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Relationship between diffuse fibrosis assessed by CMR and depressed myocardial strain in different stages of heart failure

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ABSTRACT

Objectives: To investigate the extent of the left ventricular (LV) diffuse myocardial fibrosis and the association with the degree of impaired myocardial strain in different stages of heart failure.
Background: The increased diffuse myocardial fibrosis impairs the LV systolic and diastolic function. Previous studies found that the global longitudinal strain (GLS) impacted survival in patients with heart failure with preserved ejection fraction (HFpEF). However, limited data are available regarding the association between the degree of diffuse myocardial fibrosis and the severity of impaired myocardial strain in HFpEF.
Methods: Sixty-six consecutive participants with heart failure (HF), and 15 healthy controls underwent cardiac magnetic resonance (CMR) examination. T1 mapping to calculate extracellular volume fractions (ECV) were used to assess diffuse myocardial fibrosis. ECV and myocardial strains were compared among the 3 groups. Associations between these two factors were also explored.
Results: The patients with HFpEF showed increased myocardial ECV fractions (32.9 % ± 3.7 % vs. 29.2 % ± 2.9 %, $p < 0.001$) compared with the control group. The patients with HFm + rEF also had increased myocardial ECV fractions (36.8 % ± 5.4 % vs. 32.9 % ± 3.7 %, $p < 0.001$) compared with HFpEF. The myocardial ECV was significantly correlated with the GLS ($r = 0.422$, $p = 0.020$), global circumferential strain (GCS) ($r = 0.491$, $p = 0.006$), and global radial strain (GRS) ($r = -0.533$, $p = 0.002$) in the HFpEF groups, but no significant correlation was found in the HFm + rEF group (GLS: $r = -0.002$, $p = 0.990$; GCS: $r = 0.153$, $p = 0.372$; GRS: $r = 0.070$, $p = 0.685$)
Conclusions: In patients with HF, only patients with HFpEF exhibited a significant correlation between increased diffuse myocardial fibrosis and impaired myocardial strain. Diffuse myocardial fibrosis plays a unique role in affecting myocardial strain in patients with HFpEF.

1. Introduction

Heart failure (HF) is a clinical condition and can be categorized into heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF) based on the volume of blood that leaves the heart per contraction [1]. The HFrEF and HFpEF had different etiology, epidemiology, and treatment behavior [2–3]. The HFpEF was seen approximately in half of all patients with HF and showed an increase in adverse outcomes, including mortality, hospitalization, and a decreased quality of life [4–5].

Previous clinical and experimental studies found that diffuse myocardial fibrosis caused diastolic dysfunction by elevating the left ventricular (LV) filling pressure and wall stiffness, which was the main

Abbreviations: ECV, extracellular volume; EF, ejection fraction; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; HF, heart failure.

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pathophysiological mechanism underlying HFpEF [6–7]. Several parameters were recognized as prognostic markers in HFpEF, including LV diffuse fibrosis [8–9], LV myocardial strain [10], right ventricular (RV) function [11], and LV end-diastolic pressure [12]. Although the LVEF in HFpEF was not significantly reduced, the systolic function was possibly impaired, particularly in patients with LV hypertrophy [13]. The myocardial strain which is defined as the relative change in fiber length from end diastole to end systole is another variable to quantify the LV systolic function [14]. However, the association of diffuse myocardial fibrosis with the severity of impaired myocardial stain in patients with HFpEF remains unclear.

The myocardial strain measured by tissue tracking from the cardiovascular MRI assessed the LV systolic function [14]. Further, the cardiovascular MRI serves as the reference standard for evaluating ventricle structure and function [1] and noninvasive tool for the quantitative evaluation of diffuse myocardial fibrosis using T1 mapping. This study aimed to use the T1 mapping to quantify the LV diffuse myocardial fibrosis in three groups of subjects, including patients with HF with preserved ejection fraction, patients with HF with mid-range and reduced ejection fraction, and healthy control. Additionally, the study planned to investigate whether the extent of diffuse myocardial fibrosis is associated with the degree of impaired myocardial strain in different stages of heart failure.

2. Methods

2.1. Study population

In this retrospective study, patients with heart failure who underwent cardiovascular magnetic resonance (CMR) and echocardiography from January 2020 to July 2022 at our hospital, were consecutively included. This study was approved by our Ethics Committee (reference number 2022KY069) and the written informed consent was waived due to the retrospective nature of the study.

The patients with a diagnosis of HF were categorized into 2 groups according to recent guidelines [1]. They were (1) patients with HF with preserved ejection fraction (HFpEF) where the EF was $\geq$ 50 % and brain natriuretic peptide level was $>$ 35 pg/mL or N-terminal pro-brain natriuretic peptide level was $>$ 125 pg/mL at the time of diagnosis, and there was at least one of (a) the underlying LV structural abnormalities (LV end-diastole mass index of $>$115 g/m^2 for men and $>$95 g/m^2 for women from CMR) or (b) LV diastolic dysfunction (early and/or late peak diastolic mitral inflow velocity [E/A] of $<$1 from echocardiography) and (2) patients with HF with the mid-ranged and reduced ejection fraction where the EF was 40 %–49 % or reduced EF of $<$40 % (HFm + rEF). Both groups had similar additional criteria. Exclusion criteria were the acquired images of reduced quality or presence of artifacts and patients with primary severe valvular cardiac disease, acute coronary syndrome, myocarditis, restrictive pericardial disease, severe arrhythmia, and severe renal dysfunction with the glomerular filtration rate of $<$30 mL/min/1.73 m^2). The experimental groups were matched for age and gender distribution. The control group was matched by age, sex, and body mass index (BMI) and underwent an identical protocol similar to the HF subjects. These volunteers also participated in our previous studies. The final numbers of subjects involved in the analyses are shown in Fig. 1.

