JACC: CARDIOVASCULAR IMAGING
VOL. 7, NO. 10, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2014.04.022

CMR-Verified Diffuse Myocardial Fibrosis Is Associated With Diastolic Dysfunction in HFpEF

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ABSTRACT

OBJECTIVES The purpose of this study was to investigate diffuse myocardial fibrosis in patients with systolic heart failure (SHF) and in patients with heart failure with preserved ejection fraction (HFpEF) and the association with diastolic dysfunction of the left ventricle (LV).

BACKGROUND Increased diffuse myocardial fibrosis may impair LV diastolic function. However, no study has verified the association between the degree of diffuse myocardial fibrosis and the severity of impaired diastolic function in SHF and HFpEF.

METHODS Forty patients with SHF, 62 patients with HFpEF, and 22 patients without HF underwent cardiac magnetic resonance (CMR), including T1 mapping and cine CMR on a 3-T system. Extracellular volume fraction (ECV), a measure of diffuse myocardial fibrosis, was quantified from T1 mapping. Systolic and diastolic functions of the LV were assessed by cine CMR. The ECV values and LV functional indexes were compared among the 3 groups. Associations between ECV and LV diastolic function were also investigated.

RESULTS Compared with patients without HF, significantly higher ECV was found in patients with SHF (31.2% [interquartile range (IQR): 29.0% to 34.1%] vs. 27.9% [IQR: 26.2% to 29.4%], $p < 0.001$) and HFpEF (28.9% [IQR: 27.8% to 31.3%] vs. 27.9% [IQR: 26.2% to 29.4%], $p = 0.006$). Peak filling rate, a diastolic functional index assessed by cine CMR, was significantly decreased in patients with SHF (1.00 s^{-1} [IQR: 0.79 to 1.49 s^{-1}] vs. 3.86 s^{-1} [IQR: 3.34 to 4.48 s^{-1}], $p < 0.001$) and HFpEF (2.89 s^{-1} [IQR: 2.13 to 3.50 s^{-1}] vs. 3.86 s^{-1} [IQR: 3.34 to 4.48 s^{-1}], $p < 0.001$). Myocardial ECV was significantly correlated with peak filling rate in the HFpEF group ($r = -0.385$, $p = 0.002$), but no correlation was found in the SHF and non-HF groups ($r = 0.030$, $p = 0.856$ and $r = -0.238$, $p = 0.285$, respectively).

CONCLUSIONS In patients with HF, only those with HFpEF show a significant correlation between increased diffuse myocardial fibrosis and impaired diastolic function. Diffuse myocardial fibrosis plays a unique role in the pathogenesis of HFpEF. (J Am Coll Cardiol Img 2014;7:991–7) © 2014 by the American College of Cardiology Foundation.

Heart failure (HF) is a clinically defined syndrome with a wide range of ejection fraction (EF) values of the left ventricle (LV). Patients with HF can be categorized into those with impaired ejection fraction (systolic heart failure [SHF]) and those with preserved ejection fraction (HFpEF). Accumulating evidence shows that SHF and HFpEF are 2 distinct disease entities and have different etiology, epidemiology, and response to treatment (1–6). Patients with HFpEF were previously assumed to have a better prognosis than patients with depressed systolic function. Recent data suggest that mortality rates and rates of rehospitalization are not significantly different between the 2 groups. Moreover, in contrast to the improvement in survival in patients with SHF, mortality from HFpEF has

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Manuscript received February 3, 2014; revised manuscript received April 9, 2014, accepted April 22, 2014.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CMR = cardiac magnetic resonance

ECG = electrocardiography

ECV = extracellular volume fraction

EDV = end-diastolic volume

EF = ejection fraction

ESV = end-systolic volume

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

IQR = interquartile range

LV = left ventricle

MOLLI = modified Look-Locker inversion recovery

MVR = mass-to-volume ratio

PER = peak ejection rate

PFR = peak filling rate

SHF = systolic heart failure

remained the same (2). Further information regarding the changes in cardiac structure and function in patients with HFpEF is needed to understand the pathophysiology of the disease and to gain insight for a potential therapeutic approach.

Diagnosis of HFpEF requires relatively preserved systolic function and the presence of diastolic dysfunction in patients with HF. Various clinical and experimental studies have shown the significance of diffuse myocardial fibrosis as a cause of diastolic dysfunction (7–9). Thus far, it remains unclear whether the degree of myocardial fibrosis is associated with the severity of impaired diastolic function in patients with HFpEF. Furthermore, impaired diastolic function is not unique to patients with HFpEF; it also occurs in patients with SHF. The degree of diffuse fibrosis and its relationship with ventricular function in patients with SHF have not yet been reported.

