Interstitial Fibrosis, Left Ventricular Remodeling, and Myocardial Mechanical Behavior in a Population-Based Multiethnic Cohort
The Multi-Ethnic Study of Atherosclerosis (MESA) Study

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Background—Tagged cardiac magnetic resonance provides detailed information on regional myocardial function and mechanical behavior. T1 mapping by cardiac magnetic resonance allows noninvasive quantification of myocardial extracellular expansion (ECE), which has been related to interstitial fibrosis in previous clinical and subclinical studies. We assessed sex-associated differences in the relation of ECE to left ventricular (LV) remodeling and myocardial systolic and diastolic deformation in a large community-based multiethnic population.

Methods and Results—Midventricular midwall peak circumferential shortening and early diastolic strain rate and LV torsion and torsional recoil rate were determined using cardiac magnetic resonance tagging. Midventricular short-axis T1 maps were acquired in the same examination pre- and postcontrast injection using Modified Look-Locker Inversion-Recovery sequence. Multivariable linear regression (estimated regression coefficient, B) was used to adjust for risk factors and subclinical disease measures. Of 1230 participants, 114 had a visible myocardial scar by late gadolinium enhancement. Participants without a visible myocardial scar (n=1116) had no history of previous clinical events. In the latter group, multivariable linear regression demonstrated that lower postcontrast T1 times, reflecting greater ECE, were associated with lower circumferential shortening (B=-0.1; P=0.0001), lower LV end-diastolic volume index (B=0.6; P=0.0001), and lower LV end-diastolic mass index (B=0.4; P=0.0001). In addition, lower postcontrast T1 times were associated with lower early diastolic strain rate (B=0.01; P=0.03) in women only and lower LV torsion (B=0.005; P=0.03) and lower LV ejection fraction (B=0.2, P=0.01) in men only.

Conclusions—Greater ECE is associated with reduced LV end-diastolic volume index and LV end-diastolic mass index in a large multiethnic population without history of previous cardiovascular events. In addition, greater ECE is associated with reduced circumferential shortening, lower early diastolic strain rate, and a preserved ejection fraction in women, whereas in men, greater ECE is associated with greater LV dysfunction manifested as reduced circumferential shortening, reduced LV torsion, and reduced ejection fraction. (Circ Cardiovasc Imaging. 2014;7:292-302.)

Key Word: circumferential strain ■ expressed sequence tags ■ interstitial myocardial fibrosis ■ tagging ■ LV torsion ■ T1 mapping

Cardiac remodeling refers to structural and functional cardiac alterations in response to pathogenic processes and cardiovascular risk factors.1 Previous animal and human studies have shown that in patients with cardiomyopathies of various pathogeneses, myocardial fibrosis is associated with abnormal cardiac remodeling accompanied by increased ventricular wall stress and stiffness leading to mechanical dysfunction and symptomatic heart failure.2-4 Importantly, the alterations of left ventricular (LV) structure and function associated with LV remodeling and heart failure are sex dependent5-8 and represent a major cause of morbidity and mortality in the United States.9 In this context, interstitial fibrosis is a common histological feature underlying LV remodeling and heart failure because of various disease processes.10

Clinical Perspective on p 302

Cardiovascular magnetic resonance (CMR) has emerged as a noninvasive imaging method to assess myocardial structure and function with a great level of accuracy and reproducibility.11 LV ejection fraction (LVEF) is used as a global...
measure of LV performance, but it does not take into consideration incipient alterations of myocardial contractile behavior, which are commonly seen early in several cardiovascular disorders. CMR tissue tagging provides precise quantification of incipient myocardial dysfunction through the assessment of myocardial strain and torsion. Harmonic Phase analysis of tagged magnetic resonance imaging images is currently the most widely used method for analysis of tagged images particularly in population studies, with good inter- and intraobserver agreement.

The evaluation of fibrosis by magnetic resonance imaging is best assessed after injection of gadolinium contrast agents that are used to reduce the T1 relaxation time of myocardial tissue, generating specific differences of regional signal intensity. In the absence of confounding conditions, such as myocardial edema, because of inflammation or amyloidosis, myocardial extracellular expansion (ECE) results from accumulation of excess collagen in the interstitium. Although late gadolinium-enhanced (LGE) CMR allows for the assessment of macroscopic replacement myocardial fibrosis, it is limited for the evaluation of diffuse interstitial fibrosis.

T1 myocardial mapping using the Modified Look-Locker Inversion Recovery (MOLLI) sequence with high spatial resolution enables direct myocardial signal quantification, characterization of myocardial tissue composition, and assessment of interstitial fibrosis with good reproducibility. Altered T1 values have been shown to be associated with diffuse myocardial fibrosis in ischemic and nonischemic cardiomyopathies. These gadolinium contrast-based changes in myocardial T1 times correlate with histological evidence of fibrosis even in the absence of a CMR LGE-defined scar.

