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The Influence of Left Ventricular Size and Global Function on Regional Myocardial Contraction and Relaxation in an Adult Population Free of Cardiovascular Disease: A Tagged CMR Study of the MESA Cohort

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ABSTRACT

The purpose of this study is to evaluate the relationship between LV structure and function with regional myocardial function in participants of the Multi-Ethnic Study of Atherosclerosis, which is a prospective study including 4 ethnic groups free from clinical cardiovascular disease. Peak systolic strain (Ecc) and regional strain rates (SR_S and SR_E) were calculated by harmonic phase from tagged CMR of 1100 participants. The relationships of ejection fraction (EF), end-systolic volume (ESV) and end-diastolic volume (EDV) with Ecc and strain rate were studied before and after adjustment for cardiovascular risk factors. Direct linear relationships between EF and regional systolic and diastolic functions (Ecc, SR_S and SR_E) were present in almost all of the regions ($p < 0.05$, i.e., greater EF, greater Ecc, SR_S and SR_E). LVESV demonstrated a negative relationship with Ecc and SR_S (i.e., greater ESV, lower systolic function, indexed by Ecc and SR_S) in all regions ($p \leq 0.05$). LVEDV was inversely related to systolic function, indexed by SR_S ($p < 0.05$) in all regions. In conclusion, LVEF is directly related to systolic myocardial function, indexed as the absolute magnitude of systolic strain and strain rate. In addition, left ventricular size, indexed as end-diastolic and end-systolic volumes are inversely related to absolute systolic myocardial strain rate (SR_S). These results are crucial to the interpretation of strain alterations induced by left ventricular remodeling in early heart failure.

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INTRODUCTION

Heart failure is a serious and growing problem characterized by complex cardiac and systemic adaptations that vary over time, caused in large part by ischemic heart disease and chronic hypertension. Clinical heart failure is often preceded by left ventricular remodeling, a process by which mechanical, neurohormonal and possibly also genetic factors alter ventricular size, shape and function. In this regard, myocardial enlargement is often detectable before the onset of symptoms while early treatment can slow progression to overt failure (1).

Since ischemic heart disease typically produces regional abnormalities of contraction, hyperkinesis of normal areas may compensate for impaired function of abnormal regions, leaving global left ventricular function normal or only minimally depressed. Thus, assessment of regional myocardial function is more sensitive in detecting incipient ventricular dysfunction than analysis of global ventricular function.

However, the assessment of regional myocardial function should take into consideration the load dependence of parameters proposed for clinical use. Functional parameters such as stroke volume, ejection fraction (EF), fractional shortening or rate of ejection are determined not only by the intrinsic myocardial contractility but also by the pre-load and afterload imposed on the left ventricle (LV) (2, 3). In this regard, the association of global left ventricular size and function on regional mechanical parameters, such as myocardial strain and strain rate, are of paramount importance to the correct interpretation of regional alterations in regional myocardial performance over time.

Currently used indices of regional left ventricular function, such as endocardial motion and percent systolic thickening, are particularly sensitive to load alterations and variability given their dependence on accurate definition of endocardial and epicardial borders. By contrast, tagged cardiovascular magnetic resonance imaging (CMR) of the heart provides precise and reliable measurements of regional left ventricular function (4) with great accuracy and reproducibility (5). Strain data obtained from CMR tagging can evaluate not only systolic but also diastolic regional LV function objectively, without dependence on the accurate tracking of myocardial borders. By derivation of strain over time, strain rate can be calculated (6) to index the velocity of myocardial contraction and relaxation in addition to the magnitudes of segmental deformation.

The purpose of this study was to evaluate the relationships of myocardial circumferential strain (Ecc) and strain rate (SR) with parameters of LV size as well as load dependent measures of global LV function in a population-based cohort of asymptomatic participants of the Multi-Ethnic Study of Atherosclerosis (MESA).

SUBJECTS AND METHODS

Study population

The MESA study is a prospective, population-based observational cohort study of men and women free of clinical cardiovascular disease at study enrollment. Study design and population characteristics have been described (7). Briefly, 6814 men and women, aged 45-85 years old, from four different ethnic groups (Caucasian, African-American, Hispanics and Chinese) were enrolled. A major exclusion criterion was the presence of overt cardiovascular disease.

CMR protocol

In the MESA study, CMR was performed in 5004 participants as a part of the baseline exam. In this ancillary study, 1100 consecutive participants (53.9% male) underwent tagged CMR studies at enrollment in six centers (Wake Forest University, North Carolina, USA; Columbia University, New York, USA; Johns Hopkins University, Maryland, USA; University of Minnesota, Minnesota, USA; Northwestern University, Illinois, USA;, and University of California at Los Angeles, California). The participants for the tagged CMR study were randomly selected. This sub-cohort is similar to the MESA cohort in demographics aspects as previously described (8).

Images were acquired by whole body scanners (1.5 CVi, General Electric Medical Systems, Waukesha, Wisconsin, USA and Sonata/Symphony Siemens Medical Solutions, Germany) using ECG-triggered segmented *k*-space fast spoiled gradient-echo (SPGR or FLASH) pulse sequence during breath holds. After completing the standard imaging protocol, three tagged short axis slices (base to apex) were obtained. Parallel striped tags (Fig. 1) were prescribed in two orthogonal orientations (0° and 90°) using ECG-triggered fast gradient echo sequence with spatial modulation of magnetization (SPAMM) (9) and after they were superimposed as grid images (Fig. 2). The parameters for tagged CMR images were: field of view 40 cm; slice thickness 8 to10 mm; repetition time 3.5 to 7.2 ms; echo time 2.0 to 4.2 ms; flip angle 10°–12°; matrix size 256 × 96 to 140; temporal resolution 20 to 40 ms; tag spacing 7 mm.

