Journal of the American Heart Association

ORIGINAL RESEARCH

Association Between Left Ventricular Mechanical Deformation and Myocardial Fibrosis in Nonischemic Cardiomyopathy

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BACKGROUND: In patients with nonischemic cardiomyopathy, nonischemic fibrosis detected by late gadolinium enhancement (LGE) cardiovascular magnetic resonance is related to adverse cardiovascular outcomes. However, its relationship with left ventricular (LV) mechanical deformation parameters remains unclear. We sought to investigate the association between LV mechanics and the presence, location, and extent of fibrosis in patients with nonischemic cardiomyopathy.

METHODS AND RESULTS: We retrospectively identified 239 patients with nonischemic cardiomyopathy (67% male; 55±14 years) referred for a clinical cardiovascular magnetic resonance. LGE was present in 109 patients (46%), most commonly (n=52; 22%) in the septum. LV deformation parameters did not differentiate between LGE-positive and LGE-negative groups. Global longitudinal, radial, and circumferential strains, twist and torsion showed no association with extent of fibrosis. Patients with septal fibrosis had a more depressed LV ejection fraction (30±12% versus 35±14%; *P*=0.032) and more impaired global circumferential strain (–7.9±3.5% versus –9.7±4.4%; *P*=0.045) and global radial strain (10.7±5.2% versus 13.3±7.7%; *P*=0.023) than patients without septal LGE. Global longitudinal strain was similar in both groups. While patients with septal-only LGE (n=28) and free wall–only LGE (n=32) had similar fibrosis burden, the septal-only LGE group had more impaired LV ejection fraction and global circumferential, longitudinal, and radial strains (all *P*<0.05).

CONCLUSIONS: There is no association between LV mechanical deformation parameters and presence or extent of fibrosis in patients with nonischemic cardiomyopathy. Septal LGE was associated with poor global LV function, more impaired global circumferential and radial strains, and more impaired global strain rates.

Key Words: cardiac magnetic resonance imaging ■ late gadolinium enhancement ■ myocardial mechanics ■ nonischemic dilated cardiomyopathy ■ strains

Cardiovascular magnetic resonance (CMR) is the noninvasive gold standard for assessment of left ventricular (LV) function and tissue characterization by late gadolinium enhancement (LGE) in patients with nonischemic cardiomyopathy (NICM).[1,2] In NICM, presence of LV fibrosis detected by LGE is associated with adverse cardiovascular outcomes.[3,4] LGE is present in 30% to 40% of patients with NICM in the midmyocardial septum.[3,4] However, the characteristics of focal fibrosis in NICM are variable and can involve other locations such as the LV free wall.[3,4] Differences in fibrosis pattern, extent, and location in NICM may have diverse effects on LV function and mechanics. Assessment of myocardial deformation by CMR feature tracking could provide additional diagnostic and prognostic information in patients with impaired LV function, incremental to the principal measure of LV ejection fraction (LVEF).[5,6]

Previous CMR tissue tracking studies reported depressed longitudinal and circumferential shortening in

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.016797

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In patients with nonischemic cardiomyopathy, no association was found between left ventricular (LV) mechanical deformation parameters and presence or extent of fibrosis; however, the location of late gadolinium enhancement was an important determinant of LV mechanics: Septal late gadolinium enhancement was associated with poor global LV function, more impaired global circumferential strain and global radial strain compared with patients without late gadolinium enhancement.
- Our study is the first to investigate the relation between the presence of left bundle branch block and LV torsional parameters using cardiac magnetic resonance feature tracking in a large group of patients with nonischemic cardiomyopathy.
- We found that left bundle branch block and consequential cardiac dyssynchrony is associated with reverse basal circumferential rotation and reduction of LV twist and torsion.

What Are the Clinical Implications?

- We described the association of nonischemic fibrosis located in the LV septum and impaired LV function and mechanics.
- In the future, our results might have an importance in clinical prognostication of patients with nonischemic cardiomyopathy and could help to develop individual targeted therapy.

Nonstandard Abbreviations and Acronyms

DSR	diastolic strain rate
GCS	global circumferential strain
GLS	global longitudinal strain
GRS	global radial strain
LGE	late gadolinium enhancement
NICM	nonischemic cardiomyopathy
SSR	systolic strain rate

patients with NICM.[7–10] LV torsion, which is the relative rotation of the LV apex to the base generated by circumferentially oriented midmyocardial fibers, was also found to be impaired in this group.[8,11] Currently, there are no available data demonstrating how the different locations of focal nonischemic fibrosis impact LV torsion in patients with NICM.

In patients with ischemic cardiomyopathy, subendocardial-transmural scars in the coronary artery distribution are associated with impaired global and regional strains.[12–14] In patients with hypertrophic cardiomyopathy, global longitudinal strain (GLS) correlates with the extent of LGE (expressed as a percentage of LV mass) in the overall cohort, but not in the LGE-positive group separately.[15,16] In NICM, areas of LGE are most commonly located in the midmyocardium. The impact of LGE location and extent on the mechanical parameters in NICM, however, is not fully known. In this study, we sought to investigate the association between LGE and LV mechanical deformation parameters using CMR feature tracking.

METHODS

Study Population

The study was Health Insurance Portability and Accountability Act compliant and approved by the Beth Israel Deaconess Medical Center Institutional Review Board. Written informed consent was obtained from each participant for use of their CMR images for research. We retrospectively identified patients with NICM referred for a clinical CMR at our center between May 2012 and May 2019. The diagnosis of NICM was confirmed using information extracted from electronic medical records. We excluded patients with (1) hypertrophic, inflammatory, infiltrative, and arrhythmogenic cardiomyopathies; (2) ischemic coronary disease defined as a history of myocardial infarction, presence of epicardial coronary artery diameter stenosis >70%, or presence of a subendocardial/transmural pattern of LGE; (3) documented genetic arrhythmias (eg, Brugada, long QT syndrome); and (4) impaired renal function as contraindication of contrast administration. All clinical information and diagnoses were reviewed case by case using online medical records. The data that support the findings of this study are available from the corresponding author upon reasonable request.

CMR Image Acquisition

CMR imaging was performed on a 1.5 T CMR system (Achieva, Philips Healthcare, Best, The Netherlands) equipped with a 32-channel cardiac coil or a 3 T CMR system (Vida, Siemens Healthineer, Erlangen, Germany) using an 18-channel body coil. Breath-hold, retrospectively gated cine images were collected using the balanced steady-state free-precession sequence in the 2- and 4-chamber long-axis LV views in the LV outflow tract view and short-axis stack covering the entire LV (8-mm slices with 2-mm gaps). LGE images were obtained using a 3-dimensional phase-sensitive inversion-recovery sequence with a spectral fat saturation prepulse during the end-diastolic phase ≈15 minutes after administration (gadobenate dimeglumine 0.1 mmol/kg, Multihance, Bracco Diagnostics Inc.,

Monroe Township, NJ; or 0.2 mmol/kg gadopentetate dimeglumine Magnevist, Bayer Schering Pharma AG, Berlin, Germany).