However, it is not clear how ECE relates to LV remodeling and affects myocardial mechanical behavior and cardiac performance among individuals without a history of previous cardiovascular events. No studies have yet been performed to determine the relationship between interstitial myocardial fibrosis measured by T1 myocardial mapping and myocardial systolic and diastolic function in a large population study using contrast-enhanced CMR and myocardial tagging. In the current study, we aim to determine the relationship between interstitial myocardial fibrosis and deformation relative to LV remodeling in a large multiethnic cohort. We also aim to determine whether sex-associated alterations in LV structure and function parallel sex-related differences in interstitial myocardial fibrosis in a multiethnic population free of heart disease.

**Methods**

**Study Population**

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective, population-based, epidemiological study started in 2000 to investigate the prevalence and progression of subclinical cardiovascular disease in a multiethnic cohort (white, black, Hispanic, and Chinese). The study protocol was approved by the Institutional Review Board of participating institutions. The characteristics of subjects enrolled in MESA have been described previously. In this ancillary study, after obtaining informed consent, 1230 participants had simultaneous CMR imaging and included in LV end-diastolic volume calculations. Papillary muscles were excluded from LV mass calculations and included in LV end-diastolic volume calculations.

**CMR Imaging**

Cardiac magnetic resonance imaging were obtained with 1.5 T MR Systems (Avanto; Siemens Medical Solutions, Erlangen, Germany). Intravenous infusion of gadolinium contrast (gadopentate dimeglumine; Bayer Healthcare Pharmaceuticals, Whippany, NJ) was performed at 0.15 mmol/kg bolus dose. After acquisition of standard scout image, 2- and 4-chamber cine images were acquired. Short-axis cine images were then obtained with retrospective gating from above the mitral valve plane to the LV apex. Fifteen-minute gadolinium enhancement imaging was acquired in 3 long-axis slices and a stack of short-axis slices using a gradient recalled echo phase-sensitive inversion-recovery sequence. LV structural measures (LV mass and volumes) and LVEF were measured using commercially available software (CIM version 6.2; Auckland, New Zealand). MV mass and LV end-diastolic volumes were indexed to body surface area (LVMi and LVEDVi). Papillary muscles were excluded from LV mass calculations.

**T1 Mapping**

In T1 myocardial mapping, after a preparation pulse sequence, signal recovery from each voxel is sampled during multiple measurements. The associated T1 relaxation time is calculated for each pixel, and a parametric image is reconstructed, which is referred to as the T1 map. Standard 4-chamber long-axis and midcavity short-axis section orientations were used for MOLLI T1 mapping. The MOLLI single slice T1 determinations were performed before contrast and 12 and 25 minutes after contrast injection using 3 inversion-recovery pulses. We acquired a set of 11 consecutive source images at midventricle within 1 breath hold (17 heart beats), allowing for the reconstruction of 1 parametric T1 map. All source images have identical voxel sizes, image position, and phase of cardiac cycle except for different effective inversion times (TI). Scan parameters for MOLLI were: field of view 360x360 mm², flip angle 35°, repetition time 3.9 ms, echo time 1.95 ms, matrix size 256x192, and slice thickness 8 mm.

MOLLI data were processed offline using the MASS research software (MASS V2010-EXP; Leiden University Medical Center, Leiden, The Netherlands) with Levenberg–Marquardt fitting algorithm. Left ventricular endocardial and epicardial borders were traced semiautomatically on all phases in each sequence to extract the mean T1 values. Care was taken to exclude epicardial structures and blood pool from contours. Intra- and inter-reader agreement of myocardial T1 times was excellent, with intraclass correlation coefficient ranging from 0.98 to 0.99. Precontrast T1 times were negatively correlated with 12- and 25-minute postcontrast T1 times (r=-0.084 and -0.055; P<0.05, respectively), whereas 12-minute postcontrast T1 time was significantly correlated with 25-minute postcontrast T1 time (r=0.905; P<0.05).

**CMR Tagging**

Tagged images were acquired using a segmented k-space; ECG gated fast low angle shot pulse sequence. Three tagged short-axis slices were obtained (base to apex) with 2 orthogonally oriented parallel striped tags (0° and 90°) using spatial modulation of magnetization. Parameters for tagged images were field of view 360x360 mm², slice thickness 10 mm, echo time 2.5 ms, flip angle 10°, matrix size 256x128, 9 phase encoding views per segment, spatial resolution 1.4x2.8x10 mm³, temporal resolution 25 ms, tag spacing 7 mm. Tagged short-axis slices were analyzed by Harmonic Phase software (Diagnosoft, Palo Alto, CA). Average peak midventricular mid-wall circumferential shortening (Ecc, %) and early diastolic strain rate (EDSR, s) LV torsion (with and without adjusting for epicardial radius), torsional recoil rate (TRR /cm per millisecond), and LV torsion–endocardial circumferential shortening ratio (TSR) were determined. Ecc is a negative number, and more negative values indicate greater circumferential shortening. Average peak Ecc was calculated by averaging the corresponding midventricular peak segmental strain values from the 6 segments of the AHA 16-segment model. LV torsion (rad) was defined as defined by Rüssel et al (q-axxx-apex–q-basexx-base)/distance between apical and basal
slices), where \( \phi \) is rotation and \( r \) is radius. Intra- and interobserver reproducibility of Ecc and LV torsion was excellent with an intraclass correlation coefficient ranging from 0.8 to 0.9.24