CMR data analysis

LV mass, LV volumes and ejection fraction (EF) were determined for each participant using dedicated commercially available software (MASS, version 4.2 Medis, The Netherlands). LV end-diastolic volume index (LVEDi) and LV end-systolic volume index (LVESi) were defined as LV end-diastolic dimension divided by body surface area (BSA) and LV end-systolic dimension divided by BSA, respectively. Men with LVEDi greater than 92 mL/m^2 and LVESi greater than 33 mL/m^2 as well as women with LVEDi greater than 81 mL/m^2 and LVESi more than 31 mL/m^2 were considered abnormal based on previously published non-MESA data (10). All MESA participants gave informed consent for the study protocol. The Institutional Review Boards in all MESA Field Centers, CMR and US Reading Centers approved this protocol. Short-axis tagged slices were analyzed by the HARP (Fig. 3) method (Harmonic Phase, Diagnosoft, PaloAlto, California, USA) to assess strain (11, 12). Peak regional systolic circumferential strains (Ecc) were determined in 4 LV segments (anterior, lateral, inferior and septal) in the midwall layer. In each patient, by deriving strain by the time information (T) from each segment (13, 14), strain rates were

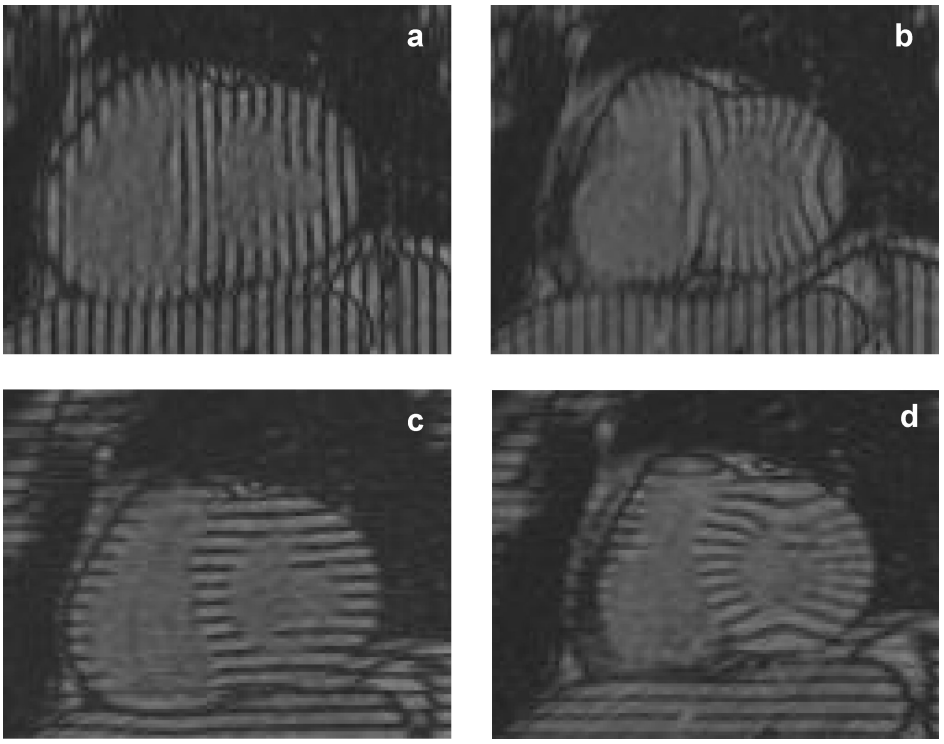

Figure 1. Myocardial tagging images from one study participant. Figures *a* and *c* are diastolic frames of short-axis slices with vertical and horizontal tags in the plane of papillary muscles. Figures *b* and *d* are systolic frames with tag deformation during myocardial contraction.

obtained from the strain measures from each time frame:

$$\mathrm{SR} = \frac{Ecc2 - Ecc1}{T2 - T1}$$

The peak systolic strain rate (SR_S), peak early filling strain rate (SR_E) and atrial induced strain rate (SR_A) were obtained from the strain measures from each segment at each time frame (Fig. 4). By convention, since Ecc and SR_S relate to systolic circumferential shortening, their value during systole is negative and a more negative value, reflects enhanced contraction. The relationships found of peak Ecc and peak SR_Swere described in absolute magnitude in the "Results" and "Discussion" sections.

Reproducibility of HARP

To assess the inter- and intraobserver agreement for myocardial MR-tagged image analysis using the HARP technique, three independent observers performed two separate quantitative strain analyses of myocardial cine MR-tagging images blindly in 24 MESA participants. Interobserver and intraobserver variability for all peak strain values (n = 2,592) related to tag persistence. Intraclass correlation coefficients R for interobserver and intraobserver agreement for peak systolic midwall ECC were 0.81 and 0.84, respectively, revealing excellent agreement(15).