2.2. Echocardiography

All participants underwent the echocardiographic procedures in a supine position using the Philips EPIQ7C cardiology ultrasound system (Blind). All images were digitally stored for the subsequent offline analysis and the analysis was performed by two experienced physicians blinded to the clinical data.

2.3. Cardiovascular MRI acquisition

All CMR images were acquired using a 3.0 T scanner (Blind) with vector-electrocardiographic gating and a 16-channel phased array surface coil combined with a 16-channel posterior coil. The cine images were acquired using the ECG-gated balanced steady-state free procession (b-SSFP) sequence with multiple breath-holds at the end-expiration on the left ventricular long-axis (2Ch, 3Ch, and 4Ch) planes and short-axis. The ventricular two-chamber and four-chamber planes were used to stack the short-axis slices covering the entire LV. The imaging parameters such as slice thickness of 8 mm, repetition time (TR) of 2.8–3.2 ms, echo time (TE) of 1.4–1.5 ms, the flip angle of 45°, the matrix size of 160 × 138 to176 × 192 mm^2, the field of view of 300 × 300–350 × 350 mm^2, and temporal resolution of 15–25 ms, were used depending on the heart rate. LGE images obtained at least 10 min after administration of

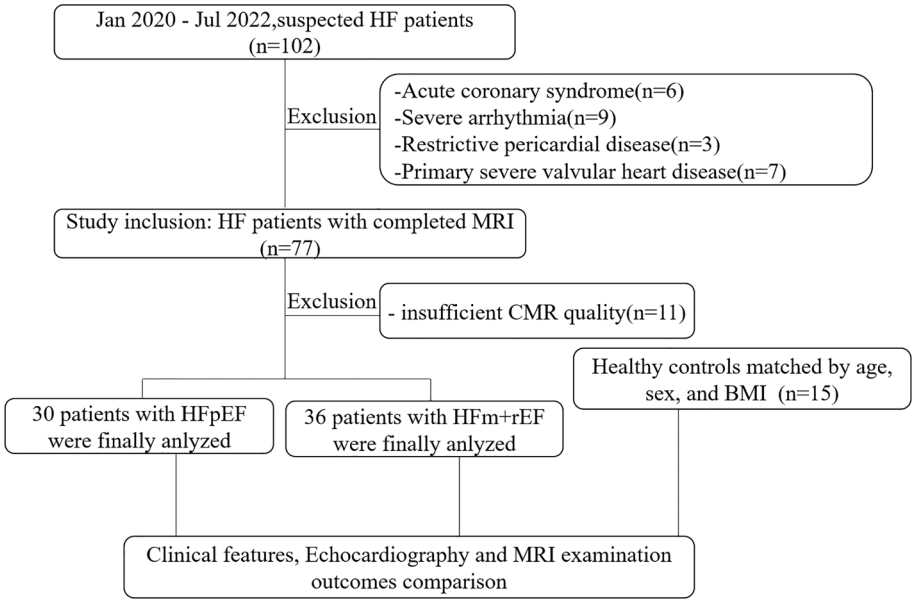

Fig. 1. Participant flowchart. CMR, cardiovascular MRI; HF, heart failure; HFpEF, patients with heart failure with preserved ejection fraction; HFm + rEF, patients with heart failure with the mid-ranged and reduced ejection fraction;BMI, body mass index.

gadopentetic acid (Gd-DTPA). T1 mapping was acquired before and 15 min after administration of Gadopentetic acid (Gd-DTPA) contrast agent using the modified look-locker inversion recovery (MOLLI) sequence on the short axis from the apex segment to the base. The imaging parameters such as TE of 1.1 ms, TR of 2.4 ms, flip angle of 20°, mid-diastolic trigger delay, slice thickness of 8 mm, the field of view of 320 × 320 mm^2, matrix size of 160 × 160, acquisition scheme of 5s(3s)3s for the native T1 maps and 4s(1s)3s(1s)2s for the post-contrast T1 maps were used.

2.4. Assessing the cardiac volume and function

All images were analyzed offline using commercially available software (cvi42; Circle Cardiovascular Imaging Inc., Calgary, AB, Canada). The LV volumetry and mass were derived from the segmentation of endocardial and epicardial contours at the end-diastole and end-systole phases, respectively. The left ventricular cavity included trabecular and papillary muscles. Finally, the left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), stroke volume (LVSV), ejection fraction (LVEF), and mass (LVM) were measured. All the volumes and mass were indexed with the body surface area (BSA) for the quantitative analysis.