Cardiac magnetic resonance (CMR) is a promising tool to evaluate the structure and function of the LV. Recent studies have shown that T1 mapping of CMR is feasible to quantify the degree of diffuse myocardial fibrosis by measuring extracellular volume fraction (ECV) of the myocardium (10–12). In this study, we used the T1 mapping technique to quantify diffuse myocardial fibrosis in 3 groups of subjects, including patients with SHF, patients with HFpEF, and patients without HF. Our goal was to test the hypothesis that the degree of diffuse myocardial fibrosis is associated with the severity of diastolic dysfunction in patients with HFpEF. We further hypothesized that the roles of diffuse myocardial fibrosis in the pathophysiology of diastolic dysfunction differ between SHF and HFpEF.

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METHODS

STUDY POPULATION. The study was approved by the institutional review board of our hospital. All study participants provided written informed consent. A total of 106 patients who had a clinical history of HF and met the following conditions were enrolled in the HF group: symptoms of HF of New York Heart Association functional class II to III or a history of symptoms/signs of HF using the Framingham criteria (13) and persistence of symptoms and signs of HF for more than 3 months. In the HF group, 66 patients with an EF >45% and LV diastolic dysfunction documented by tissue Doppler echocardiography, defined as the mean of septal and lateral mitral annular early diastolic velocity <8 cm/s (14), were assigned to the HFpEF group, and 40 patients with an EF <45% were defined assigned to the SHF group. Twenty-two patients who did not present a medical history or current manifestations of symptoms and signs of HF were recruited for the non-HF group. Subjects were excluded from the study if they had known significant valvular heart diseases indicated for percutaneous or surgical intervention, chronic atrial fibrillation, chronic pulmonary disease, active myocardial ischemia defined by a positive stress test or unrevascularized significant (70%) stenosis in coronary arteries by angiography, or an estimated glomerular filtration rate <30 ml/min/1.73 m^2.

IMAGING ACQUISITION. CMR was performed on a 3-T CMR system (Trio; Siemens, Erlangen, Germany) with an 8-channel cardiovascular phased array torso coil. Myocardial T1 mapping was performed with an electrocardiography (ECG)-triggered modified Look-Locker inversion recovery (MOLLI) sequence before and 10 min after 0.15 mmol/kg intravenous administration of the gadolinium-based contrast agent (Omniscan, GE Healthcare Inc., Princeton, New Jersey). The MOLLI protocol used 2 Look-Locker cycles to acquire 7 images over 11 heartbeats, and the scanning parameters were as follows: TR/TE, 1.9 ms/1.0 ms; flip angle, 35°; minimum inversion time, 110 ms; inversion time increment, 80 ms; matrix size, 256 × 192; slice thickness, 6 mm; spatial resolution, 1.28 mm; Generalized Autocalibrating Partially Parallel Acquisition acceleration factor, 2; number of inversions, 2; images acquired after first inversion, 5; pause, 4 heartbeats; and images acquired after second inversion, 2. Five evenly spaced short-axis slices were acquired sequentially from the LV base to apex. After post-contrast T1 acquisition, LGE images were acquired by using an ECG-triggered phase-sensitive inversion recovery prepared segmented fast gradient echo pulse sequence (15) at the same short-axis slices as those in the myocardial T1 mapping to identify the focal fibrosis or scarring.

Cine CMR was performed using a segmented balanced steady-state gradient echo pulse sequence with a retrospective ECG R-wave trigger. The scanning parameters were as follows: TR/TE, 3.0 ms/1.5 ms; flip angle, 46°; matrix size, 256 × 208; and spatial resolution, 1.21 mm. Multiple short-axis slices were prescribed from the mitral orifice to LV apex with slice thickness of 8 mm and gap of 2 mm. The true temporal resolution was 63 ms, and 30 cardiac phases were reconstructed retrospectively for each slice level.

IMAGE ANALYSIS. Quantitative analysis of myocardial ECV was performed on T1 maps. The regions of interest in the blood and the myocardium of the LV were drawn in the central area of the LV cavity and the septal myocardium on T1 maps for each slice, respectively. If the septal myocardium showed regional hyperenhancement on the LGE images, the regions of interest of the myocardium was redrawn in other unenhanced myocardial regions. The averaged T1 values of the segmented regions of interest were then computed. After subtracting the pre-contrast values from the post-contrast values, the changes in the relaxation rate (1/T1) in the blood and the myocardium were obtained. Myocardial ECV values were calculated by using the ratio of the change in relaxation rate in the myocardium to that in the blood and multiplied by (1 − hematocrit). We averaged each myocardial ECV value over 5 short-axis slices for each subject (16).