Statistical Analysis

Cardiac functional parameters were expressed as mean ± standard error (SE). Multivariable linear regression was used to determine the relationships of LV volumes and EF with regional systolic strain (Ecc), strain rate (SR_S) and early diastolic strain rate (SR_E). We considered the first model to be the multiple linear regression of Ecc, SR_S or SR_E with respect to EF, ESV and EDV adjusted for age, gender, body mass index, systolic and diastolic blood pressure. In the second model, in order to assess if LV mass, cardiac rhythm, ethnicity and use of BP medications modify the relationship between global and regional function parameters over and above the effect of blood pressure, we added the variables end-diastolic left ventricular mass, heart rate, race/ethnicity and use of antihypertensive medication (model 2) as measures of the presence and severity of sub-clinical hypertensive heart disease. For all measures, a two-sided p value $\leq$ 0.05 was considered as statistically significant.

RESULTS

Demographics and prevalence of global LV function abnormalities

Demographic and hemodynamic data from the 1100 participants who underwent cardiac MR imaging and tagging studies are presented in Table 1. Approximately 54% of the study participants were men. Approximately two-thirds of the study population was either Caucasian or African American.

Mean LV end-diastolic and end-systolic volumes were 123.7 ± 1.0 and 39.6 ± 0.5 mL (mean ± se), respectively. Abnormal end-diastolic volume index was present in 67 (34 were male)

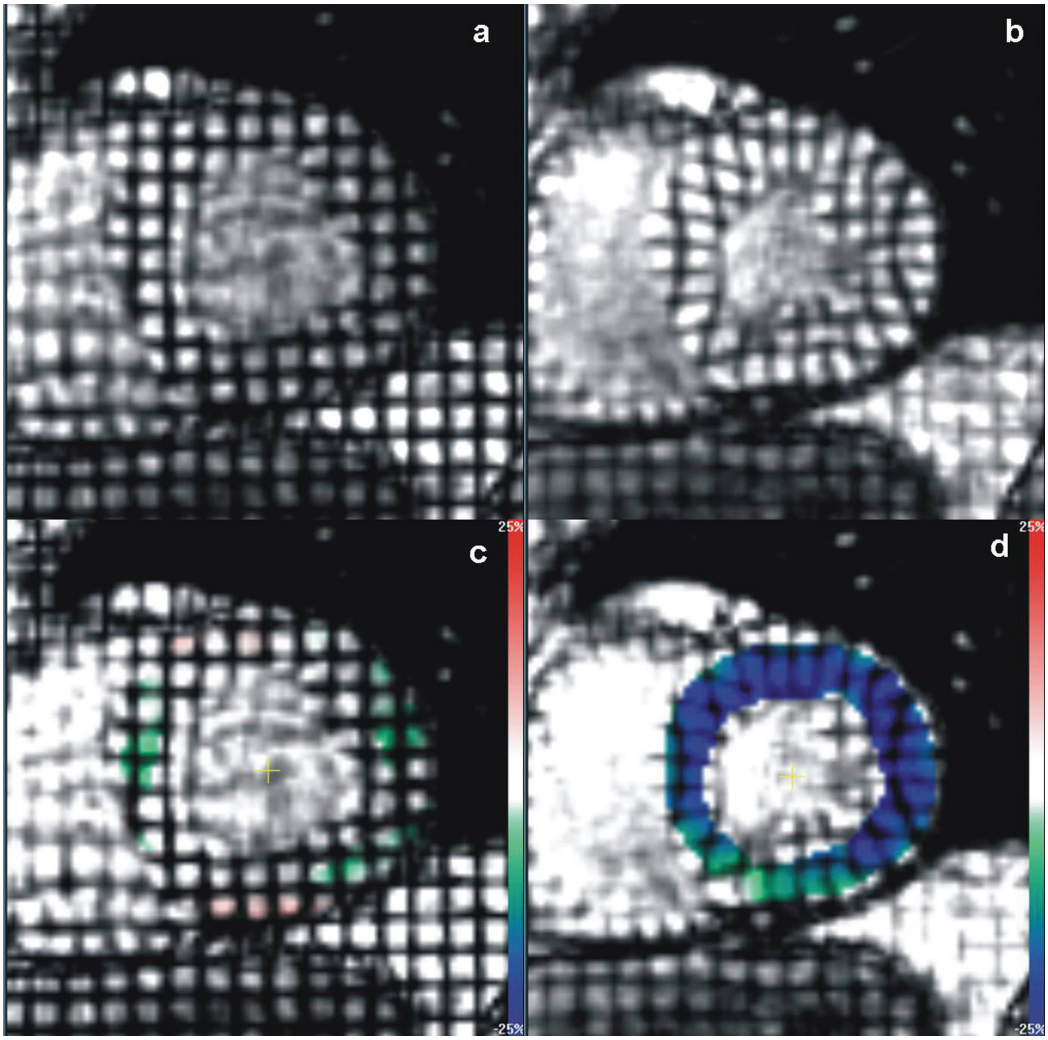

Figure 2. Short axis tagged grid MR images from one study participant. (*a*) and (*c*) diastole and (*b*) and (*d*) end-systole. (*c*) and (*d*) are color-coded maps superimposed on tagged MR short-axis images, in (c) end-systole image showing the regional extent of circumferential shortening.

participants; abnormal LV end-systolic index was present in 80 (65 were male) participants. Forty-nine subjects (41 were male) had reduced LV ejection fraction (EF $< 55\%$), whereas, only 4 individuals (0.4%) had both reduced EF and high EDV index; 34 individuals (23 were male) had high EDV and ESV indices with normal EF and only 1 men had a reduced EF with both high ESV and ESV indices.

The influences of Age, Gender and Race on the relationships of EF, EDV and ESV with parameters of regional systolic and diastolic function

The associations between parameters of left ventricular volumes or global function with indices of myocardial contraction and relaxation did not differ by age, gender or race (i.e., no interactions were noted). Therefore, these groups were studied together in the regression models.