2.5. Measurements of T1 mapping and ECV mapping

T1 maps and extracellular volume fraction maps were performed using the T1 mapping module with the CVI[42] software. The endocardial and epicardial contours of the left ventricular basal, middle and apical segments were manually delineated. The native and post-contrast T1 values were calculated from 16 regions based on the American Heart Association (AHA) 17-segment model apex being excluded [15]. Finally, the global and regional T1 values were evaluated at the same times. Hematocrit were obtained through a blood draw within three days before the MRI examination. The ECV maps were automatically performed based on the previously described formula as follows [16]:

$$ECV = (1 - hematocrit)\frac{\left(\frac{1}{T1_{myopost}} - \frac{1}{T1_{myopre}}\right)}{\left(\frac{1}{T1_{bloodpost}} - \frac{1}{T1_{bloodpre}}\right)}$$

2.6. Measurement of myocardial strain

Myocardial strain analysis was done on the short axis and long axis (2Ch, 3Ch, and 4Ch) cine images. The endocardial and epicardial borders were traced semiautomatically and manually corrected if needed. The software automatically tracked the myocardial motions in each cardiac cycle. Three-directional myocardial strains, global longitudinal, radial, and circumferential strains were calculated according to the American Heart Association (AHA) 17-segments model [15], with the apex being excluded. Finally, the global and regional myocardial strain were evaluated at the same times.

2.7. Reproducibility

Fifteen participants were randomly selected from the population. In these participants, the LV myocardial measurement by native T1, ECV fraction, and myocardial strain were repeatedly measured by the same observer and another blinded observer.

2.8. Statistical analysis

Statistical analyses were performed with SPSS Version 20.0 and MedCalc Version 20.015. The variables were presented as means ± standard deviations, medians with interquartile ranges, or numbers with percentages, as appropriate. The categorical variables, including demographic characteristics, risk factors, etiology of HF, and medications used were compared among different groups of patients using chi-square tests. The continuous variables, including clinical characteristics, myocardial native T1, myocardial ECV, myocardial strain, and LV functional indexes were compared by one-way ANOVA and nonparametric Kruskal Wallis test as appropriate. The pairwise multiple comparison procedures were performed using the Dunn's method and Mann-Whitney *U* test, as appropriate. For the potential association between the myocardial ECV, native T1, and myocardial strain, each functional index in each group was tested by the Pearson and Spearman rank correlation test as appropriate. The receiver operating characteristic curve (ROC) analysis selected the cutoff values to distinguish patients with HFpEF from normal controls. Delong test for the comparison of AUC results. The P-value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of healthy controls and patients

Thirty-six patients with HFm + rEF (n = 33, LVEF of ≤40 %; n = 3, 40 % < LVEF < 50 %), 30 patients with HFpEF, and 15 patients without HF were included in the study [Fig. 1]. The baseline characteristics of

Table1
The clinical characteristics of the study population.

	HFm + rEF (n = 36)	HFpEF (n = 30)	Controls (n = 15)	p
Age (year)	55 ± 14	56 ± 10	55 ± 12	0.513
Male, n (%)	28 (77)	19 (63)	8 (53)	0.186
Body surface area (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.968
Body mass index (kg/m^2)	24.6 ± 4.0	25.2 ± 3.8	25.2 ± 2.6	0.750
SBP (mmHg)	126 (114–133)	127 (120–140)	124 (121–127)	0.299
DBP (mmHg)	74 (70–82)	75 (67–81)	74 (72–75)	0.681
Risk factors				
Diabetes mellitus	11 (31)	7 (23)	0 (NA)	0.512
Hypertension	16 (44)	16 (53)	0 (NA)	0.472
Dyslipidemia	32 (89)	21 (70)	0 (NA)	0.055
Known myocardial infarction	8 (22)	3 (10)	0 (NA)	0.185
Atrial fibrillation	6 (17)	3 (10)	0 (NA)	0.432
Stroke	5 (14)	3 (10)	0 (NA)	0.302
Etiologies for HF				
Coronary artery disease	10 (28)	7 (23)	0 (NA)	0.681
Dilated cardiomyopathy	20 (56)*6 (16)*	0 (0)23 (77)	0 (NA) 0 (NA)	<0.001 <0.001
Others				
Medications				
Aspirin	22 (61)*	9 (30)	0 (NA)	0.009
Angiotensin-converting enzyme inhibitor	11 (31)*	0 (0)	0 (NA)	<0.001
Angiotensin receptor blocker	23(64) *	7(23)	0(NA)	<0.001
Laboratory Values				
Hematocrit (%)	43.8 ± 6.1	42.0 ± 5.8	41.9 ± 4.6	0.359
GFR (mL/min)	74.5 (55.0–86.2)	77.5 (62.7–91.9)	–	0.455
Creatinine (mg/dl)	72.1 (60.7–82.1)	72.4 (60.7–82.1)	–	0.643
NT-proBNP (ηg/l)	986 (512–1433)*	306 (203–586)	–	<0.001

Note: All data are expressed as the mean ± SD, percentage (number of participants), or median (interquartile range) as appropriate.
Abbreviations: NA, not applicable in controls ; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N terminal pro B type natriuretic peptide; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFm + rEF, heart failure with mid-ranged and reduced ejection fraction; GFR, glomerular filtration rate.
*P-value of < 0.05, compared with HFpEF group. ** P-value of < 0.05, compared with the control group.

the healthy controls and patients are summarized in Table 1. No significant differences were observed in age, sex, blood pressure, BSA, and BMI among the groups. Healthy controls did not have risk factors and a history of cardiovascular medication use compared to patients.