**Statistical Analysis**

All continuous variables are presented as mean±SD and categorical variables as frequencies and percentages. Comparisons between the participants with and without visible scar were performed using \( t \) tests and \( \chi^2 \) tests for continuous variables and categorical variables, respectively. Multivariable linear regression analyses (estimated regression coefficient, \( B \)) were performed to evaluate the effect of covariates, including demographic and traditional risk factors. Extracellular matrix expansion was assessed using pre- and postcontrast times (12 and 25 minutes) separately as independent variables. Model 1 reflected (univariate) unadjusted relations of myocardial fibrosis to measures of LV structure (LV mass, LV end-diastolic volume) and function (LVEF, Ecc, EDSSR, LV torsion, TTR, and TSR). Model 2 was adjusted for age, sex, ethnicity, body surface area, heart rate, glomerular filtration rate, systolic and diastolic blood pressure, antihypertensive medication use, history of diabetes mellitus, and current smoking status. Model 3 was adjusted for LV mass and end-diastolic volume in addition to model 2 covariates. Eight participants had missing covariates data. Because of the design of study, the missing covariates were assumed to be missing completely at random. These missing participants were excluded for the models. The associations of postcontrast T1 measures with lower circumferential shortening (greater ECE) were associated with lower circumferential shortening but without any change in LVEF in univariate regression analyses. Moreover, lower postcontrast T1 times were associated with both lower LVEDVi and LVMi (\( B=−0.111; \) SE, 0.02; \( P<0.05 \))) compared with the group without a visible scar. There were no significant differences in heart rate and systolic or diastolic blood pressure between the 2 groups. A higher percentage of participants in the group with a visible scar had a history of diabetes mellitus (20.9% versus 13.8%; \( P=0.001 \))) and were current smokers (13.2% versus 6.8%; \( P=0.01 \))) when compared with the group without an LGE-defined scar.

**LV Structure and Function in Participants Without an LGE-Defined Myocardial Scar**

In participants without an LGE-defined myocardial scar (n=1116), lower 12- and 25-minute postcontrast T1 times (greater ECE) were associated with lower circumferential shortening but without any change in LVEF in univariate regression analyses. Moreover, lower postcontrast T1 times were associated with both lower LVEDVi and LVMi (Table 2). After adjustment for traditional cardiovascular risk factors, the associations of lower postcontrast T1 times were significant with lower circumferential shortening (\( B=−0.111; \) SE, 0.02; \( P<0.001 \))), lower LVEF (\( B=0.135; \) SE, 0.05; \( P<0.05 \))), lower LVEDVi (\( B=0.623; \) SE, 0.09; \( P<0.05 \))), and LVMi (\( B=0.496; \) SE, 0.07; \( P<0.05 \); Table 2). Moreover, the associations of postcontrast T1 measures with lower circumferential shortening persisted even after adjustment for measures of LV remodeling, such as LV end-diastolic mass.
and volume. However, postcontrast T1 times were associated with an unaltered LV TSR in all the models ($P=0.0001$).

Figure 2 demonstrates the T1 mapping results and corresponding CMR tagging images with no evidence of ECE and normal circumferential strain reflected by more negative Ecc. Conversely, Figure 3 demonstrates a similar data set from a participant with a shorter postcontrast T1 time indicating greater ECE, in the absence of an LGE-defined myocardial scar and less negative Ecc indicating lower levels of systolic myocardial deformation.

The relationships for precontrast T1 times were, however, different than those found for postcontrast T1 times. Greater precontrast T1 time was associated with greater as opposed to lesser circumferential shortening (Table I in the Data Supplement). After adjustment for traditional cardiovascular risk factors, precontrast T1 associations remained significant for greater circumferential shortening ($B=0.082$; $SE=0.02; P=0.0001$). LVEF, LVMi, and LVEDVi were unrelated to precontrast T1 times after adjustment for traditional cardiovascular risk factors. The associations of greater precontrast T1 times with greater Ecc ($B=−0.074; SE=0.01; P<0.001$) persisted after adjusting for LV end-diastolic mass and volume.