Ejection fraction and Regional LV systolic and diastolic function

A direct linear relationship was present between EF and Ecc (considering absolute values) in all regions ($p < 0.05$) that remained significant after multivariable adjustments (Table 3a). EF and SR_S showed similar relationships except for strain in the anterior wall in model 2 (Table 3b, Fig. 5). Left ventricular ejection fraction was positively associated with peak myocardial relaxation (SR_E) in anterior, inferior and septal LV regions ($p < 0.05$). However, this association remained significant only in the septal wall ($p = 0.047$, regression coefficient [RC] $= 0.007$; 95% CI $= 0.00008, 0.01400$) after adjustment for age, gender, systolic and diastolic blood pressure (Model 1).

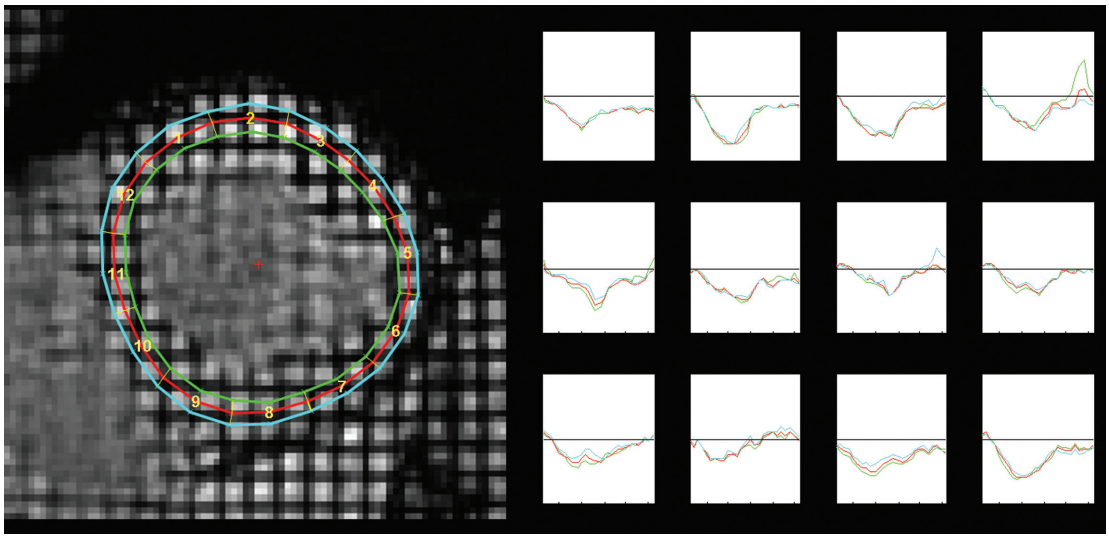

Figure 3. Example of one study participant. HARP analysis of short-axis tagged MR image. (left) circular mesh with 12 segments is defined by the user to represent the region of measurement in the left ventricular wall (green ‗ subendocardial layer, red ‗ midwall, blue ‗ subepicardial layer). Points on the grid are then automatically tracked through all the image sections in the data set, and strain values are calculated from the trajectory of each point. (right) Plots of circumferential shortening strain (Ecc) in each segment of the three layers.

LV End-systolic volume and regional LV systolic and diastolic function

The left ventricular ESV was inversely related to the magnitude of myocardial strain (Ecc), i.e., greater volume was associated with reduced regional function ($p < 0.05$, Fig. 6), except in the anterior wall after adjustment for the covariates included in Models 1 and 2 (Table 4a). End-systolic volume was also inversely related to systolic strain rate (SR_S) in all regions ($p < 0.05$, Fig. 6). The association remained significant (Table 4b) after multivariable adjustment (Models 1 and 2). LV ESV was also inversely related to peak diastolic relaxation (SR_E) in the anterior and septal regions for the simple linear regression and for Model 1 in the septal wall ($p = 0.042$, RC = -0.003; 95% CI = −0.007, −0.0001).

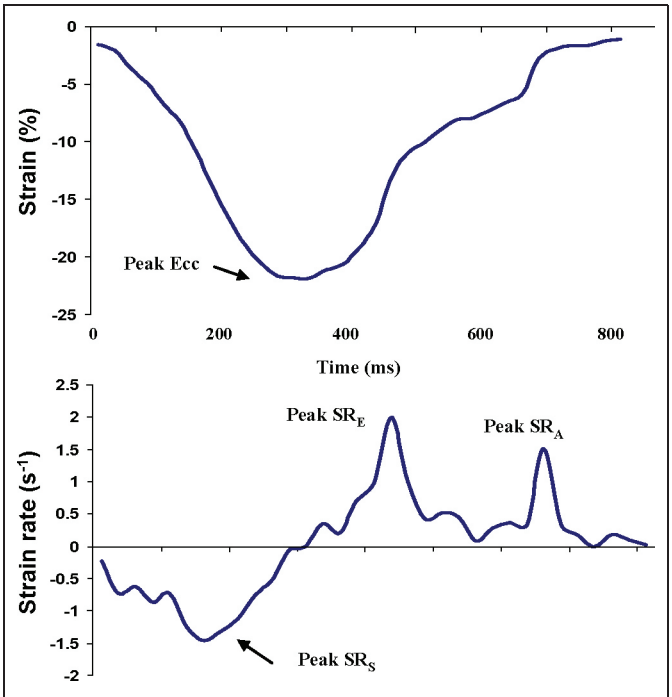

Figure 4. Representative circumferential shortening strain (upper) curves and strain rate (lower) from one participant. This example is demonstrating a typical strain rate pattern with a marked E′ wave in early diastole and a less pronounced A′ wave close to end diastole.