3.2. LV functional parameters from echocardiography and CMR

Comparisons of echocardiographic and MRI parameters between groups are listed in Table 2. Compared with the HFpEF groups, the patients with the HFm + rEF showed larger left atrium (LA anteroposterior diameter, 46.5 ± 8.1 mm vs. 39.7 ± 5.2 mm, P < 0.001) by echocardiography, larger left ventricle (LV end-diastole volume index, 145.8 ± 46.2 mL/m^2 vs. 76.5 ± 16.7 mL/m^2, P < 0.001, greater LV end-diastole mass index (87.7 g/m^2 [IQR: 70.1–114.1 g/m^2] vs 65.7 g/m^2 [IQR: 54.2–94.4 g/m^2], p < 0.001), higher LV myocardial ECV fractions (36.8 % ± 5.4 % vs. 32.9 % ± 3.7 %, p < 0.001), and native T1 times (1362.1 ± 43.6 ms vs. 1347.7 ± 47.7 ms, p < 0.001) from CMR. Compared with the controls group, the patients with the HFpEF also showed greater LV end-diastole mass index (65.7 g/m^2 [IQR: 54.2–94.4 g/m^2] vs. 47.6 g/m^2 [IQR: 44.6–51.9 g/m^2], p < 0.001), higher myocardial ECV fractions (32.9 % ± 3.7 % vs. 29.2 % ± 2.9 %, p < 0.001), and native T1 times (1362.1 ± 43.6 ms vs. 1260.8 ± 26.0 ms, p < 0.001)(Fig. 2).No significant difference was detected in native T1 times and ECV fractions between patients with positive LGE and patients with negative LGE in both HFpEF (Native T1:1360.8 ± 49.8 ms vs.1330.8 ± 40.7 ms, p = 0.088; ECV:33.8 % ± 4.1vs.31.9 ± 3.0, p = 0.178) and HFm + rEF (Native T1:1360.9 ± 44.1 ms vs.1364.6 ± 44.2 ms, p = 0.814; ECV:37.1 % ± 5.7vs.36.4 ± 5.0, p = 0.717) groups. The LV torsion was reduced in patients with the HFm + rEF compared with the HFpEF group (p < 0.001) but was similar between the HFpEF group and the control group (P > 0.05). The global longitudinal strain, circumferential strain, and radial strain decreased significantly among the three groups (Fig. 3).

Table 2
Echocardiographic and MRI characteristics of the study population.

	HFm + rEF (n = 36)	HFpEF (n = 30)	Controls (n = 15)	p
Echocardiography parameters				
E/A < 1	22(61) *, **	26(87) **	0	<0.001
LA anteroposteriordiameter (mm)	46.5 ± 8.1*, **	39.7 ± 5.2	35.7 ± 3.5	<0.001
CMR parameters				
LVEDVi (mL/m^2)	145.8 ± 46.2*, **	76.5 ± 16.7	72.3 ± 11.5	<0.001
LVESVi (mL/m^2)	106.2 ± 39.6*, **	32.7 ± 8.9	27.6 ± 4.7	<0.001
LVMi (g/m^2)	87.7 (70.1–114.1)*, **	65.7 (54.2–94.4)**	47.6 (44.6–51.9)	<0.001
LVEF (%)	28.3 ± 8.9*, **	57.4 ± 5.1	61.8 ± 3.0	<0.001
Native T1 (ms)	1362.1 ± 43.6**	1347.7 ± 47.7**	1260.8 ± 26.0	<0.001
ECV (%)	36.8 ± 5.4*, **	32.9 ± 3.7**	29.2 ± 2.9	<0.001
Presence of LGE	24(67) **	17(57) **	0	<0.001
GLS (%)	−7.2 ± 2.6*, **	−12.6 ± 3.6**	−18.5 ± 2.0	<0.001
GCS (%)	−7.1 ± 2.7*, **	−16.1 ± 3.5**	−20.0 ± 2.3	<0.001
GRS (%)	9.6 ± 3.9*, **	22.7 ± 6.3**	34.3 ± 3.6	<0.001
Torsion (deg/cm)	0.61 ± 0.36*, **	1.62 ± 0.64	1.73 ± 0.42	<0.001

Abbreviations: E/A, early/late peak diastolic mitral inflow velocity; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; ECV, extracellular volume; LGE, late gadolinium enhancement; GRS, global radial strain; GCS, global circumferential strain; GLS, global longitudinal strain.
*P-value of < 0.05, compared with HFpEF group. ** P-value of < 0.05, compared with the control group.