CMR Image Analysis

LV Deformation Analysis by Tissue Tracking

LV deformation analysis was performed using CVI42 (v. 5.10.1, Circle Cardiovascular Imaging Inc. Calgary, Canada).[16–18] LV endo- and epicardial borders were manually traced at end diastole in ECG-gated balanced steady-state free precession short- and long-axis (2- and 4-chamber, LV outflow tract) sequences. Automatic border tracking was applied to track image features throughout the cardiac cycle. Tracking was visually reviewed and manually corrected. Global circumferential (GCS), longitudinal (GLS), and radial (GRS) strains were assessed. Corresponding systolic (SSR) (SSR_C, SSR_L, SSR_R) and diastolic strain rates (DSR) (DSR_C, DSR_L, DSR_R) were also evaluated, representing the velocity of the deformation during systole and diastole. Global circumferential and radial strain values were calculated as the average of the mean curves of all LV segments on the short-axis stack, and longitudinal strain values as the average of the mean curves of the long-axis slices (2- and 4-chamber, LV outflow tract). The basal and apical circumferential peak systolic rotations were measured on short-axis cines. As viewed from the apex, the basal rotation is clockwise and expressed as a negative value, while apical rotation is counterclockwise and expressed as a positive value. Systolic rotation was expressed as a net maximum extent of rotation in the anticipated direction (eg, clockwise [+] basal rotation was calculated as zero value) and as a magnitude of rotation regardless of the direction of movement. LV twist was defined as the net difference between the apical and basal rotation; twist per unit length was calculated by dividing LV twist by base-to-apex length of the LV.[19] LV torsion, representing the rotation of the apex relative to the base, was calculated as follows:

$$((\Theta_{apical} \times r_{apical}) - (\Theta_{basal} \times r_{basal}))/D$$

where Θ, r, and D represent rotation, radius, and base-to-apex length, respectively.[19–21] Inter- and intraobserver variability of LV mechanical parameters was tested on 40 randomly selected scans. To enable calculating the strain, a minimum of 25 cardiac phases were required in cine images; therefore, we had to exclude patients who had fewer than 25 time frames in the standard cine images.

LGE Analysis

LGE presence, extent (g), and LGE% (ie LGE [g]/LV mass [g]×100) were assessed by a reader with 5 years of CMR imaging experience using a 5 SD threshold. This threshold was chosen based on prior studies involving identification of LGE in patients with NICM.[22–24] The scar location of LGE was assessed using the 17-segment American Heart Association model.

Statistical Analysis

Statistical analyses were performed using MedCalc 13.2.2 (MedCalc Software, Ostend, Belgium). The Kolmogorov–Smirnov test was used to assess the normal distribution of the data. Continuous variables were reported as mean±SD or median with an interquartile range (IQR) for normally distributed and skewed continuous variables, respectively. Categorical and ordinal variables were reported as frequencies or percentage. Comparisons between groups were made using the Student *t* test, Wilcoxon rank sum test, or Fisher's exact test. The associations between variables were assessed using linear or logistic regression. Interobserver agreement was evaluated with an intraclass correlation coefficient.[25] A *P* value of <0.05 was considered to be significant.

RESULTS

Study Population

The final cohort comprised 239 patients (67% male; mean age, 55±14 years). Ninety-two patients (39%) had hypertension, 51 patients (21%) had diabetes mellitus, and 55 patients (23%) had hyperlipidemia. Forty patients (17%) had a history of at least 1 nonsustained/sustained ventricular tachycardia or ventricular fibrillation episode before the CMR scan, while 25 patients (11%) had documented atrial fibrillation or atrial flutter. Fifty-six (23%) patients had left bundle branch block (LBBB) at the time of the CMR scan. Patients who were LGE negative had LBBB more often than patients who were LGE positive (31% versus 15%; *P*=0.038) (Table 1).

Presence of Focal Fibrosis

LGE was present in 109 patients (46%). The mean age, sex, and body surface area were similar among LGE-negative and LGE-positive groups (Table 1). Patient comorbidities such as hypertension, diabetes mellitus, and hyperlipidemia were similar between LGE-positive and LGE-negative groups. Twenty-two patients (17%) in the LGE-negative group and 18 patients (17%) in the LGE-positive group had a history of documented ventricular tachycardia/ventricular fibrillation. LV and right ventricular (RV) end-diastolic volume, mass, and mass index were higher in the LGE-positive group, although LVEF was similar (Table 1). Regarding LV mechanics, none of

Table 1. Patients' Characteristics and Cardiac Magnetic Resonance Parameters in Non-Ischemic Cardiomyopathy Patients

Variables	Total N=239	LGE Positive N=109	LGE Negative N=130	*P* Value (LGE Positive vs LGE Negative)
Age, y	55±14	55±14	54±14	0.855
Male, n (%)	159 (67)	74 (68)	85 (65)	0.683
BSA, m^2	2.00±0.3	2.10±0.26	2.00±0.28	0.423
Clinical history				
Heart rate, beat/min	76±17	76±17	75±17	0.453
Hypertension, n (%)	92 (39)	48 (44)	44 (34)	0.108
Diabetes mellitus, n (%)	51 (21)	18 (17)	33 (25)	0.096
Hyperlipidemia, n (%)	55 (23)	23 (21)	32 (24)	0.521
VT/VF, n (%)	40 (17)	18 (17)	22 (17)	0.933
LBBB, n (%)	56 (23)	16 (15)	40 (31)	0.038*
AF/AFL, n (%)	25 (11)	12 (11)	14 (11)	0.953
Left ventricle				
LVEDV, mL	268±85	282±93	257±76	0.022*
LVEDVi, mL/m^2	131±36	137±39	128±32	0.040*
LVESV, mL	184±89	197±100	174±78	0.049*
LVESVi, mL/m^2	90±40	95±44	86±34	0.084
LVSV, mL	83±26	84±26	81±26	0.471
LVSVi, mL/m^2	41±12	41±13	41±12	0.758
LVEF, %	34±14	33±14	34±13	0.535
LVM, g	146±49	154±47	140±49	0.017*
LVMi, g/m^2	72±20	75±19	69±21	0.045*
Right ventricle				
RVEDV, mL	184±60	193±64	177±55	0.036*
RVEDVi, mL/m^2	91±25	94±26	88±24	0.105
RVESV, mL	105±56	106±61	105±52	0.914
RVESVi, mL/m^2	51±25	55±27	48±23	0.029*
RVSV, mL	79±25	80±24	79±26	0.651
RVSVi, mL/m^2	39±12	39±11	39±12	0.976
RVEF, %	46±14	44±15	47±13	0.113
RVEDV/LVEDV	0.71±0.2	0.71±0.19	0.71±0.20	0.990
Left ventricular fibrosis				
LGE, g		5.0 [3.8–6.3]	…	…
LGE%		3.4 [2.8–4.4]	…	…