LV End-diastolic volume and Regional LV systolic and diastolic function

Left ventricular size, indexed by the left ventricular end-diastolic volume (EDV) was inversely related to the magnitude of myocardial strain (Ecc) in the inferior wall only (simple linear regression and Model 1, Table 5a). However, was significantly direct related to Ecc in the anterior and septal walls (i.e., increased LV volume associated with enhanced wall function) after adjustment for age, gender, blood pressure (Model 1, for anterior wall) and after LV mass, BMI, HR, race and use of anti-hypertensive medication (Model 2, for anterior and septal walls). However, we found strong associations between EDV and SR_S in all unadjusted analyses as well for all multivariable analyses with the exception of the septal wall in Model 2 (Table 5b), reflecting the strong association of EDV on the velocity of myocardial contraction. EDV was also inversely related to diastolic strain rate (SR_E) in both the anterior and septal regions in the unadjusted model ($p < 0.05$). After adjustment for variables in models 1 and 2, relationships between EDV and SR_E became non-significant.

Table 1. Demographic and hemodynamic of 1100 participants

Characteristics	**Value** *
Age (yr)	66.2 ± 0.3
Male (%)	53.9
Race (%)	
Caucasian	33.1
Chinese American	9.2
African American	28.0
Hispanic	29.7
Systolic Blood Pressure (mmHg)	128.3 ± 0.6
Diastolic Blood Pressure (mmHg)	72 ± 0.31
Heart rate (bpm)	62.7± 0.3
BMI (Kg/m^2)	27.8 ± 0.1
BSA	1.85 ± 0.01
Hypertension (%)	43.6
Diabetes (%)	17.5
Cigarette smoking (%)	
Former	37.5
Current	11.9
Triglycerides (mg/dL)	128. 3 ± 2.3
Total Cholesterol (mg/dL)	194.0 ± 1.1
HDL C (mg/dL)†	50.9 ± 0.5
LDL (mg/dL)†	117.5 ± 0.9
Taking meds for Hypertension	33.1
Taking meds for High Cholesterol	19.7
Taking meds for Diabetes	11.2

*Values are mean ± SE.
BSA = body surface area, BMI = body mass index, HDL = high-density lipoprotein cholesterol, LDL =low-density lipoprotein cholesterol.

DISCUSSION

This is the first study relating indices of left ventricular size and global function to regional parameters of myocardial mechanics in a large population of men and women of varied age and ethnicity. We reported an inverse relationship between left ventricular end-diastolic volume and myocardial strain rate. While left ventricular ejection fraction was directly related to both the magnitude and velocity of circumferential strain, the inverse relationships between end-systolic volume and strain and strain rate reflected the combined association of left ventricular size (*chronic* pre-load influence on strain rate) and global function (inverse relationship with the magnitude of circumferential strain). This is also the first study to investigate the relationship between LV volumes (at both end-diastole and end-systole) and diastolic strain rate. We report the relative independence of diastolic indices to differences in LV volumes with positive relationships between EF and segmental early diastolic strain rate only in the unadjusted model.

Table 2. Values of CMR characteristics of 1100 cases studied

Variables	Mean ± se
LVEDV (mL)	123.7 ± 1.0
LVESV (mL)	39.7 ± 0.5
LVEDVi (mL/m^2)†	66.8 ± 0.4
LVESVi (mL/m^2)†	21.2 ± 0.3
LVEDM (g)	146.6 ± 1.3
LVEF (%)	68.6 ± 0.2

*Values are mean ± SE.
†Values corrected for body surface area (BSA).
LVEDV = LV end-diastolic volume, LVESV = LV end-systolic volume, LVEDM = LV end-diastolic mass, LVEF = LV ejection fraction.

Table 3. LV Ejection fraction with Systolic myocardial Strain _Ecc (%) and Systolic Strain rate_SR$_S$ (1/s)_Regression Coefficients for LVEF

	Model 1‡	Model 2§
3a_Systolic myocardial Strain_Ecc (%)		
Anterior	−0.087 (−0.124, −0.051)†	−0.081 (−0.119, −0.043)†
Lateral	−0.044 (0.080, −0.009)*	−0.042 (−0.08, −0.004)*
Inferior	−0.153 (−0.192, −0.113)†	−0.153 (−0.195, −0.112)†
Septal	−0.133 (−0.166, −0.099)†	−0.11 (−0.145, −0.076)†
3b_Systolic Strain rate_ SR$_S$ (1/s)		
Anterior	−0.009(−0.015, −0.003)*	−0.004 (−0.01, 0.002)
Lateral	−0.011 (−0.019,−0.004)*	−0.006 (−0.012, −0.0001)*
Inferior	−0.015 (−0.022,−0.008)†	−0.012 (−0.019, −0.005) *
Septal	−0.011(−0.020, −0.003)*	−0.008 (−0.014, −0.002)*

Regression coefficients (95% confidence interval) represent difference in strain Ecc (3a) and systolic strain rate (3b) per 1% increase in ejection fraction.
*$p < 0.05$, $^\dagger p < 0.001$.
‡Age, gender, BMI, systolic and diastolic BP were included in the multiple linear regression models as covariates (Model 1).
§Left ventricular end–diastolic mass, heart rate, race, and use of medicine to control hypertension were included (Model 2).