3.3. Association of native T1 value and ECV with myocardial strain

The correlation analysis was performed between myocardial ECV, native T1, and myocardial strain for each patient group to investigate the correlation between diffuse myocardial fibrosis and myocardial strain. The myocardial ECV was significantly correlated with the GLS (r = 0.422, p = 0.020), GCS (r = 0.491, p = 0.006), and GRS (r = −0.533, p = 0.002) in the HFpEF group (Fig. 4). There was no significant correlation between the myocardial ECV and the myocardial strain in the HFm + rEF group (GLS: r = −0.002, p = 0.990; GCS: r = 0.153, p = 0.372; GRS: r = 0.070, p = 0.685). There was also no significant correlation between the native T1 and myocardial strain in the HFm + rEF group and HFpEF group.

To investigate the ischemic and nonischemic etiological factors affecting myocardial ECV fractions and native T1 times, the HFm + rEF and HFpEF groups were categorized into 2 subgroups separately basing on cardiac catheterization and resting myocardial perfusion image in cardiac magnetic resonance, patients with coronary artery disease (CAD) and patients without CAD. There were 7 and 10 patients with CAD in both HFpEF and HFm + rEF groups, respectively. There were no significant differences in the myocardial ECV fractions between patients with and without CAD for the HFpEF (33.6 % ± 2.8 % vs. 32.8 % ± 4.0 %, p = 0.587) and HFm + rEF (35.7 % ± 5.2 % vs. 37.3 % ± 5.5 %, p = 0.437). Similarly, native T1 times, GLS, GCS, GRS, and LV torsion exhibited no significant differences between patients with and without CAD for the HFm + rEF and HFpEF groups.

3.4. Differentiation of patients with HFpEF from normal controls

The diagnostic performance of T1 mapping and myocardial strain indices (Fig. 5). Native T1 times exhibited the highest AUC- ROC (0.956), and were significantly higher than ECV fractions (0.783, p < 0.05). Using a cut-off value of 1297 ms for the native T1 times, patients with HFpEF were distinguished from the normal subjects at a sensitivity of 86.7 % and specificity of 100 %.

3.5. Intra-observer and inter-observer reproducibility

The intra-class correlation coefficients (ICCs) were 0.942, 0.950, 0.887, 0.967, and 0.950 for the native T1, ECV, GRS, GCS, and GLS, respectively. The inter-class correlation coefficients from the interobserver analysis were 0.860, 0.931, 0.840, 0.925, and 0.931 for the native T1, ECV, GRS, GCS, and GLS, respectively.

4. Discussion

In this study, T1 mapping and tissue tracking techniques were used to quantify diffuse myocardial fibrosis and myocardial strain in patients with HF. The native T1 times and ECV fractions were increased whereas the global longitudinal strain, global circumferential strain, and global radial strain were reduced compared with healthy controls, but the LV torsion was preserved in patients with HFpEF. The patients with HFm + rEF exhibited significant increases in native T1 times and ECV fractions but decreases in GLS, GCS, GRS, and LV torsion compared with patients with HFpEF. The increased ECV fractions were noticed, indicating the extent of diffuse myocardial fibrosis [17], and were significantly correlated with the degree of impaired myocardial strain in the HFpEF group. Furthermore, Our CMR results suggested that native T1 times had the better measures of discrimination to distinguish the patients with HFpEF from normal subjects with a sensitivity of 86.7 % and a specificity of 100 %.

Borbely et al. [18] used endomyocardial biopsy to measure the

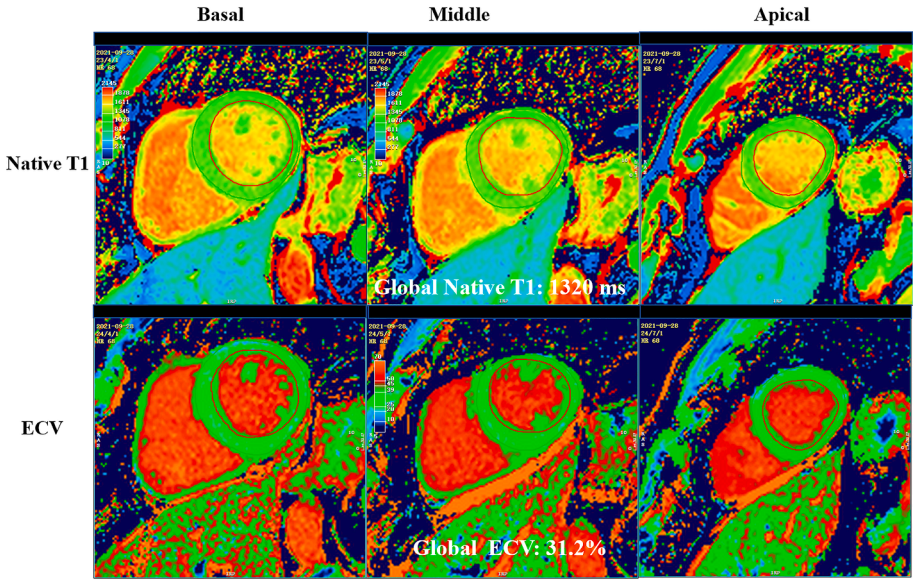

Fig. 2. Representative T1 mapping from a patient with HFpEF at the left ventricular basal (left column), middle (middle column), and apical (right column) short-axis segment with a modified look-locker inversion recovery (MOLLI) sequence showing the native T1 maps (upper row)and calculated extracellular volume (ECV) maps of the same segment (bottom row).