### Sex-Specific Changes in LV Structure and Function in Participants Without an LGE-Defined Myocardial Scar

In participants without an LGE-defined myocardial scar, compared with men, women had greater LVEF (64.1±6.2 versus 60.1±5.6 in men; $P=0.0001$), greater circumferential shortening (−16.06±3.2 versus −15.04±3.1 in men; $P=0.0001$), higher diastolic function (0.11±0.04 versus 0.09±0.03 in men; $P=0.0001$), greater LV torsion (4.6±1.2 versus 3.8±1.1 in men; $P=0.0001$), greater LV torsion (rad) adjusted for epicardial radius (9.1±1.9 versus 8.3±2.1 in men; $P=0.0001$), greater TRR (−25.1±9.2 versus −21.1±7.9 in men; $P=0.0001$), greater TSR (0.57±0.17 versus −0.54±0.15 in men; $P=0.003$), lower LVMi (58.1±8.6 versus 72.1±11.1 in men; $P=0.0001$), and lower LVEDVi (62.2±10.7 versus 68.8±13.8 in men; $P=0.0001$).

Multivariable analyses demonstrated sex-specific differences in the associations between indices of ECE and measures of myocardial deformation among MESA participants without clinical events or visible myocardial scars (Table 3). In men, lower 12- and 25-minute postcontrast T1 times (greater ECE) were associated with lower circumferential shortening ($B=−0.08; SE=0.03; P<0.05$), lower LV torsion (rad) ($B=0.005; SE=0.002; P<0.05$), and lower LVEF ($B=−0.248; SE=0.004; P<0.05$) after adjustment for traditional risk factors. In women, lower 12- and 25-minute postcontrast T1 times were associated with lower circumferential shortening ($B=−0.132; SE=0.03; P<0.05$) and lower EDSR ($B=−0.009; SE=0.004; P<0.05$), but LVEF remained unchanged after adjustment for traditional risk factors (Figure 4). Without adjustment for epicardial radius, lower postcontrast T1 times were associated with increased LV torsion in women ($B=−0.002; SE=0.001; P<0.05$ in model 2), whereas they were unchanged in men. Also, lower postcontrast T1 times were associated with lower LVEDVi and LVMi in both men and women. Moreover, after further adjustment for LV end-diastolic mass and volume, the associations of lower 12- and 25-minute postcontrast T1 times remained significant for lower circumferential shortening in both men and women. In addition, lower postcontrast T1 time was associated with lower EDSR in women and lower LV torsion (rad) in men. However, there was no significant association between TSR and postcontrast T1 times ($B=−0.0007; P=0.248$; $SE=0.002$; $P=0.05$ for men and women, respectively, in model 3).

Greater precontrast T1 time, however, was associated with greater circumferential shortening in women only ($B=−0.105; SE=0.02; P<0.05$; Table II in the Data Supplement). The associations of higher precontrast T1 time with greater circumferential strain in women remained significant after adjustment for measures of LV remodeling, including LV end-diastolic mass and end-diastolic volume.

### Myocardial Fibrosis and Deformation in MESA Participants With a Visible LGE-Defined Replacement Scar

Participants with a visible scar had higher LVMi (78.2 versus 64.8 g/m²; $P=0.0001$) and LVEDVi (70 versus 65.4 mL/
m²; P=0.01) and significantly lower EF (56.8 versus 62.2%; P=0.0001) when compared with the group with no visible myocardial scar (Table 1). Also, they had higher precontrast T1 times (985.5 versus 975.8 ms; P=0.01) and lower 12-minute (444.2 versus 454.6 ms; P=0.008) and 25-minute (508.4 versus 518.3 ms; P=0.01) postcontrast T1 and less myocardial

Table 2. Association of Postcontrast T1 Times With LV Structural and Functional Measures in Participants Without a Late Gadolinium-Enhanced Scar

<table>
<thead>
<tr>
<th>Measure</th>
<th>12 Min R²</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>25 Min R²</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecc</td>
<td>0.27</td>
<td>-0.082  (0.02)*</td>
<td>-0.111 (0.02)*</td>
<td>-0.101 (0.02)*</td>
<td>0.28</td>
<td>-0.095 (0.02)*</td>
<td>-0.122 (0.02)*</td>
<td>-0.125 (0.02)*</td>
</tr>
<tr>
<td>EDSR</td>
<td>0.13</td>
<td>0.004   (0.003)</td>
<td>0.006 (0.003)†</td>
<td>0.007 (0.003)*</td>
<td>0.13</td>
<td>0.003 (0.003)</td>
<td>-0.003 (0.003)</td>
<td>0.004 (0.003)</td>
</tr>
<tr>
<td>Torsion</td>
<td>0.12</td>
<td>-0.001  (0.001)</td>
<td>0.001 (0.001)</td>
<td>0.002 (0.001)</td>
<td>0.11</td>
<td>-0.001 (0.001)</td>
<td>0.001 (0.001)</td>
<td>0.002 (0.001)</td>
</tr>
<tr>
<td>TRR</td>
<td>0.11</td>
<td>-0.032  (0.06)</td>
<td>-0.101 (0.07)</td>
<td>-0.151 (0.07)*</td>
<td>0.11</td>
<td>-0.006 (0.06)</td>
<td>-0.066 (0.07)</td>
<td>-0.113 (0.07)</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.12</td>
<td>-0.007  (0.04)</td>
<td>0.135 (0.05)†</td>
<td>...</td>
<td>0.12</td>
<td>-0.037 (0.04)</td>
<td>0.094 (0.05)†</td>
<td>...</td>
</tr>
<tr>
<td>LV EDVi</td>
<td>0.22</td>
<td>0.813   (0.09)*</td>
<td>0.623 (0.09)*</td>
<td>...</td>
<td>0.21</td>
<td>0.748 (0.09)*</td>
<td>0.512 (0.09)*</td>
<td>...</td>
</tr>
<tr>
<td>LVMi</td>
<td>0.48</td>
<td>0.993   (0.08)*</td>
<td>0.496 (0.07)*</td>
<td>...</td>
<td>0.48</td>
<td>0.997 (0.08)*</td>
<td>0.509 (0.07)*</td>
<td>...</td>
</tr>
</tbody>
</table>