Load dependence of regional LV function

Previous experimental studies have investigated in detail the load dependence of currently used indices of global and regional left ventricular function (13, 16, 17). However, most studies available demonstrated enhancement of peak systolic strains with acute changes in volume and higher LV filling pressures (13, 16). Other experimental models showed that while indices based on the speed of myocardial contraction like LV dp/dt are highly dependent on pre-load (18) and that those based on myocardial displacement or deformation are highly after-load dependent (19).

On the other hand, compared to normal subjects, patients with idiopathic dilated cardiomyopathy were found to have markedly reduced fiber shortening strain (20). Moreover, fiber shortening has been shown to be decreased in individuals with normal global LV function and LV hypertrophy (21). Our results supported those findings by demonstrating the association of systolic myocardial strain rate on the LV end-diastolic volume in a population of asymptomatic men and women without history of previous heart disease. While the magnitude of myocardial strain is roughly unassociated with pre-load (except in the inferior wall) in Model 1, interestingly, after adjustments for variables such as current blood pressure levels, LV mass (index of chronic hypertension) and anti-hypertensive medication use, we found a positive relationship between LV end-diastolic volume and circumferential strain in the anterior and septal walls of the

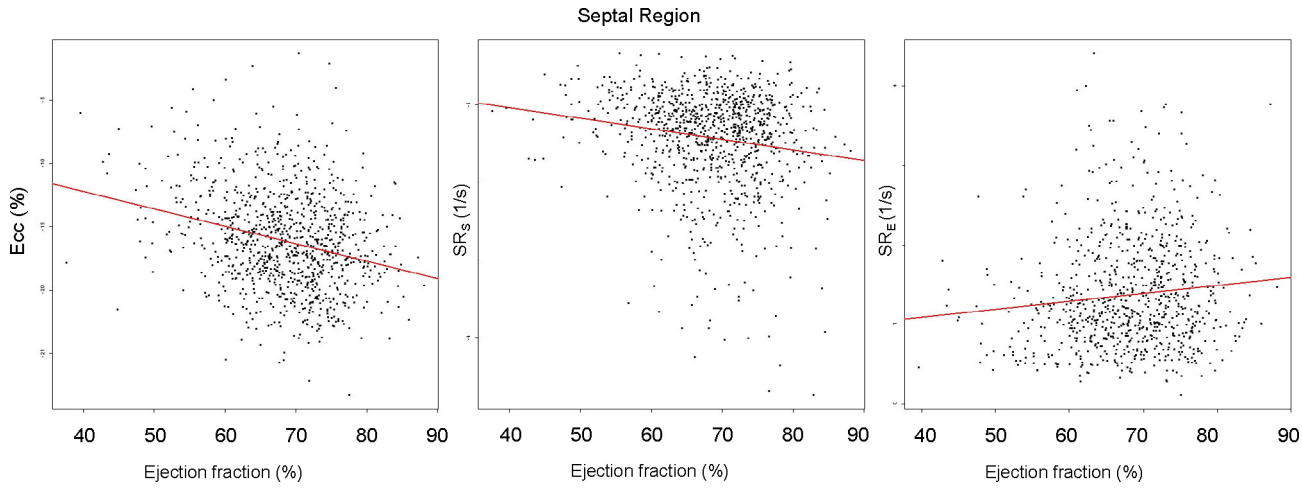

Figure 5. Plot of regional myocardial function (Ecc, SR_S, SR_E) if setal region versus left ventricular ejection fraction. The regression lines are based on data from all 1100 subjects.

LV. Experimentally, diastolic strain augments with preload at low levels of afterload but decreases with preload at high levels of afterload (16). However, the differences in the direction of the association between LVEDV and regional strain could in part result from chance and/or multiple statistical testing.

While the systolic relationships between EF and peak circumferential strain were not surprising, the direct relationships with both systolic and most importantly diastolic strain had not been documented previously in a human population. These relationships were of great importance given the common use of ejection fraction and diastolic strain rate as indices of LV function. In addition, the relationships with ejection fraction are important to explain those found between LV end-systolic volume and segmental indices of myocardial mechanics based on myocardial deformation in the circumferential orientation. The LV end-systolic volume is a hybrid index that incorporates the combined influences of LV end-diastolic volume and that of global systolic function. It has been used in the past to assess LV remodeling (22) and other morbid LV processes such as aortic regurgitation (23) given its accuracy for myocardial failure associated with specific cardiac pathologies. Our results suggest that end-systolic volume behaves as a functional index in relation to the magnitude of circumferential strain (inversely related to systolic myocardial strain like LV ejection fraction) and as a pre-load index (such as the end-diastolic volume) relative to systolic strain rate. These relationships are very important as myocardial strain indices become part of the clinical cardiologist's armamentarium in the assessment of cardiac disease.