AF indicates atrial fibrillation; AFL, atrial flutter; BSA, body surface area; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LVM, left ventricular mass; LVMi, left ventricular mass index; LVSV, left ventricular stroke volume index; LVSV, left ventricular stroke volume; RVEDV, right ventricular end-diastolic volume; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVESVi, left ventricular end-systolic volume index; RVSV, right ventricular stroke volume; RVSVi, right ventricular stroke volume index; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Significant value (*P*<0.05).

the investigated mechanical parameters discriminated between the LGE-positive and LGE-negative cohorts (Table 2). GLS, GCS, and GRS correlated with LVEF in the whole cohort and in the LGE-negative and LGE-positive groups separately (Figure 1A). The corresponding SSRs (SSR_C, SSR_L, SSR_R) and DSRs (DSR_C, DSR_L, DSR_R) also correlated with LVEF (all *P*<0.05). The presence of LGE did not correlate significantly with LV mechanical parameters (GLS, GCS, GRS) or strain rates (SSR_C, SSR_L, SSR_R, DSR_C, DSR_L, DSR_R) in the whole cohort (correlation coefficients [*R*] <2 and *P* values are not significant). Similarly, torsion and twist did not correlate with presence of LGE.

Extent of Focal Fibrosis

In the LGE-positive group, the median amount of the fibrosis was 5.0 g (IQR, 3.8–6.3) and LGE% was 3.4%

Table 2. Left Ventricular Mechanical Parameters in Patients With and Without Fibrosis

Variables	LGE Positive (N=109)	LGE Negative (N=130)	*P* Value
GCS, %	−9.2±4.4	−9.0±4.1	0.804
SSR_C (1/s)	−0.50±0.23	−0.52±0.24	0.532
DSR_C (1/s)	0.47±0.22	0.53±0.28	0.058
GLS, %	−8.7±4.1	−8.6±4.0	0.731
SSR_L (1/s)	−0.46±0.19	−0.50±0.20	0.999
DSR_L (1/s)	−0.46±0.19	−0.49±0.19	0.112
GRS, %	13.0±8.0	12.4±7.3	0.606
SSR_R (1/s)	0.68±0.35	0.67±0.38	0.952
DSR_R (1/s)	−0.65±0.39	−0.65±0.50	0.932
Basal systolic rotation, °			
Net clockwise	−1.4±1.0	−1.6±1.2	0.161
Magnitude	−1.2±1.5	−1.4±1.5	0.170
Apical systolic rotation, °			
Net counterclockwise	1.6±2.9	1.2±2.7	0.074
Magnitude	1.7±3.0	1.2±2.9	0.249
Twist, °	2.9±2.8	2.8±2.4	0.607
Twist per length, °/cm	0.44±0.4	0.41±0.4	0.649
Torsion, $°s^{-1}$	1.43±1.1	1.31±0.9	0.374

DSR_c indicates circumferential diastolic strain rate; DSR_L, longitudinal diastolic strain rate; DSR_R, radial diastolic strain rate; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LGE, late gadolinium enhancement; SSR_C, circumferential systolic strain rate; SSR_L, longitudinal systolic strain rate; and SSR_R, radial systolic strain rate.

*Significant value (*P*<0.05).

(IQR, 2.8–4.4). There was no correlation between the extent of fibrosis and ejection fraction, volumes and mass indexes, or any LV mechanical parameters (GCS, GLS, GRS, SSR_C, SSR_L, SSR_R, DSR_C, DSR_L, DSR_R, twist, twist per length and torsion). To further analyze the impact of LGE extent on LV mechanical parameters, we divided the LGE-positive cohort into subgroups with LGE% <3.41% (n=54) and LGE% >3.41% (n=55). Patients with greater LGE% had higher LV mass (LV mass index, 79±19 g/m^2 versus 71±19 g/m^2; *P*=0.026), but no difference was found regarding LV function or mechanical parameters. To further stratify patients with LGE, we compared patients who were LGE positive with LVEF >35% (n=43) and severely impaired LV function (LVEF <35% n=66) and found that LGE% did not correlate with global strain values (Figure 1B).

Location of Focal Fibrosis

Midmyocardial fibrosis was present in 74 patients (31% of whole cohort), while subepicardial LGE in a noncoronary distribution was present in 21 patients (9%). LGE mainly involved the basal segments (36%), specifically the basal antero- and inferoseptal segments, followed by the basal and midinferolateral segments (Figure 2). Twenty-three (10%) patients had LGE limited to the RV anterior or inferior insertion zones. Comparisons between patients with (n=52) and without midmyocardial septal fibrosis (n=187) showed that the septal LGE group had a decreased LVEF (35±14% versus 30±12%; *P*=0.032) and more severely impaired circumferential and radial strains (GCS, −9.7±4.4% versus −7.9±3.5%; *P*=0.045; GRS, 13.3±7.7% versus 10.7±5.2%; *P*=0.023). SSRs and DSRs were more impaired in patients with septal LGE than in patients with nonseptal LGE. However, GLS, SSR_L, and DSR_L were not associated with septal LGE (Table S1). Figure 3 shows a patient with septal midmyocardial LGE with impaired GCS and GRS but relatively preserved GLS. Comparisons between patients with (n=48) and without free-wall LGE (n=191) showed that LVEF and global strain (GCS, GLS, GRS), SSR, and DSR were also similar. Only the basal circumferential rotation was lower in patients with LGE involving the LV free wall (Table S2).

In the LGE-positive group, LGE was observed only in the septum or LV free wall in 28 (12%) patients and 32 (13%) patients, respectively. When comparing the two groups, patients with septal-only LGE had lower LVEF and more depressed GCS, GLS, GRS, SSRs, and DSRs (Table 3). Importantly, LGE was predominantly located in the basal segments in both groups, and the extent of fibrosis did not differ between groups.

Twist and Torsion

Basal and apical circumferential rotation, twist, twist per LV length, and torsion were similar in patients with and without LGE (Table 2). The apical rotation was reversed in 29% of the LGE--negative group and in 32% of the LGE-positive group, while basal rotation was detected in the counterclockwise rotation in 19% of the LGE-negative and in 21% of the LGE-positive group. Figure 4 shows representative examples of basal and apical systolic rotations (magnitude) in 3 patients with different LGE patterns. The apical rotation was reversed in 56% (33/56) of patients in the LBBB-positive group and in only 22% (40/183) of patients without LBBB; therefore, apical circumferential rotation was more impaired in patients with LBBB (net counterclockwise rotation, 0.8±1.1 versus 2.4±1.8; *P*<0.001; magnitude, −0.9±2.7 versus 2.0±2.5; *P*<0.001). On the contrary, basal rotation was reversed in 9% (5/56) of patients in the LBBB-positive group and in 24% (43/183) of patients in the LBBB-negative group. Basal circumferential rotation was less impaired in LBBB-positive group (net clockwise, −2.2±1.2 versus