Estimated regression coefficient (SE in parenthesis). The coefficient represents the change in LV measures per 10 ms change in postcontrast T1 time, with adjustments for multiple variables. BSA indicates body surface area; DBP, diastolic blood pressure; Ecc, circumferential strain; EDSR, early diastolic strain rate; GFR, glomerular filtration rate; LVEDVi, LV end-diastolic volume index; LVEF, LV ejection fraction; LVMi, LV mass index; SBP, systolic blood pressure; and TRR, torsional recoil rate.

Model 1: unadjusted.
Model 2: adjusted for age, sex, race, BSA, GFR, heart rate, SBP, DBP, antihypertensive medication use, history of diabetes mellitus, smoking status.
Model 3: adjusted for age, sex, race, BSA, GFR, heart rate, SBP, DBP, antihypertensive medication use, history of diabetes mellitus, smoking status, LV end-diatostic mass and volume.

For model 2 if model 3 is not available.

*P<0.001, †P<0.05, ‡P=0.06.

Figure 2. Delayed gadolinium-enhanced image (LGE), T1 mapping parametric image, and corresponding cardiovascular magnetic resonance tagging strain curve from a participant without an LGE-defined myocardial scar and no evidence of extracellular expansion. A normal circumferential strain is reflected by more negative circumferential strain (Ecc).

T1 mapping image analysis provided the post contrast T1 times of 57.4 ms and 61.2 ms at 12 and 25 minutes post contrast respectively.

Tagging analysis yields an average mid-ventricular mid wall peak Ecc of -21.2 %. LV Ejection fraction: 60%
deformation as measured by lower circumferential shortening (−13.6% versus −15.5%; \( P = 0.0001 \)) when compared with participants without a visible myocardial scar. In addition, they had lower diastolic function as measured by lower EDSR (0.86 versus 1.04 s\(^{-1} \); \( P = 0.0003 \)) and TRR (−20.1 versus −23.2 °/cm per second; \( P = 0.03 \)) and higher TSR (−0.65±0.19 versus −0.56±0.16) when compared with participants without a visible myocardial scar.

Moreover, among participants with an LGE-defined visible scar, greater ECE indexed as lower 12-minute postcontrast T1 was associated with lower circumferential shortening (Figure 5) and lower LVEF (\( B = −0.011 \) and 0.04; SE, 0.008 and 0.02, respectively; \( P < 0.05 \)). Greater ECE indexed as shorter 12- and 25-minute postcontrast T1 times were also associated with lower LVMI (\( B = 0.085 \) and 0.086; SE, 0.03 and 0.03, respectively; \( P < 0.05 \)) in an unadjusted univariate analysis (given relatively small sample size). Greater precontrast T1 time was associated with lower EF (\( B = −0.77 \); \( P < 0.05 \)).

**Discussion**

This study demonstrates marked fibrosis-associated differences in LV remodeling in a large, multiethnic population cohort. We found that a greater degree of myocardial ECE as measured by postcontrast T1 time was associated with reduced circumferential shortening, reduced LV torsion (rad), and reduced EF in MESA participants without an LGE-defined scar. Furthermore, in this population, increasing ECE was associated with a marked decrease in LV mass and end-diastolic volume. The association of ECE with altered myocardial deformation indices persisted after adjustment for traditional cardiovascular risk factors and measures of LV remodeling, such as LV mass and LV end-diastolic volume.

An explanation for the decrease in LV mass in association with ECE is offered by animal and human histomorphometric studies, which have demonstrated an age-related increase in the number of collagen fibers and a decrease in the absolute number of myocytes despite concomitant hypertrophy of the remaining myocytes.\(^ {25–27} \) In MESA participants, because there were no identified confounding conditions, such as myocardial edema or amyloidosis, myocardial ECE seems to result from the accumulation of excess collagen fibers in the interstitium.\(^ {28} \) The increased myocardial collagen deposition associated with decreased LVMI may contribute to reduced LVEDVi and impaired myocardial contractility. The accumulation of fibrotic tissue may influence LV systolic performance in 2 ways. First, cardiomyocyte apoptosis results in a decreased number of myocytes, leading to impaired systolic contraction; second, cardiomyocyte hypertrophy results in altered calcium metabolism, leading to LV dysfunction.\(^ {29} \)
With greater fibrosis, both men and women have lower circumferential shortening, whereas lower EDSR was noted only in women and lower LV torsion (rad) and lower EF was noted only in men. Therefore, sex differences seem to exist in the cardiac adaptation to ECE, with men developing greater global LV dysfunction than women even though the circumferential shortening was lower in both sexes. Such differences could be related to differences in LV architecture, neurohumoral factors, and exposure to cardiovascular risk factors, the latter developing at an earlier age in men. Previous studies have demonstrated sex differences in cardiac remodeling with women having higher LV torsion than men. Reduced circumferential shortening and differences in cardiac remodeling with women having higher LV preservation of LVEF.32