For LV function and mass analysis, endocardial and epicardial contours of the LV were determined at each slice level on cine CMR and the area enclosed by each contour was computed (17). LV volumes for each time point were then determined using the Simpson rule to obtain the volume-time curve of the LV. End-diastolic volume (EDV) and end-systolic volume (ESV) of the LV were assessed from the volume-time curve for the maximal and minimal values and were used to compute EF. To obtain the rate of change in LV volume (dV/dt), LV volumes at each cardiac phase were first normalized by EDV to eliminate "pseudonormal filling" of the LV (18). We calculated the differential of the volume change (dV/dt) and performed interpolation with a cubic b-spline function with an interval of 1 ms. From the interpolated curve of dV/dt, systolic and diastolic functional indexes were determined at the minimal and maximal values as peak ejection rate (PER) and peak filling rate (PFR), respectively. LV mass was computed as the difference between LV epicardial volume at end-diastole and EDV multiplied by the density of the myocardium (1.05 g/ml). LV geometric remodeling was determined from the mass-to-volume ratio (MVR) by calculating the ratio of LV mass with respect to EDV. LV volumes and mass indexed to body surface area were also measured from EDV, ESV, and LV mass divided by body surface area. Image analysis was performed using software developed in-house provided by MATLAB 7.9 (MathWorks, Inc., Natick, Massachusetts).

STATISTICAL ANALYSIS. Because the Shapiro-Wilk test showed that most of the variables were not normally distributed, all statistical analyses were performed by nonparametric methods. Continuous variables were expressed as medians and interquartile ranges (IQRs), and categorical variables were expressed as percentages. Categorical variables, including demographics, etiology of HF, and medication use, were compared among different groups of patients by using chi-square tests. Continuous variables, including clinical characteristics, myocardial ECV, and LV functional indexes and mass, were tested by the nonparametric Kruskal-Wallis test, and the Mann-Whitney *U* test was used for post-hoc analysis for comparison of the medians between different groups. The potential association between myocardial ECV and each functional index was tested by the Spearman rank correlation test. To test whether the association between ECV and each functional index was significantly different among the 3 groups, the correlation coefficient was transformed by the formula given by Kullback (19) and the significance and post-hoc analyses were performed by chi-square tests. A value of $p < 0.05$ was considered significant. Statistical analyses were performed using SPSS software package version 19 (SPSS Inc., Chicago, Illinois).

RESULTS

All subjects successfully underwent CMR except for 4 patients who had severe arrhythmia causing failure of ECG synchronization during the study session; these 4 patients were excluded from the image analysis. Consequently, 40 patients with SHF, 62 patients with HFpEF, and 22 patients without HF were enrolled in the study. The demographics of the study population are summarized in **Table 1**. There was no significant difference in age among groups, but there were more male patients in the SHF group compared with the HFpEF group (80% male vs. 52% male, $p = 0.001$) and the non-HF group (80% male vs. 32% male, $p < 0.001$). In the HF group, patients with SHF had a higher rate of prior myocardial infarction (40% vs. 12%, $p < 0.001$) than patients with HFpEF, whereas patients with HFpEF had a higher rate of hypertension than patients with SHF (75% vs. 39%, $p < 0.001$). There was no significant difference between patients with HFpEF and patients without HF in comorbidities except for a greater incidence of coronary artery disease (CAD) in patients with HFpEF (52% vs. 18%, $p < 0.001$).

MYOCARDIAL ECV AND T1 TIME. Group comparisons of myocardial ECV and T1 time are listed in **Table 2**. The myocardial ECV in patients with SHF was significantly higher than that in patients with HFpEF (31.2% [IQR: 29.0% to 34.1%] vs. 28.9% [IQR: 27.8% to 31.3%], $p = 0.001$) and patients without HF (31.2% [IQR: 29.0% to 34.1%] vs. 27.9% [IQR: 26.2% to 29.4%], $p < 0.001$). Patients with HFpEF also had significantly higher myocardial ECV than patients

TABLE 1 Basic Demographics of the Studied Subjects

	SHF (n = 40)	HFpEF (n = 62)	Non-HF (n = 22)
Age, yrs	63 (57–72)	69 (60–72)	63 (59–75)
Male	80*†	52	32
Body surface area, m^2	1.73 (1.62–1.87)	1.71 (1.62–1.82)	1.65 (1.56–1.79)
Risk factors			
Hypertension	39*†	75	82
Diabetes mellitus	23	25	18
Dyslipidemia	46	48	59
Chronic kidney disease	10	5	5
Stroke	3	2	5
Myocardial infarction	40*†	12	0
Peripheral arterial occlusive disease	3	3	5
Etiologies for HF			
Coronary artery disease	46†	52†	18
Dilated cardiomyopathy	15	6	0
Medications			
Aspirin	40†	31†	14
Clopidogrel	28	18	9
Angiotensin-converting enzyme inhibitor	15	3	5
Angiotensin receptor blocker	44	55	41

Values are median (interquartile range) or %. *p < 0.05 compared with the HFpEF group. †p < 0.05 compared with the non-HF group.