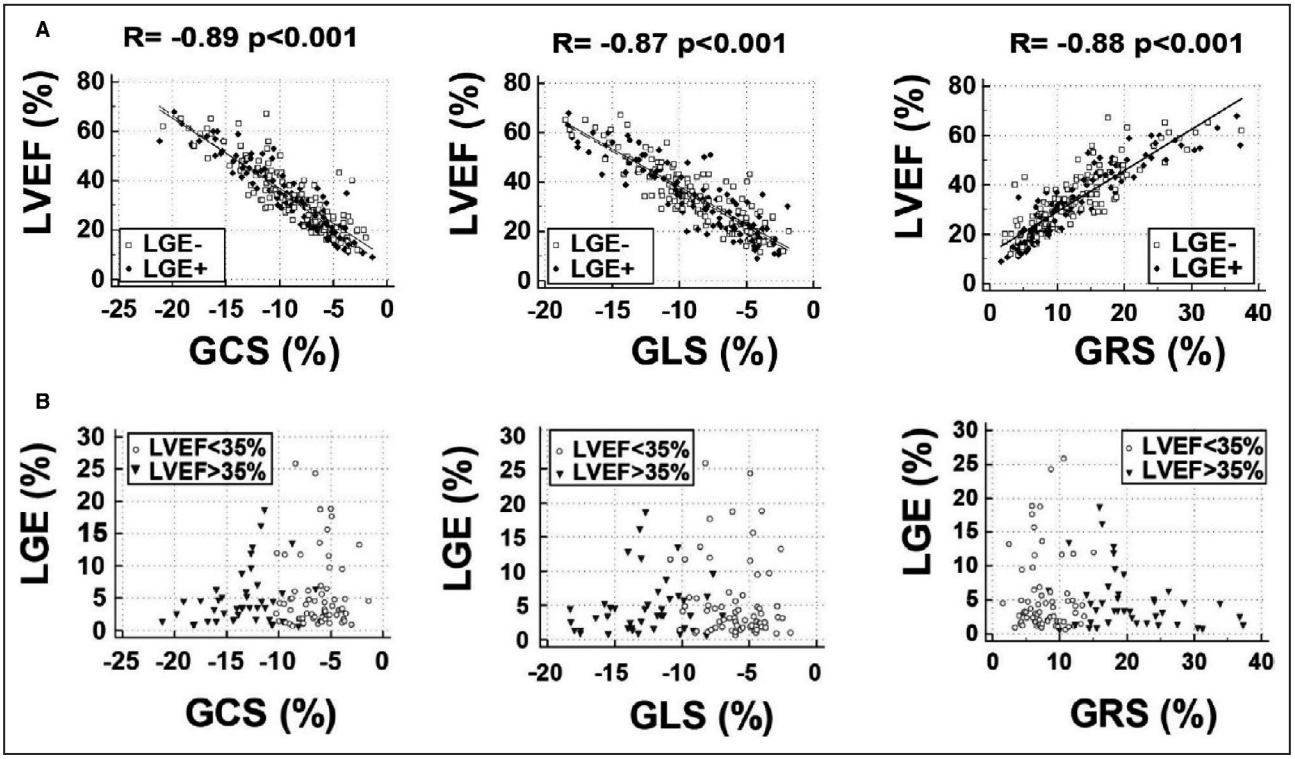

Figure 1. The associations of global strain values with left ventricular function and fibrosis.
A, Global strain values correlate with left ventricular ejection fraction. Left ventricular global strain values (circumferential [GCS], longitudinal [GLS], and radial [GRS]) correlated with left ventricular ejection fraction (LVEF) in the whole cohort and patients with (black rhombus) and without (empty square) late gadolinium enhancement (LGE) separately. **B**, Global strain values are not associated with late gadolinium enhancement (LGE). In patients with LGE (n=109), the extent of fibrosis (LGE%) did not correlate with global strain values in patients with moderately (LVEF >35%) (black triangle) or highly impaired (LVEF <35%) (empty circle) LV function.

–1.3±1.09; *P*=0.040; magnitude, –2.0±1.4 versus –1.0±1.5; *P*<0.001). LV twist (1.3±2.1 versus 3.3±2.6; *P*<0.0001) and LV torsion (1.0±0.8 versus 1.5±1.1; *P*=0.002) were more impaired in patients with LBBB (Table S3).

When comparing isolated septal LGE and isolated free-wall LGE groups with similar degrees of fibrosis (LGE%, 4.4 [IQR, 3.0–5.8] versus 5.1 [IQR, 3.4–6.9]; *P*=0.540), torsional parameters were found to be similar (Table 3). Extent of fibrosis did not correlate with twist or torsion in the whole LGE=positive group, but did correlate in patients with LVEF >35%; LGE% correlated with the magnitude of apical systolic rotation (*r*=0.36; *P*=0.018), twist (*r*=0.38; *P*=0.012) and torsion (*r*=0.39; *P*=0.010).

Reproducibility of CMR Feature Tracking Parameters

Excellent intra- and interobserver reproducibility was observed for global strain values (GCS, GLS, and GRS) (Table 4). SSR had good reproducibility, while DSR values were less reproducible. The net basal and apical rotation (rotation in the anticipated direction) had higher intraclass correlation coefficient values compared with the magnitude of rotation (maximum rotation regardless of direction) (Table 4). Twist, twist per length, and torsion demonstrated good intra- and interobserver reproducibility.

DISCUSSION

In this retrospective study of 239 patients with NICM, we found that CMR feature tracking–derived LV mechanical parameters of global strain (GCS, GLS, GRS), SSR (SSR_C, SSR_L, SSR_R), DSR (DSR_C, DSR_L, DSR_R), twist, and torsion were all impaired regardless of presence or absence of LGE. LV mechanical deformation parameters did not significantly correlate with extent of focal myocardial fibrosis. Patients with septal LGE had lower LVEF coupled with decreased GCS and GRS compared with patients without septal fibrosis. However, GLS was similar in both groups. In patients with similar extents of LV fibrosis, the septal location of LGE was associated with more depressed LV systolic function, including lower LVEF, global strains, SSRs, and DSRs compared with patients wherein LGE was limited to the LV free wall.

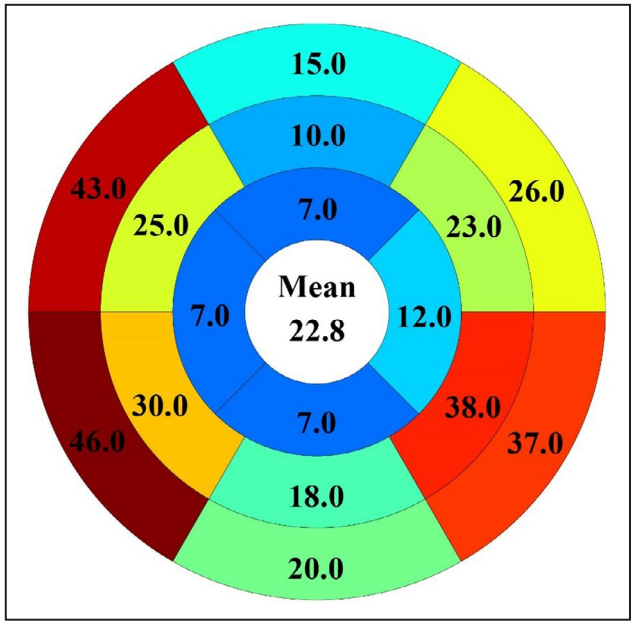

Figure 2. The distribution of LGE in all patients with fibrosis (n=109).
The most frequent location of LGE was the basal septum (43% [n=40] and 46% [n=42]), followed by the basal (37% [n=34]) and mid inferolateral segments (38% [n=35]).