With greater ECE, greater diastolic dysfunction as measured by lower EDSR with a preserved EF was noted in women only. Previous studies have demonstrated that female sex is a dominant risk factor for the development of heart failure with preserved EF.31 Heart failure with preserved EF is a result of alterations in ventricular–vascular coupling, leading to diastolic and systolic dysfunction. The accumulation of excess collagen affects the viscoelasticity of myocardium, compromising the cardiac muscle fiber shortening and, during diastole, limiting torsional recoil and ventricular suction. Furthermore, the presence of myofibroblasts may have an additional effect on contractile tonus, thus aggravating diastolic dysfunction.34 In univariate analyses, greater ECE was associated with greater TRR, whereas in multivariate analysis, the relationship between greater ECE and TRR lost statistical significance. Previous smaller clinical investigations have demonstrated similar findings of unchanged TRR in patients with diabetes mellitus with diastolic dysfunction and normal EF.35

In our study, increased ECE was associated with an unaltered TSR. Aging is associated with increased interstitial...
myocardial fibrosis, and previous studies have suggested a predominance of subendocardial involvement. However, recent animal and human studies have shown that there is a significant increase in collagen fibers content of LV myocardium with age and that perimysial and endomysial collagen fibers increase in number and thickness, suggesting uniform myocardial involvement. This might explain the reason for unaltered TSR in association with diffuse interstitial myocardial fibrosis.

In our study, the presence of LGE-defined myocardial scar was accompanied by changes in postcontrast T1 times, suggesting that greater ECE is not detected by delayed enhancement CMR. MESA participants with an LGE-defined scar also had greater global and regional myocardial dysfunction than those without a visible myocardial scar. Previous studies have shown lower postcontrast T1 times in patients with heart failure, even in areas remote from those with delayed gadolinium enhancement. In those studies, reduced systolic performance was also detected in noninfarcted areas, suggesting the presence of diffuse interstitial myocardial fibrosis and pathological remodeling in corresponding areas. Fibrosis-associated alterations of LV structure and function in this study differed between T1 times measured before or after contrast administration. Among MESA participants without an LGE-defined myocardial scar or history of previous cardiovascular event, greater ECE as measured by lower postcontrast T1 times was associated with decreased circumferential shortening, whereas higher precontrast T1 times were associated with greater circumferential shortening. Precontrast T1 times can comprise myocardial signal from both the intra- and extracellular spaces. In healthy individuals, precontrast T1 times may reflect factors other than extracellular interstitial fibrosis. However, as the ventricle remodels in response to overt myocardial damage, precontrast T1 time may be more influenced by extracellular fibrosis as documented in previous clinical studies. Several previous studies have documented consistent correlations between postcontrast T1 times and diffuse interstitial myocardial fibrosis. In this study, T1 times measured at 12 and 25 minutes after contrast administration were more consistent indices of greater ECE.

The equilibrium contrast-CMR technique is another non-invasive method described by Flett et al. to assess diffuse myocardial fibrosis. In equilibrium contrast-CMR, a bolus of contrast administration followed by a continuous infusion to achieve equilibrium. Although equilibrium contrast-CMR has been validated against histologically derived collagen volume fraction, the technique requires continuous infusion of gadolinium contrast with longer scanning time. Using the MOLLI sequence, however, the images are obtained in a single breath-hold, and the image acquisition is, therefore, faster.

**Clinical Implications**

Gadolinium-enhanced T1 mapping techniques can detect and quantify diffuse myocardial interstitial fibrosis. The current

![Figure 4. Sex-specific differences between myocardial extracellular expansion (ECE) represented by postcontrast T1 time and LV circumferential strain (Ecc), left ventricular (LV) torsion, early diastolic strain rate (EDSR), and LV ejection fraction (EF) in the group without late gadolinium-enhanced-defined scar. Figure demonstrates that with greater ECE (shorter postcontrast T1 times), men have greater LV dysfunction manifested as decreased LV ejection fraction when compared with women, despite lower circumferential shortening in both sexes. Women have unchanged LV torsion (rad) when compared with men but have more diastolic dysfunction as measured by lower EDSR with shorter postcontrast T1 times. All these relationships are statistically significant (P<0.05).](image-url)
study demonstrates a relationship between contrast-enhanced myocardial T1 time and myocardial mechanical behavior, as well as ventricular remodeling among multiethnic individuals without a history of previous cardiovascular events. The current study also demonstrates sex-specific differences in diffuse interstitial fibrosis associated with cardiac remodeling. Contrast-enhanced T1 mapping techniques may eventually assist in monitoring the effectiveness of therapy aimed at regression of myocardial fibrosis and altering ventricular remodeling.