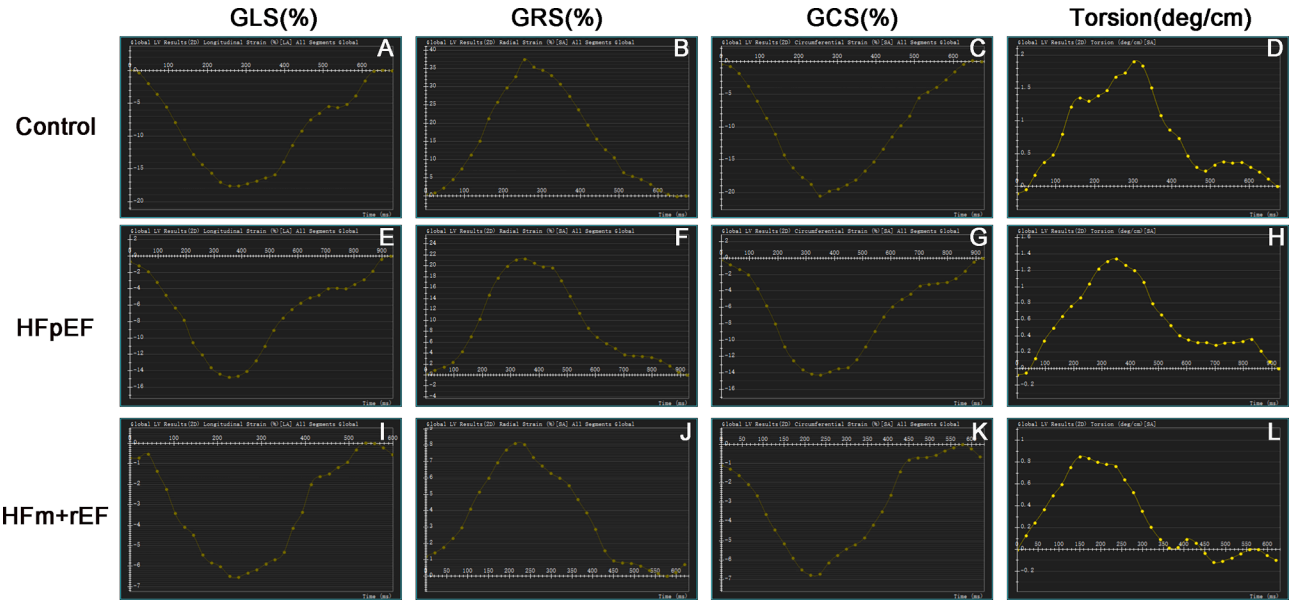

Fig. 3. Examples of global longitudinal strain (GLS: Left first column), global radial strain (GRS: Left second column), global circumferential strain (GCS: Left third column), and LV torsion (Torsion: Left fourth column) from a control subject (upper row), a patient with the heart failure with preserved ejection fraction (HFpEF: middle row), and a patient with the heart failure with mid-range and reduced ejection fraction (HFm + rEF: bottom row). Notice the presence of normal torsion in a patient with HFpEF but lower global longitudinal, radial, and circumferential strain compared with the control subject.

degree of myocardial fibrosis and found that the patients with HFpEF had significantly higher collagen volume fractions compared with the patients without HF. Myocardial T1 time is a measure of how fast the nuclear spin magnetization returns to its equilibrium state after a radiofrequency (RF) pulse, and it can be measured before and after the gadolinium-based contrast agent administration. The increase in the native T1 times was due to the myocardial fibrosis burden or the result of other pathological features, such as edema, depending on the intracellular and extracellular factors [19]. We eliminated the interference of myocardial edema by the criteria of exclusion in our study. Bull et al. [20] correlated the native T1 with the histological features in patients with diffuse fibrosis and suspicion of having myocardial fibrosis secondary to aortic stenosis. Therefore, T1 mapping technique was used to quantify diffuse myocardial fibrosis is feasible in this study.