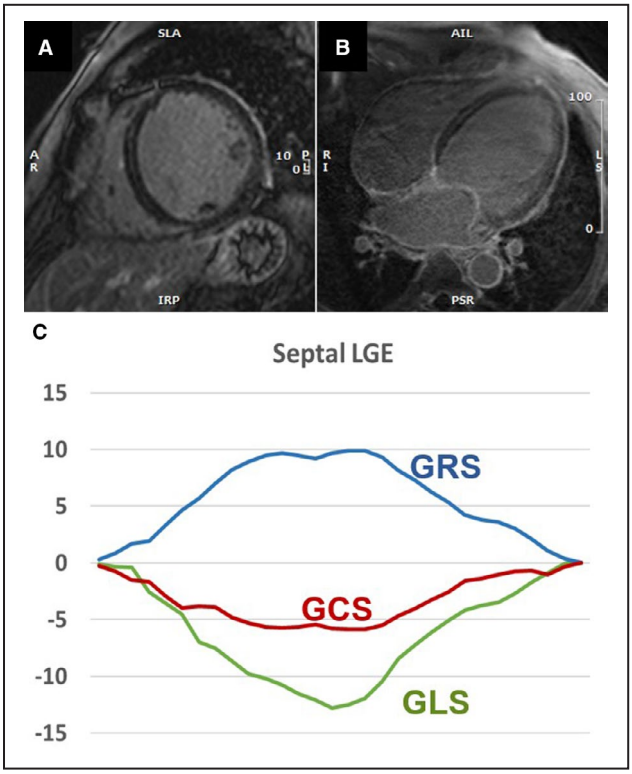

Figure 3. Patient with septal midmyocardial late gadolinium enhancement with impaired circumferential and radial shortening.
Patient with septal late gadolinium enhancement (LGE) on short-axis (**A**) and long axis (**B**) LGE images. Patient has low left ventricular ejection fraction (LVEF=34%) with impaired global circumferential (GCS) and radial (GRS) strains but relatively less impaired longitudinal (GLS) strain values (**C**), suggesting that the impaired circumferential movement is associated with decreased LVEF.

LV Mechanics in NICM

CMR feature tracking can assess cardiac performance in a wide variety of cardiac pathologies. The technique can be applied to quantification of LV and RV strain values, DSRs and SSRs, and LV myocardial torsion. Previous studies reporting data on healthy subjects showed that CMR feature tracking–derived GLS, GCS, and GRS values were not associated with age or sex.[26] The observed global LV mechanical parameters were lower in our NICM cohort than in healthy subjects.[5,17,26,27] In this study, we quantified GLS, SSR_L, and DSR_L as the sum of the three long-axis apical views. GLS did not differentiate between patients with and without LGE in both the whole group and among patients with LVEF >35%. GLS, SSR_L, and DSR_L were not different in patients with or without septal LGE. GCS and GLS are major contributors to LV stroke volume and LVEF, but data describing the relative contributions of circumferential and longitudinal shortening are controversial.[28–30] Previously, longitudinal shortening was believed to be the main driver of LVEF.[29,30] However, an increasing number of studies report that midwall circumferential shortening has greater impact on LVEF than longitudinal shortening and can contribute as much as two-thirds of the stroke volume.[31,32] In NICM, the LGE located in the midmyocardial wall affects myocardial fibers responsible for circumferential shortening of the LV. We found that the septal location of LGE was associated with circumferential and radial shortening, but not with longitudinal shortening.

In the vast majority of prior CMR feature tracking studies, GCS and GRS are measured on a single short-axis slice or in 3 short-axis slices.[8,18,26] In the current study, global strain values were calculated as the average of the mean curves of all LV segments on short-axis slices for comprehensive assessment of all LV mechanical parameters accounting for LGE location and whole heart LV remodeling. Excellent/good inter- and intraobserver reproducibility were detected for circumferential and radial mechanical values, and intraclass correlation coefficient values of GLS and GRS were comparable with previously published data in patients with NICM.[33]

Previous studies show that presence of LBBB in NICM patients is related to impaired LV mechanics with reduction of LV twist.[34,35] In agreement, we found that LBBB and consequential cardiac dyssynchrony is associated with reverse basal circumferential rotation and reduction of LV torsion and twist. Our study is the first to investigate the relation between presence of LBBB and

Table 3. Left Ventricular Parameters of Patients With Isolated Free-Wall Versus Isolated Septal Fibrosis

Variables	Only Free-Wall LGE N=28	Only Septal LGE N=32	*P* Value
LVEF, %	38±16	30±12	0.026*
LVEDVi, mL/m^2	125±40	144±34	0.056
LVESVi, mL/m^2	82±46	103±38	0.048*
LVSVi, mL/m^2	44±14	40±13	0.336
LVMi, g/m^2	73±20	75±17	0.694
GCS, %	−10.1±5.1	−7.6±3.0	0.004*
SSR_C (1/s)	−0.61±0.21	−0.45±0.18	0.003*
DSR_C (1/s)	0.54±0.20	0.40±0.20	0.011*
GLS, %	−10.2±4.6	−7.4±2.9	0.044*
SSR_L (1/s)	−10.1±5.1	−7.6±3.0	0.003*
DSR_L (1/s)	16.2±9.8	10.0±4.6	0.002*
GRS, %	16.2±9.8	10.0±4.6	0.002*
SSR_R (1/s)	0.85±0.38	0.59±0.29	0.004*
DSR_R (1/s)	−0.78±0.43	−0.54±0.31	0.018*
Basal systolic rotation			
Net clockwise, °	−1.22±1.2	−1.60±−0.38	0.186
Magnitude, °	−0.83±1.65	−1.45±1.26	0.110
Apical systolic rotation			
Net counterclockwise, °	3.12±2.42	2.19±1.87	0.099
Magnitude, °	2.56±3.29	1.45±2.89	0.171
Twist, °	3.39±3.36	2.89±2.50	0.516
Twist per length, °/cm	0.48±0.47	0.43±0.37	0.645
Torsion, °s^{-1}	1.41±1.39	1.41±0.91	0.989
LGE, g	4.1 (3.0–5.6)	6.0 (3.6–7)	0.367
LGE%	4.4 (3.0–5.8)	5.1 (3.4–6.9)	0.540

DSR_C indicates circumferential diastolic strain rate; DSR_L, longitudinal diastolic strain rate; DSR_R, radial diastolic strain rate; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; LVSVi, left ventricular stroke volume index; SSR_C, circumferential systolic strain rate; SSR_L, longitudinal systolic strain rate; and SSR_R, radial systolic strain rate.