Limitations
Because the participants in our sample were between 52 and 92 years of age, it is not possible to generalize these results to younger adults. The analysis of the association between myocardial fibrosis and measures of myocardial deformation were cross-sectional across a large cohort of individuals and future longitudinal investigations using serial cardiac magnetic resonance imaging examinations are needed to assess the possibility of cohort effect involving the associations of myocardial fibrosis with LV function and progressive LV remodeling. Furthermore, T1 times are nonspecific measures of gadolinium distribution, and other processes that result in expansion of the extracellular space beyond fibrosis may also result in lower postcontrast T1 times. In our protocol, the MOLLI sequence was obtained only at the midventricular level; hence, the ECE in other regions of the heart could not be assessed. Recent studies have used the extracellular volume fraction or fibrosis index as a marker of ECE. The extracellular volume fraction incorporates pre- and postcontrast T1 times adjusted for hematocrit, which was not available for all the participants, precluding extracellular volume fraction estimation.

Conclusions
Increased interstitial myocardial fibrosis indexed as increased ECE is characterized by a distinct pattern of altered myocardial deformation in the general population. In MESA participants without a history of previous clinical events and without a CMR LGE-defined scar, greater ECE is associated with lower LV end-diastolic mass and volumes. ECE is also associated with reduced circumferential shortening independent of LV mass and end-diastolic volume. However, this relationship is sex dependent. In women, ECE is also associated with greater diastolic dysfunction and preserved LVEF, whereas in men, ECE is associated with greater global LV dysfunction manifested as lower LV torsion and lower EF. Finally, in participants with LGE-defined myocardial scar, greater ECE is associated with reduced circumferential shortening and reduced EF.

Acknowledgments
We thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

Interstitial myocardial fibrosis is a common histological feature underlying cardiac remodeling because of various disease processes. We used cardiac magnetic resonance imaging to examine how this extracellular expansion from interstitial myocardial fibrosis relates to cardiac structural and functional remodeling among men and women without a history of previous cardiovascular events and without a cardiac magnetic resonance imaging-defined myocardial scar. Myocardial T₁ mapping was used to assess extracellular expansion, and tagging was used to assess regional myocardial function. We observed that with increased extracellular matrix expansion, both men and women have reduced left ventricular end-diastolic mass and volume and reduced circumferential shortening. However, only women had reduced early diastolic strain rate and preserved ejection fraction, whereas men had reduced left ventricular torsion and reduced ejection fraction. These findings indicate that there are sex-specific differences in diffuse interstitial fibrosis associated with cardiac remodeling. These observations suggest a mechanism by which interstitial myocardial fibrosis can predispose to heart failure in men and women.
Interstitial Fibrosis, Left Ventricular Remodeling, and Myocardial Mechanical Behavior in a Population-Based Multiethnic Cohort: The Multi-Ethnic Study of Atherosclerosis (MESA) Study

Sirisha Donekal, Bharath A. Venkatesh, Yuan Chang Liu, Chia-Ying Liu, Kihei Yoneyama, Colin O. Wu, Marcelo Nacif, Antoinette S. Gomes, W. Gregory Hundley, David A. Bluemke and Joao A.C. Lima

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### Supplemental Table 1. Association of pre-contrast T1 times with LV structural and functional measures in participants without LGE scar: Estimated Regression coefficient (standard error in parenthesis)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecc</td>
<td>0.27</td>
<td><strong>-0.072 (0.02)</strong></td>
<td><strong>-0.082 (0.02)</strong></td>
</tr>
<tr>
<td>EDSR</td>
<td>0.13</td>
<td>0.001 (0.002)</td>
<td>0.0006 (0.002)</td>
</tr>
<tr>
<td>Torsion</td>
<td>0.11</td>
<td>0.007 (0.005)</td>
<td>0.002 (0.006)</td>
</tr>
<tr>
<td>TRR</td>
<td>0.11</td>
<td>-0.073 (0.06)</td>
<td>0.041 (0.06)</td>
</tr>
<tr>
<td>LV EF</td>
<td>0.12</td>
<td>0.01 (0.04)</td>
<td>-0.086 (0.04)</td>
</tr>
<tr>
<td>EDVi</td>
<td>0.19</td>
<td>-0.162 (0.08)</td>
<td>0.108 (0.08)</td>
</tr>
<tr>
<td>LVMi</td>
<td>0.46</td>
<td><strong>-0.311 (0.08)</strong></td>
<td>0.036 (0.06)</td>
</tr>
</tbody>
</table>

*= p<0.05, **=p<0.001

The Coefficient represents the change in LV measures per 10ms change in precontrast T1 time, with adjustments for multiple variables.