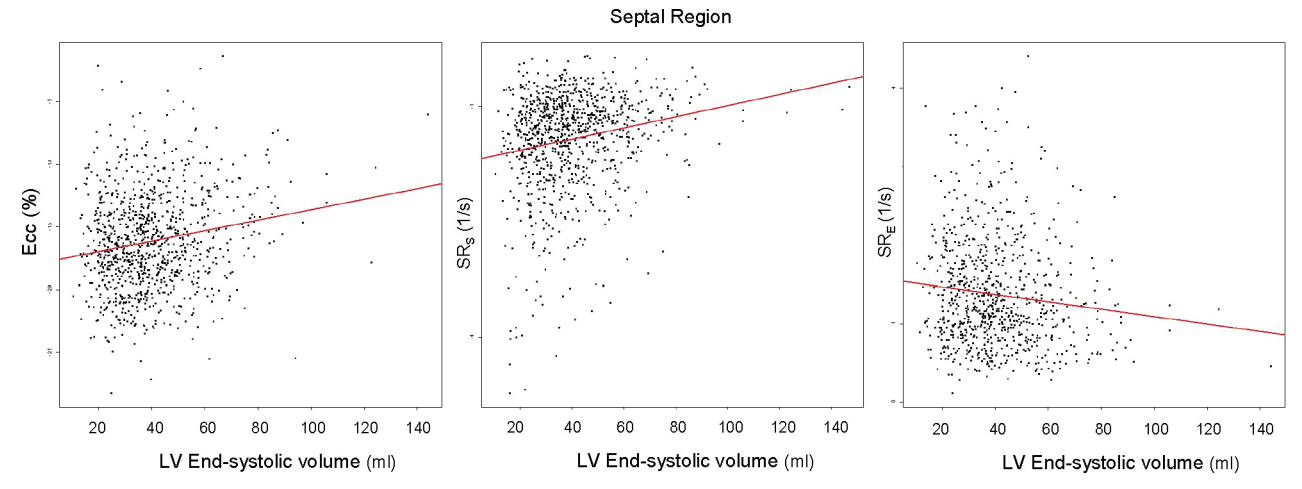

Figure 6. Plot of regional myocardial function (Ecc, SR_S, SR_E) of setal region versus left ventricular end-systolic volume. The regression lines are based on data from all 1100 subjects.

Table 4. LV End−systolic volume with Systolic myocardial Strain _Ecc (%) and Systolic Strain rate_SR_S(1/s)_ Regression Coefficients for LVESV

	Model 1‡	Model 2§
4a_Systolic myocardial Strain_Ecc (%)		
Anterior	0.014 (−0.003, 0.031)	0.008 (−0.013, 0.030)
Lateral	0.019 (0.04, 0.034)*	0.022 (0.001, 0.043)*
Inferior	0.058 (0.039, 0.076)†	0.070 (0.044, 0.091)†
Septal	0.040 (0.024, 0.056)†	0.028 (0.009, 0.050)*
4b_Systolic Strain rate_SR_S (1/s)		
Anterior	0.007 (0.004, 0.010)†	0.004 (0.001, 0.007)*
Lateral	0.008 (0.004,0.011)†	0.005 (0.002, 0.009)*
Inferior	0.008 (0.004, 0.0111)†	0.008 (0.004, 0.012)†
Septal	0.004 (0.0001, 0.008)*	0.005 (0.002, 0.009)*

Regression coefficients (95% confidence interval) represent difference in strain Ecc (4a) and systolic strain rate (4b) per 1ml increase in ESV.
*$p < 0.05$, †$p < 0.001$.
‡Age, gender, BMI, systolic and diastolic BP were included in the multiple linear regression models as covariates (Model 1)
§Left ventricular end–diastolic mass, heart rate, race and use of medicine to control hypertension were included (Model 2).

Clinical studies utilizing strain and strain rate measured by CMR tagging and Doppler-echocardiography

The seminal studies which described myocardial deformation in experimental animals (24–26) have been translated to clinical application through the utilization of CMR with tissue tagging (27) and more recently Doppler-echocardiography (28–31). Myocardial strain measurements by echocardiography have been validated against sonomicrometers (13) and CMR tissue tagging (6), considered the gold-standard non-invasive technique because of its independence relative to the orientation of measured strains. Very recently, these techniques have been applied to the study of LV function in experimental (26) and different population studies (8, 21, 26, 32–36). These observations underscore the importance of this work that establishes first hand the relationships between global indices of LV function and local myocardial strain and strain rate, in an asymptomatic population free of cardiovascular symptoms.

Table 5. LV End–diastolic volume with Systolic myocardial Strain Ecc (%) and Systolic Strain Rate SR_S (1/s)_Regression Coefficients for LVEDV

	Model 1‡	Model 2§
5a_Systolic myocardial Strain_Ecc (%)		
Anterior	−0.009 (−0.019, −0.001)*	−0.023 (−0.036, −0.012)†
Lateral	0.0014 (−0.007, 0.010)	0.001 (−0.011, 0.013)
Inferior	0.01 (0.0002,0.020) *	−0.0004 (−0.014, 0.013)
Septal	−0.018 (−0.010, 0.006)	−0.020 (−0.03, −0.008)†
5b_Systolic Strain rate_SR_S(1/s)		
Anterior	0.003 (0.002, 0.005)†	0.002 (0.001, 0.005)*
Lateral	0.003 (0.002, 0.005)†	0.003 (0.001, 0.005)*
Inferior	0.002 (0.001, 0.005)*	0.003 (0.001, 0.005) *
Septal	0003 (0.002, 0.005)†	−0.003 (−0.004, 0.004)

Regression coefficients (95% confidence interval) represent difference in strain Ecc (5a) and systolic strain rate (5b) per 1 ml increase in EDV.
*$p < 0.05$, †$p < 0.001$.
‡Age, gender, BMI, systolic and diastolic BP were included in the multiple linear regression models as covariates (Model 1).
§Left ventricular end–diastolic mass, heart rate, race, and use of medicine to control hypertension were included (Model 2).