*Significant value (P<0.05).

impaired LV torsional parameters using CMR feature tracking in a large group of patients with NICM.

Nonischemic LV Fibrosis

Myocardial fibrosis is a common histopathologic finding in patients with NICM caused by an elevated amount of collagen and extracellular matrix proteins produced by activated fibroblasts.[36,37] Myocardial fibrosis is the main contributor of the complex structural and functional cardiac abnormalities observed in patients with NICM, and the pattern of myocardial fibrosis can be identified with LGE imaging. Comparison of LGE extent across CMR studies can be challenging because of the wide variety of quantification techniques. Our data support heterogeneity of nonischemic fibrosis in NICM, as the majority of LGE-positive cases (70%) had LGE detected in >1 LV segment (median number of LGE-positive segments is 3). LGE was most commonly identified in the basal (43%–46%) and mid (25%–30%) antero- and inferoseptal segments, while the second-most-common LGE location was the inferolateral wall (37%–38%). Literature data show that LGE data assessed by the 3 SD method may be suggestive of more diffuse processes or "micro-scarring."[38] We performed LGE quantification using both 5 SD and 3 SD methods. Using 3 SD quantification in the LGE-positive group, the median amount of fibrosis was 11.0 g (IQR, 7.9–14.0) and the median LGE% was 7.5% (IQR, 6.0–9.0). The results of 5 SD and 3 SD LGE data were similar, and no correlation was found between 3 SD LGE% and LV function nor between 3 SD LGE% and different mechanical parameters. Finally, we decided to report the 5 SD data to make a more direct comparison with literature data reporting larger sample sizes.[3,4,7]

LV Mechanics and Focal Fibrosis

Previous CMR feature tracking studies reported that CMR feature tracking derived mechanical parameters are useful to detect ischemic scar.[12–14,39,40] However, limited studies are available reporting associations between LV mechanics and structural remodeling in patients with NICM.[8,41,42] Taylor et al[8] reported that the commonly observed septal midmyocardial LGE in NICM is associated with depressed GCS, twist, and torsion. In our study, septal LGE was also associated with impaired GCS and GRS, but not with torsion or twist. Patients with NICM with relatively preserved LVEF (>35%) is a significant burden in terms of prevalence, cardiovascular morbidity, and mortality. Based on our findings, LGE% did not correlate with global strain values (GCS, GLS, GRS) in this group; however, LGE% did correlate with the magnitude of apical systolic rotation and torsional parameters. These results may suggest that instead of global strain and strain rates, regional LV mechanical parameters could help better characterize the subgroup of patients with NICM with relatively preserved LV function. Further studies are needed to evaluate the role of regional strain values and torsional parameters in the prediction of outcomes in this subgroup of patients with preserved LV function. The correlation between LV fibrosis/scar and LV mechanics is influenced by multiple factors. Regardless of the amount or characteristics of the scar, LV wall thickness and global LV shape may also be important factors when studying the effect of scarring on LV mechanics. In HCM, for example, although LGE also has a nonischemic pattern, fibrosis in the hypertrophied segments (with

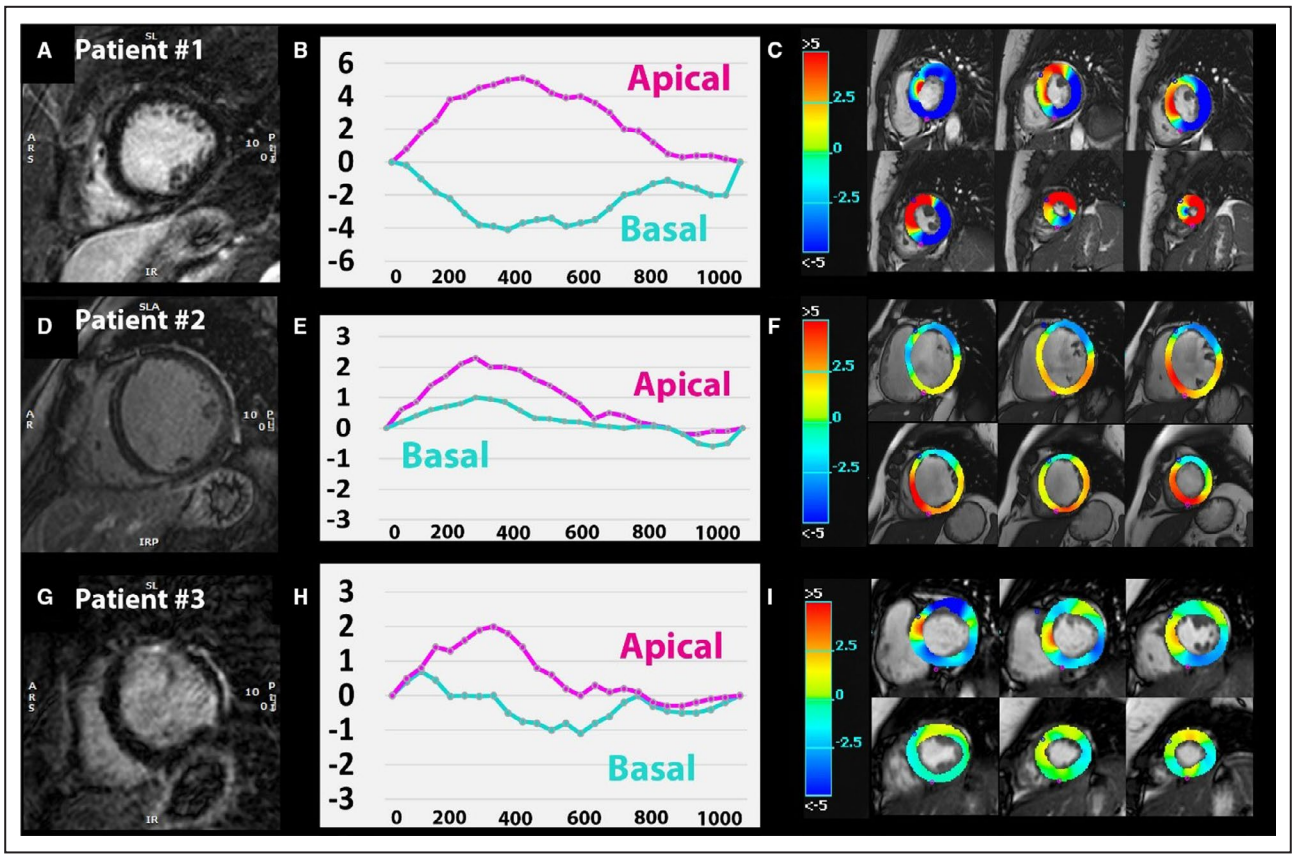

Figure 4. The location of LGE impacts LV mechanics.
Representative late gadolinium enhancement (LGE) images in 3 patients (first column **A**, **D**, and **G**), basal and apical circumferential rotation curves over time (second column **B**, **E**, and **H**), and circumferential rotation displayed as color-coded parametric maps (third column **C**, **F**, and **I**). Patient 1 without LGE (**A**) with physiologic clockwise basal rotation (negative curve [**B**] and blue basal slices on circumferential displacement map [**C**]) and counterclockwise apical rotation (positive curve on [**B**] and red apical slices on [**C**]). In patient 2, midmyocardial septal fibrosis (**D**) and reversed basal rotation (positive curve on **E**) were detected with dominant counterclockwise motion on the color-map (**F**). Patient 3 has free-wall LGE (**G**) and shows impaired basal rotation (partly positive basal curve on [**H**] and light blue/green colors on [**I**]).