Two main types of myocardial fibrosis were reported based on the pathogenesis of cardiomyopathy. Type I exhibits interstitial reactive fibrosis with a diffuse distribution within the interstitium, and in the other type, the myocytes are replaced with fibrosis [21]. The myocardial ECV fractions are predominantly reflective of changes in the extracellular space. It is calculated by normalization of myocardial T1 time with blood T1 time and eliminates some potentially confounding effects from the post-contrast T1 measurements, such as variations in the clearance of contrast from blood, the timing of post-contrast MOLLI acquisition, the amount of contrast injected, and magnetic field strength [19]. Therefore, myocardial ECV may be a better indicator than the native T1 time in evaluating the extracellular matrix expansion such as diffuse

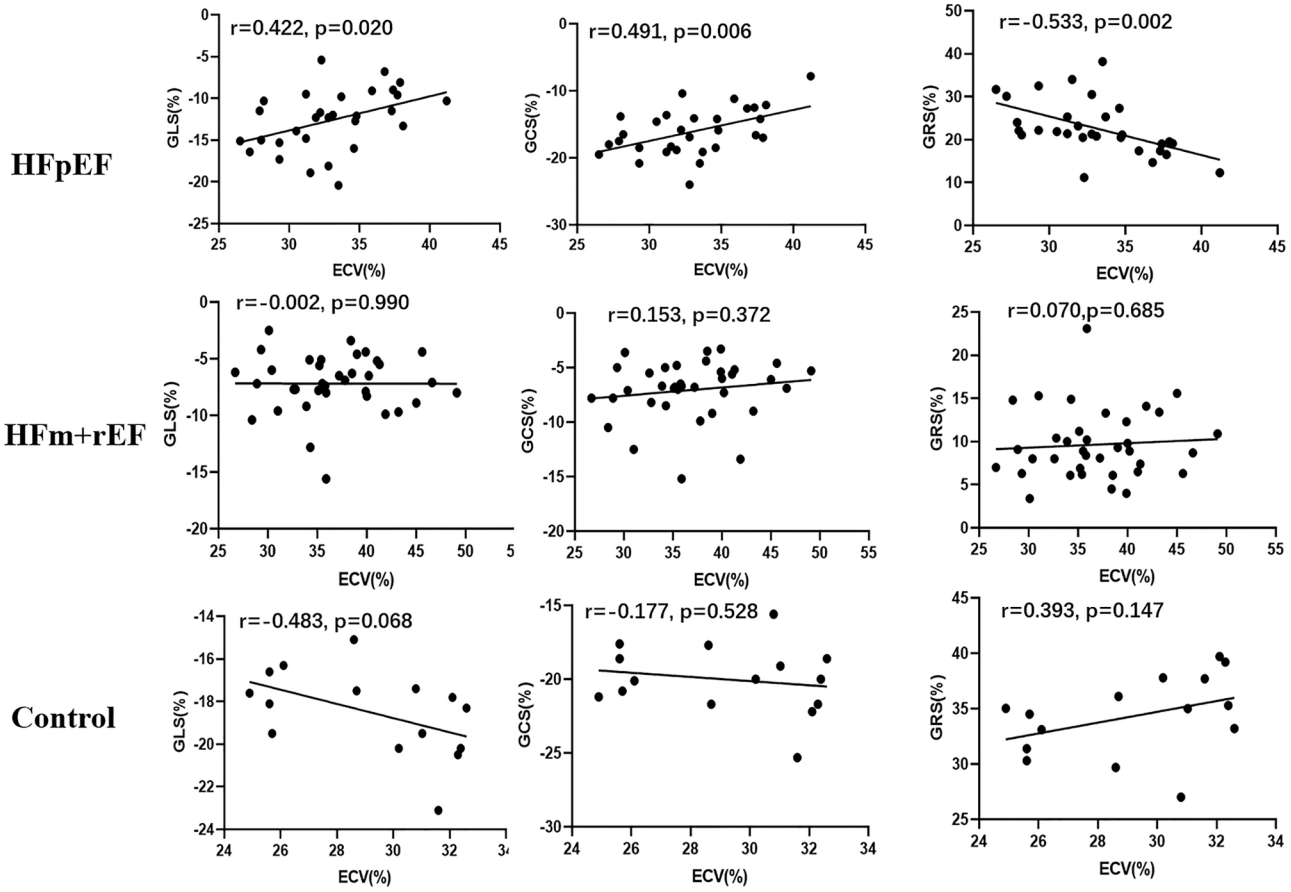

Fig. 4. Correlations of myocardial extracellular volume fraction (ECV) with global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) in patients with heart failure with preserved ejection fraction (HFpEF) and patients with the heart failure with mid-range and reduced ejection fraction (HFmrEF), and healthy controls.

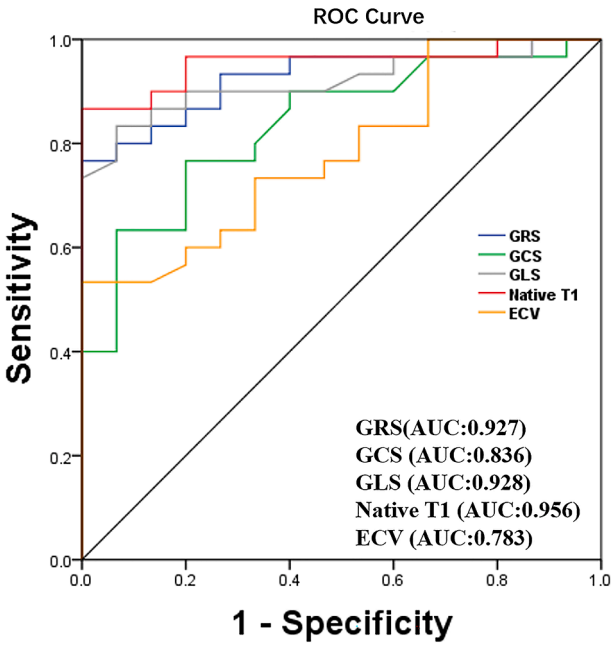

Fig. 5. The ROC curve analysis of the CMR-derived LV parameters for differentiating patients with HFpEF from healthy controls. ROC, receiver operating characteristic; AUC, area under ROC curve; ECV, extracellular volume; GRS, global radial strain; GCS, global circumferential strain; GLS, global longitudinal strain.