- **Model 1**: Unadjusted
- **Model 2**: Adjusted for age, gender, race, BSA, GFR, heart rate, SBP, DBP, Anti hypertensive medication use, History of Diabetes, Smoking status.
- **Model 3**: Adjusted for age, gender, race, BSA, GFR, heart rate, SBP, DBP, Anti hypertensive medication use, History of Diabetes, Smoking status, LV end diastolic mass and volume.

**R²**: R-squared values for model 3 (for model 2 if model3 is not available)

EDSR= Early diastolic strain rate, LV Torsion =LV Torsion adjusted for epicardial radius, TRR= Torsional recoil rate, BSA=Body Surface Area, LV EF=LV Ejection fraction, LVEDVi=LV End diastolic volume index, LVMi= LV mass index, SBP= Systolic blood pressure, DBP= Diastolic blood pressure, GFR= Glomerular Filtration rate.
Supplemental Table 2. Gender specific changes in LV structure and function with pre-contrast T1 times in participants without LGE scar: Estimated Regression Coefficient (Standard Error in parenthesis)

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 3</td>
</tr>
<tr>
<td>Ecc</td>
<td>0.25</td>
<td>-0.086 (0.02)*</td>
<td>-0.105 (0.02)**</td>
<td>-0.090 (0.02)*</td>
</tr>
<tr>
<td>EDSR</td>
<td>0.13</td>
<td>0.002 (0.003)</td>
<td>0.005 (0.003)</td>
<td>0.004 (0.003)</td>
</tr>
<tr>
<td>Torsion</td>
<td>0.15</td>
<td>0.001 (0.007)</td>
<td>-0.003 (0.007)</td>
<td>-0.007 (0.007)</td>
</tr>
<tr>
<td>TRR</td>
<td>0.09</td>
<td>0.055 (0.08)</td>
<td>0.034 (0.08)</td>
<td>0.023 (0.08)</td>
</tr>
<tr>
<td>LV EF</td>
<td>0.02</td>
<td>-0.074 (0.05)</td>
<td>-0.075 (0.05)</td>
<td>-</td>
</tr>
<tr>
<td>EDVi</td>
<td>0.16</td>
<td>0.1 (0.09)</td>
<td>0.157 (0.09)</td>
<td>-</td>
</tr>
<tr>
<td>LVMi</td>
<td>0.23</td>
<td>0.075 (0.07)</td>
<td>0.031 (0.07)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 3</td>
</tr>
<tr>
<td>Ecc</td>
<td>0.28</td>
<td>0.01 (0.03)</td>
<td>-0.035 (0.03)</td>
<td>-0.038 (0.03)</td>
</tr>
<tr>
<td>EDSR</td>
<td>0.14</td>
<td>-0.008 (0.004)</td>
<td>-0.005 (0.004)</td>
<td>-0.004(0.004)</td>
</tr>
<tr>
<td>Torsion</td>
<td>0.10</td>
<td>0.011 (0.09)</td>
<td>0.003 (0.01)</td>
<td>0.004 (0.009)</td>
</tr>
<tr>
<td>TRR</td>
<td>0.05</td>
<td>0.015 (0.09)</td>
<td>0.027 (0.09)</td>
<td>0.022 (0.09)</td>
</tr>
<tr>
<td>LV EF</td>
<td>0.07</td>
<td>-0.108 (0.07)</td>
<td>-0.099 (0.07)</td>
<td>-</td>
</tr>
<tr>
<td>EDVi</td>
<td>0.13</td>
<td>-0.233 (0.16)</td>
<td>0.052 (0.15)</td>
<td>-</td>
</tr>
<tr>
<td>LVMi</td>
<td>0.19</td>
<td>0.002 (0.12)</td>
<td>0.102 (0.11)</td>
<td>-</td>
</tr>
</tbody>
</table>

* = p<0.05, ** = p<0.001

The Coefficient represents the change in LV measures per 10 ms increase in precontrast T1 time, with adjustments for multiple variables.

Model 1: Unadjusted
Model 2: Multivariate linear regression adjusted for age, race, BSA, GFR, heart rate, SBP, DBP, Anti hypertensive medication use, History of Diabetes, Smoking status.
Model 3: Adjusted for age, race, BSA, GFR, heart rate, SBP, DBP, Anti hypertensive medication use, History of Diabetes, Smoking status, LV end diastolic mass and volume.

R²: R-squared values for model 3 (for model 2 if model3 is not available)
EDSR=Early diastolic strain rate, LV Torsion =LV Torsion adjusted for epicardial radius, TRR=Torsional recoil rate, BSA=body surface area, LVEF=Ejection fraction, LVEDVi=LV End diastolic volume index, LVMi = LV mass index, SBP= Systolic blood pressure, DBP= Diastolic blood pressure, GFR= Glomerular Filtration rate.