disorganized myofibers) may have a different effect on LV mechanics compared with NICM, wherein LGE is located in the normal/thin wall of a dilated LV.

In the previously mentioned multicenter CMR feature tracking study,[7] higher extents of LGE were found in subgroups with more depressed GLS, although patients with more impaired strain had predominantly ischemic etiology.[7] In our study, strain values were generally impaired regardless of presence or absence of LGE. This observation remained when we compared patients who were LGE positive and patients who were LGE negative with an LVEF >35%. The extent of LGE did not correlate with LV mechanical parameters. However, the location of fibrosis affected LV mechanics. Patients with septal fibrosis had lower LVEF and impaired GCS and GRS strain values compared with patients without septal LGE. Longitudinal shortening was relatively preserved, supporting the notion that impaired circumferential movement is responsible for the impaired pump function.

LGE in the LV free wall did not affect global LV function, but was associated with impaired basal circumferential rotation and compensatory "hyperdynamic" apical rotation. As a result, twisting and torsion were not different between patients with or without free-wall LGE. Our results suggest that regional fibrosis may influence regional circumferential displacement without changing the global twisting motion.

Halliday et al[4] reported that the presence of septal LGE is associated with a large increase in the risk of cardiac mortality and sudden cardiac death. They also showed that a risk assessment model including the presence and location of LGE was superior to models based on LGE extent and pattern. In our study, patients with septal LGE had lower LVEF and impaired GCS and GRS but preserved GLS. Furthermore, septal-only LGE was associated with depressed global strains and strain rates (SSR, DSR) compared with LGE involving the LV free wall. Our data support that the location of LGE is an important determinant of LV

Table 4. Inter- and Intraobserver Reproducibility of Left Ventricular Mechanical Parameters

Variables	ICC of Intraobserver N=40	ICC of Interobserver N=40
GCS (%)	0.99 (0.98–0.99)	0.97 (0.96–0.99)
SSR_C (1/s)	0.98 (0.97–0.99)	0.94 (0.90–0.97)
DSR_C (1/s)	0.97 (0.95–0.99)	0.94 (0.89–0.97)
GLS (%)	0.97 (0.96–0.99)	0.94 (0.89–0.97)
SSR_L (1/s)	0.89 (0.80–0.94)	0.83 (0.70–0.91)
DSR_L (1/s)	0.79 (0.63–0.88)	0.68 (0.47–0.81)
GRS (%)	0.99 (0.98–0.99)	0.97 (0.96–0.99)
SSR_R (1/s)	0.97 (0.96–0.99)	0.90 (0.82–0.95)
DSR_R (1/s)	0.75 (0.58–0.86)	0.73 (0.54–0.84)
Basal rotation		
Net clockwise, °	0.81 (0.64–0.90)	0.75 (0.58–0.86)
Magnitude, °	0.74 (0.50–0.86)	0.68 (0.40–0.83)
Apical rotation		
Net counterclockwise, °	0.93 (0.86–0.96)	0.88 (0.78–0.88)
Magnitude, °	0.90 (0.83–0.95)	0.86 (0.73–0.92)
Twist, °	0.88 (0.78–0.93)	0.72 (0.53–0.84)
Twist per length, °/cm	0.82 (0.69–0.90)	0.77 (0.61–0.87)
Torsion, $°s^{-1}$	0.81 (0.67–0.89)	0.76 (0.54–0.87)

DSR_c, circumferential diastolic strain rate; DSR_L, longitudinal diastolic strain rate; DSR_R, radial diastolic strain rate; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; ICC, intraclass correlation coefficient; SSR_C, circumferential systolic strain rate; SSR_L, longitudinal systolic strain rate; and SSR_R, radial systolic strain rate.

mechanics, while the extent of LGE does not correlate with mechanical parameters.

Limitations

Our study has several limitations. This is a single-center retrospective study of patients who were referred for a clinical CMR. Our cohort was mainly White and men, which is not necessarily representative of all patients with NICM. Since LGE located at the RV insertion points has uncertain clinical and prognostic significance,[43–45] categorization of these patients as LGE positive or LGE negative is variable in the literature.[3,4,8] In this study, patients with LGE limited to the RV anterior or inferior insertion zones (n=23) were categorized as LGE positive but were excluded from the subgroup of patients who were LGE positive with septal wall fibrosis. In this study, the vast majority of patients who were LGE positive had LGE% ≤5% (n=74), in whom more extensive fibrosis of the LV wall (especially LGE% >10%) might impact global LV mechanical parameters. Importantly, the LGE quantities of small/moderate extent and the LGE distribution in our cohort is consistent with previously reported data.[3,4,44] T1 mapping is an emerging CMR technique that can identify diffuse myocardial fibrosis in a wide variety of clinical settings including NICM. In this study, T1 maps are not available. Diffuse fibrosis may therefore be underestimated, which is one of the major limitations of the study.

CONCLUSIONS

In patients with NICM, LV mechanical parameters are universally impaired. The presence of LGE is not associated with impaired global strain (GCS, GLS, GRS), strain rate (SSR_C, SSR_L, SSR_R, DSR_C, DSR_L, DSR_R), or LV twisting motion. However, if extent of LGE is the same, the septal location of LGE is associated with more profound LV systolic dysfunction, impaired strain, and strain rate compared with LGE involving the LV free wall.

ARTICLE INFORMATION

Received April 17, 2020; accepted August 26, 2020.

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Sources of Funding

Dr Nezafat receives grant funding by the National Institutes of Health 1R01HL129185-01, 1R01HL129157, 1R01HL127015, and R01HL15474401, (Bethesda, MD); and the American Heart Association 15EIA22710040 (Waltham, MA).

Disclosures

None.

Supplementary Materials

Tables S1–S3

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Supplemental Material

Table S1. Cardiac magnetic resonance left and right ventricular mechanical parameters in non-ischemic cardiomyopathy patients with and without septal fibrosis.

