. Thus, measures of LV synchrony may reflect subtle alterations in myocardial function along the wide spectrum from health to disease. Further research is needed to investigate the mechanisms underlying these findings.

Several limitations of this study merit consideration. Our study sample included middle-aged to older men and women between 45 and 84 years of age. Thus, the findings reported herein cannot be generalized to individuals outside the age range of our study sample. Because our study sample included individuals of predominantly European ancestry, with few individuals of black or other racial/ethnic groups, the extent to which our results may apply to these other groups is also unknown. In addition, the myocardial strain measurements reported in our sample may differ from measurements made in a similar sample but using software produced by a different vendor.[21] Unlike some prior studies, however, we used a software algorithm and package that can be applied to images acquired from any echocardiography ultrasound machine (ie, nonvendor specific). Thus, compared with vendor-specific approaches, our methods for performing strain-based analyses are potentially more generalizable to other clinical research and practice settings. We did not analyze strain rate or regional strain values because the precision of these measurements is thought to be lower than that of global or averaged strain measurements acquired from speckle-tracking–based methods when they are applied to images recorded at lower frame rates. Accordingly, clinical studies demonstrating the potential prognostic use of speckle-tracking echocardiography have focused on global strain measures.[9,14,15,18] We also did not perform analyses of shear strains, twist, or torsion because the additional digital images required for these measurements were not available in our study sample.

In summary, we have reported reference limits for measures of LV global myocardial strain and synchrony in a healthy sample of middle-aged to older adults. Because of the influence that a few outlier values may have when using the empirical estimates, we used the quantile regression method to define these limits. Overall, our data underscore the important influences of age and sex on measurements of myocardial mechanical function in relatively healthy individuals. Thus, as with conventional measures of cardiac morphology and function, demographic and clinical characteristics are important considerations when evaluating strain-based measures of LV mechanical function for clinical or research purposes. Further investigations are needed to evaluate the use of our community-based reference limits with respect to the incidence of clinically important outcomes in the community.

Disclosures

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CLINICAL PERSPECTIVE

There is a growing interest in applying measures of myocardial strain and segmental synchrony in clinical investigations and in practice. However, data are limited regarding the reference ranges of these measures in healthy individuals. We performed speckle-tracking–based echocardiographic measures of left ventricular myocardial strain and segmental synchrony in a healthy sample of 738 middle-aged to older Framingham Heart Study participants. Using quantile regression to estimate reference values in this sample, we determined the following age- and sex-based upper limits: −14.4% to −17.1% in women and −14.4% to −15.2% in men for longitudinal strain; −22.3% to −24.7% in women and −17.9% to −23.9% in men for circumferential strain; 121 to 165 ms in women and 143 to 230 ms in men for longitudinal segmental synchrony (defined as the SD of regional time-to-peak strains); and 200 to 222 ms in women and 216 to 303 ms in men for transverse segmental synchrony. Notably, after adjusting for traditional measures of cardiovascular risk, women had ≈1.7% greater longitudinal strain, ≈2.2% greater transverse strain, and ≈3.2% greater circumferential strain ($P<0.0001$ for all) compared with men. Older age and higher diastolic blood pressure, even within the normal range, were associated with worse transverse segmental synchrony ($P<0.001$). Overall, clinical covariates accounted for ≤12% of the variation in myocardial strain or synchrony. These findings may aid in interpreting left ventricular strain-based measures obtained in future clinical research and practice.