CMR measurements of global LV volume and LV mass

In the MESA study, global LV size, structure and function was assessed by untagged CMR (7, 37), and a subset of the MESA cohort also underwent myocardial tissue tagging to study myocardial performance in relation to sub-clinical atherosclerosis (33) and LV hypertrophy (21) among several other sub-clinical conditions. The present study demonstrated fundamental relationships of LV size and global function with regional indices of myocardial contraction and relaxation in asymptomatic individuals without history of previous heart disease.

Compensatory or non-compensatory changes occurs in the heart itself, which include ventricular enlargement, alterations in the shape and structure on the whole organ, cell slippage and reorientation, hypertrophy of individuals myocytes, and modification of the intracellular matrix (e.g., fibrosis). The enlargement could be progressive or immediate. An important question is whether damage to the myocardium (loss of contractile function) causes compensatory ventricular enlargement in both the damaged area and the normal tissue, or whether enlargement of the heart as a consequence of the initial damage is the principal determinant of subsequent reduced function. In the context of acute myocardial infarction, there has been evidence supporting both theories. Ventricular enlargement developed before the onset of overt heart failure in the patients studied by Vasan et al., even in those subjects without prior myocardial infarctions (38). However, reduced function may have been the consequence of repeated subclinical events or an increased rate of loss of myocardial cells. The resultant myocardial damage could lead to cardiac enlargement and systolic dysfunction, which has been thought to be related to contractile failure and could be a consequence of a structural increase in ventricular chamber volume, with a more anatomic basis for heart failure. Chamber dilation occurs as an early response that results in the reduced wall motion that is mandated to generate a normal stroke volume from a large ventricular end-diastolic volume (39, 40). Studies in echocardiography have shown that circumferential (midwall) shortening contribute to the magnitude of the LV ejection fraction, and EF is indeed the result of the shortening of differently oriented myocardial fibers across the wall thickness (41). Ejection fraction has been shown already to be related to midwall shortening. Rademarkers et al. (42) evaluated the impact of myocardial infarct over time analyzing 16 patients after a transmural infarct with MR tagging imaging. They found a consistent inverse relationship between increased regional loading and

reduced regional EF (42), but those analysis were not controlled for LV mass.

The association between ESV and regional myocardial function (with peak Ecc and SR_S as well) can be explained by several mechanisms. Since LV systolic function and LV afterload were interrelated, meaning that higher afterload (represented by LV ESV), greater the pressure generated, but the less the amount of shortening (43). The results for EDV and systolic function were very strong when we consider SR_S, but were not so strong and homogeneous with peak Ecc, comparing to the results of ESV. The reasons for these results are uncertain. A possible explanation is that Ecc is not so sensitive to EDV alterations as ESV is, since is well know that ESV (afterload) is more related to global function than preload (EDV), and the anterior and septal wall presented different results (more volume better function) after adjustments, because the association was controlled for afterload parameters (blood pressure and LV mass). These results agree in part with the results from De Simone et al. that show that midwall shortening in the normotensive subjects remained unrelated to the end-diastolic volume even after the effect of the end-systolic stress had been removed (44).

Indeed, the increase in LV size and resultant change in LV geometry from the normal prolate ellipse to a more spherical shape creates several mechanical burdens for the failing heart.

Methodologic limitations

The present study represents a cross sectional analysis of a multi-ethnic population. Consequently, we cannot imply causality by describing relationships between EF and LVESV and regional myocardial alterations. Loading conditions could not been changed during the MR study, so each study reflected one loading condition per individual. Further prospective studies should be performed, and longitudinal inferences await confirmation from such future observations. Diastolic results were not so strongly associated with EF and LV volumes; part of these results could be attributed to difficulties in analyzing diastolic strain rate due to the lower temporal resolution of MR relative to the speed of diastolic relaxation. CMR tagging studies have lower temporal resolution than studies by Doppler. All our efforts therefore were made to provide reliable data, so the best SR_E curves were analyzed, although some had to be excluded due to tag fading. Due to the design of the MESA, only individuals asymptomatic for CV disease were enrolled. Therefore, it would be difficult to extrapolate these results to people with symptoms of CAD or heart failure.

Clinical implications

Our findings underscore the need to reconsider the concept of what is 'normal' myocardial function in a population free of cardiovascular symptoms.

As far as we know, this was the first study that shows the ability of CMR tagged derived Ecc and strain rate to index LV ejection fraction and as a sensitive method for detecting alterations in global LV functional abnormalities in a large population free of cardiovascular symptoms.

The relationship between diastolic strain rate and LV volumes show less dependence of diastolic indices to differences in LV volumes and EF in the unadjusted model. It is not inconceivable that the objectivity and accuracy of strain and strain rate measurements will position these indices as the preferred methods to assess LV function clinically in the future.

CONCLUSIONS

This study demonstrates for the first time in a large group of asymptomatic individuals that measures of regional myocardial function, especially systolic strain rate, are sensitive to cardiac LV end systolic and end diastolic volumes, as well as to global LV function. The results also reveal the potential of tagged CMR of evaluating regional LV function, showing that it can be a sensitive method for detecting subtle alterations in regional function.

ABBREVIATIONS

CHF = Congestive heart failure
Ecc = Circumferential shortening strain
LV = Left ventricular
MESA = Multi-Ethnic Study of Atherosclerosis
CMR = Cardiovascular magnetic resonance
HARP = Harmonic phase
SR_S = early diastolic strain rate
SR_E = peak systolic strain rate

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