Variables	No septal LGE N = 187	Septal LGE N = 52	P value
LVEDVi (ml/m^2)	130 ± 36	140 ± 35	0.236
LVESVi (ml/m^2)	88 ± 40	101 ± 40	0.046*
LVSVi (ml/m^2)	42 ± 12	39 ± 12	0.175
LVEF (%)	35 ± 14	30 ± 12	0.032*
LVMi (g/m^2)	71 ± 21	74 ± 18	0.317
RVEDVi (ml/m^2)	91 ± 25	89 ± 25	0.594
RVESVi (ml/m^2)	50 ± 28	52 ± 27	0.724
RVSVi (ml/m^2)	42 ± 11	37 ± 11	0.026*
RVEF (%)	46 ± 14	44 ± 15	0.436
RVEF/LVEF	1.4 ± 0.4	1.6 ± 0.5	0.023*
RVEDV/LVEDV	0.73 ± 0.20	0.66 ± 0.18	0.039*
GCS (%)	-9.7 ± 4.4	-7.9 ± 3.5	0.045*
SSR_C (1/s)	-0.54 ± 0.22	-0.44 ± 0.22	0.007*
DSR_C (1/s)	0.52 ± 0.26	0.41 ± 0.18	0.042*
GLS (%)	-8.9 ± 4.2	-8.0 ± 3.5	0.161
SSR_L (1/s)	-5.00 ± 0.21	-0.45 ± 0.21	0.143
DSR_L (1/s)	0.48 ± 0.19	0.44 ± 0.18	0.178
GRS (%)	13.3 ± 7.7	10.7 ± 5.2	0.023*
SSR_R (1/s)	0.71 ± 0.35	0.59 ± 0.29	0.022*
DSR_R (1/s)	-0.69 ± 0.46	-0.55 ± 0.28	0.045*

Basal systolic rotation			
Net Clockwise (°)	-1.5 ± 1.1	-1.4 ± 1.1	0.653
Magnitude (°)	-1.3 ± 1.5	-1.2 ± 1.5	0.682
Apical systolic rotation			
Net Counterclockwise (°)	2.1 ± 1.8	1.9 ± 1.7	0.756
Magnitude (°)	1.4 ± 2.8	1.1 ± 2.8	0.593
Twist (°)	2.7 ± 2.6	2.3 ± 2.7	0.423
Twist per length (°/cm)	0.39 ± 0.39	0.35 ± 0.43	0.504
Torsion ($°s^{-1}$)	1.23 ± 1.08	1.19 ± 1.21	0.856

DSR_C= circumferential diastolic strain rate; DSR_L= longitudinal diastolic strain rate; DSR_R= radial diastolic strain rate; GCS= global circumferential strain; GLS= global longitudinal strain; GRS= global radial strain; LGE= late-gadolinium enhancement; LVEDVi= left ventricular end-diastolic volume index; LVESVi= left ventricular end-systolic volume index; LVEF=left ventricular ejection fraction; LVMi= left ventricular mass index; LVSVi= left ventricular stroke volume index; RVEDV= right ventricular end-diastolic volume; RVEDVi= right ventricular end-diastolic volume index; RVESVi= left ventricular end-systolic volume index; RVEF= right ventricular ejection fraction; RVSVi= right ventricular stroke volume index; SSR_C= circumferential systolic strain rate; SSR_L= longitudinal systolic strain rate; SSR_R= radial systolic strain rate; *Significant value ($P < 0.05$)

Table S2. Cardiac magnetic resonance left ventricular mechanical parameters in non-ischemic cardiomyopathy patients with and without free wall fibrosis.

Variables	No free wall LGE N = 191	Free wall LGE N = 48	P value
LVEDVi (ml/m^2)	133 ± 35	128 ± 39	0.397
LVESVi (ml/m^2)	91 ± 38	88 ± 45	0.540
LVSVi (ml/m^2)	41 ± 12	41 ± 12	0.898
LVEF (%)	34 ± 14	35 ± 15	0.473
LVMi (g/m^2)	72 ± 20	73 ± 20	0.599
GCS (%)	-8.9 ± 4.0	-9.9 ± 4.7	0.102
SSR_C (1/s)	-0.51 ± 0.22	-0.54 ± 0.26	0.377
DSR_C (1/s)	0.50 ± 0.26	0.50 ± 0.19	0.923
GLS (%)	-8.5 ± 3.4	-9.7 ± 4.5	0.058
SSR_L (1/s)	-0.48 ± 0.20	-0.52 ± 0.21	0.291
DSR_L (1/s)	0.47 ± 0.19	0.48 ± 0.16	0.751
GRS (%)	12.4 ± 6.9	14.4 ± 8.7	0.085
SSR_R (1/s)	0.67 ± 0.34	0.77 ± 0.36	0.096
DSR_R (1/s)	-0.65 ± 0.44	-0.7 ± 0.39	0.45
Basal systolic rotation			
Net Clockwise (°)	-1.6 ± 1.1	-1.1 ± 1.2	0.032*
Magnitude (°)	-1.4 ± 1.4	-0.7 ± 1.7	0.008*
Apical systolic rotation			
Net Counterclockwise (°)	1.9 ± 1.7	2.6 ± 2.2	0.033*
Magnitude (°)	1.1 ± 2.7	1.9 ± 3.2	0.141

Twist (°)	2.6 ± 2.4	2.6 ± 3.4	0.954
Twist per length (°/cm)	0.38 ± 0.37	0.38 ± 0.51	0.951
Torsion ($°s^{-1}$)	1.23 ± 1.00	1.17 ± 1.52	0.714

DSRc= circumferential diastolic strain rate; DSRL= longitudinal diastolic strain rate; DSRR= radial diastolic strain rate; GCS= global circumferential strain; GLS= global longitudinal strain; GRS= global radial strain; LGE= late-gadolinium enhancement; LVEDVi= left ventricular end-diastolic volume index; LVESVi= left ventricular end-systolic volume index; LVEF=left ventricular ejection fraction; LVMi= left ventricular mass index; LVSVi= left ventricular stroke volume index; SSRC= circumferential systolic strain rate; SSRL= longitudinal systolic strain rate; SSRR= radial systolic strain rate; *Significant value ($P < 0.05$)

Table S3. Cardiac magnetic resonance left ventricular mechanical parameters in non-ischemic cardiomyopathy patients with and without left bundle branch block (LBBB).

Variables	LBBB+ N = 56	LBBB- N = 183	P value
Basal systolic rotation			
Net Clockwise (°)	-2.2 ± 1.2	-1.3 ± 1.1	0.040*
Magnitude (°)	-2.0 ± 1.4	-1.0 ± 1.5	0.001*
Apical systolic rotation			
Net Counterclockwise (°)	0.8 ± 1.1	2.4 ± 1.8	0.001*
Magnitude (°)	-0.9 ± 2.7	2.0 ± 2.5	0.001*
Twist (°)	1.3 ± 2.1	3.3 ± 2.6	0.001*
Torsion ($°s^{-1}$)	1.0 ± 0.8	1.5 ± 1.1	0.002*