myocardial fibrosis. In this study, myocardial ECV in HFm + rEF was higher than in HFpEF, indicating that patients with HFm + rEF have a greater degree of diffuse myocardial fibrosis than patients with HFpEF. A previous study found an association between increased diffuse myocardial fibrosis and diastolic dysfunction in HFpEF [22]. In the current study, no significant association was found between the native T1 time and impaired LV global myocardial strain in the patients with HFpEF and HFm + rEF. However, the ECV showed a significant correlation with the impaired LV global myocardial strain in patients with HFpEF, not in patients with HFm + rEF. A previous study on histopathology of HF displayed the replacement of myocytes with fibrosis in the terminal stages of HF [23]. This type of fibrosis also affects the LV function independently of diffuse myocardial fibrosis. For patients with HFm + rEF, the prevalence of LGE is higher than that in HFpEF (67 % vs. 57 %) and higher volume of LGE can be observed during image analysis compared with patients with HFpEF. Therefore, consolidated replacement fibrosis may have more contribution to affect ventricular dysfunction in patients with HFm + rEF compared with patients with HFpEF.

The myocardial strain was a more sensitive early marker for contractile dysfunction than the LVEF [13,24,25]. In this study, the longitudinal, radial, and circumferential strains were measured by tissue tracking technique in patients with HF. The patients with HFpEF exhibited lower longitudinal, radial, and circumferential strains than the healthy subjects, indicating the impaired systolic function, and its significant correlation with the extent of diffuse myocardial fibrosis in patients with HFpEF. The LV torsion was a consequence of the contraction of individual myofibers interacting with three-dimensional architecture, which is mainly responsible by subepicardial fibers [26].

In this study, the LV torsion was calculated by the difference in rotation between apical and basal slices divided by the distance from the apical to basal slices. Previous studies involving histopathological analyses demonstrated that the endocardium was most susceptible to being affected by interstitial fibrosis [27]. Thus, the explanation for the preserved torsion may have been that subepicardial layers were not affected in the patients with HFpEF. However, with the disease progression, the mid-myocardial and subepicardial layers might have been affected by pathological changes, and the LV torsion might have been reduced in the later stages of HF. In the current study, LV torsion was significantly higher in patients with HFpEF compared with HFm + rEF. The preserved LV torsion may have been a compensatory mechanism for the left ventricular global systolic function in HF.

5. Limitations

The current study also had several limitations. First, this study had no histological evidence to validate the changes in left ventricular myocardial native T1 value and myocardial ECV because all subjects did not undergo endomyocardial biopsy evaluation. However, the increases in the native T1 and ECV might have been due to diffuse myocardial fibrosis in heart failure, as reported in previous literature [17]. Second, it was a single-center retrospective study with relatively small sample size. The echocardiographic index to evaluate the diastolic function parameters was the early/late peak diastolic mitral inflow velocity (E/A), which was not applicable in HF with atrial fibrillation. However, the entirety of the diagnostic criteria was comprehensively considered and ensured that the patients met the inclusion criteria. Finally, in the HFpEF group, 53 % of patients suffered from hypertension which might have also caused diffuse myocardial fibrosis. When comparing the HFpEF and HFm + rEF groups, which had a comparable prevalence of hypertension, this study supported that diffuse myocardial fibrosis was increased in patients with HF despite the presence of hypertension.

Conclusions

In patients with HF, increased native T1 and ECV were detected indicating the extent of diffuse myocardial fibrosis. The degree of impaired myocardial strain was associated with the increased diffuse myocardial fibrosis, reflecting the LV systolic dysfunction in patients with HFpEF. This study support diffuse myocardial fibrosis is a key factor in the pathophysiology of patients with HFpEF and plays as a diagnostic reference for the assessment of various type of heart failure.

Clinical perspectives

Competency in medical knowledge:

HFpEF was seen approximately in half of all hospitalized patients for heart failure and is associated with a poor prognosis. Using CMR, the present study shows that the degree of impaired myocardial strain was associated with the increased diffuse myocardial fibrosis in patients with HFpEF.

Translational outlook

As diffuse fibrosis is recognized as prognostic markers and reversible. Our findings demonstrate the utility of myocardial strain in assessing patients with HFpEF. The measurement of myocardial strain could be used to inform clinicians about whether HF medications could improve the degree of diffuse myocardial fibrosis in HFpEF.

Guarantor

The scientific guarantor of this publication is Dr. Lei Zhang.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Xiance Zhao is an employee of Philips Healthcare. However, control of all data and information submitted for publication was given to authors not affiliated with Philips Healthcare.

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