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; SHF = systolic heart failure.

without HF (28.9% [IQR: 27.8% to 31.3%] vs. 27.9% [IQR: 26.2% to 29.4%], p = 0.006). For pre-contrast myocardial T1 time, no significant difference was found among the groups (Table 2). Post-contrast myocardial T1 time in the SHF group was significantly shorter than that in the HFpEF group (545 ms [IQR: 529 to 612 ms] vs. 613 ms [IQR: 568 to 655 ms], p = 0.002) and non-HF group (545 ms [IQR: 529 to 612 ms] vs. 649 ms [IQR: 615 to 677 ms], p < 0.001). Patients with HFpEF also had significantly shorter post-contrast myocardial T1 time than patients without HF (613 ms [IQR: 568 to 655 ms] vs. 649 ms [IQR: 615 to 677 ms], p = 0.016). To investigate whether ischemic and nonischemic etiologies had different effects on myocardial ECV and T1 time, we categorized the SHF and HFpEF groups into 2 subgroups separately: patients with CAD and patients without CAD. There was no significant difference in myocardial ECV between patients with and without CAD for SHF (31.8% [IQR: 29.5% to 35.3%] vs. 31.2% [IQR: 28.2% to 34.1%], p = 0.352) and HFpEF (29.9% [IQR: 28.1% to 31.5%] vs. 28.7% [IQR: 27.4% to 31.4%], p = 0.117). Similarly, pre-contrast and post-contrast myocardial T1 time showed no significant differences between patients with and without CAD for both SHF and HFpEF groups.

TABLE 2 Left Ventricular Function and Mass for Patients With and Without HF

	SHF (n = 40)	HFpEF (n = 62)	Non-HF (n = 22)
ECV, %	31.2 (29.0 to 34.1)*†	28.9 (27.8 to 31.3)†	27.9 (26.2 to 29.4)
Pre-T1, ms	1,209 (1,153 to 1,251)	1,201 (1,159 to 1,238)	1,185 (1,170 to 1,214)
Post-T1, ms	545 (529 to 612)*†	613 (568 to 655)†	649 (615 to 677)
EDV, ml	174 (144 to 226)*†	91 (72 to 116)	81 (69 to 101)
ESV, ml	116 (95 to 154)*†	22 (14 to 34)	16 (12 to 25)
EDV index, ml/m^2	106 (80 to 129)*†	53 (43 to 66)	48 (43 to 60)
ESV index, ml/m^2	76 (52 to 92)*†	12 (8 to 12)	9 (7 to 14)
EF, %	33 (26 to 40)*†	78 (64 to 81)	80 (74 to 84)
PER, s^{-1}	−1.53 (−1.80 to −1.18)*†	−3.45 (−4.00 to −2.76)	−3.56 (−3.97 to −3.17)
PFR, s^{-1}	1.00 (0.79 to 1.49)*†	2.89 (2.13 to 3.50)†	3.86 (3.34 to 4.48)
LVM, g	153 (128 to 183)*†	121 (95 to 150)†	88 (74 to 102)
LVM index, g/m^2	91 (72 to 102)*†	68 (57 to 84)	54 (49 to 59)
MVR	0.86 (0.76 to 1.02)*†	1.27 (1.03 to 1.51)†	1.12 (0.95 to 1.33)

Values are median (interquartile range). *p < 0.05 compared with the HFpEF group. †p < 0.05 compared with the non-HF group.

ECV = extracellular volume fraction; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LVM = left ventricular mass; MVR = mass-to-volume ratio; PER = peak ejection rate; PFR = peak filling rate; post-T1 = post-contrast T1 time; pre-T1 = pre-contrast T1 time; other abbreviations as in Table 1.

FUNCTIONAL INDEXES OF THE LV. LV function and mass quantified by cine CMR are summarized in Table 2. LV functional indexes, including EDV, ESV, EF, PFR, PER, and LV mass, were all significantly different in the SHF group as compared with the HFpEF and non-HF groups. Comparing the HFpEF with non-HF group, only PFR was significantly lower (2.89 s^{-1} [IQR: 2.13 to 3.50 s^{-1}] vs. 3.86 s^{-1} [IQR: 3.34 to 4.48 s^{-1}], p < 0.001) in the HFpEF group. Despite a significantly higher LV mass in the HF group, MVR was significantly smaller in the SHF group as compared with the non-HF group (0.86 [IQR: 0.76 to 1.02] vs. 1.12 [IQR: 0.95 to 1.33], p = 0.012), whereas MVR was significantly larger in the HFpEF group as compared with the non-HF group (1.27 [IQR: 1.03 to 1.51] vs. 1.12 [IQR: 0.95 to 1.33], p = 0.023).

CORRELATION BETWEEN MYOCARDIAL ECV AND LV FUNCTION. To further investigate the correlation between diffuse myocardial fibrosis and LV function, we performed correlation analysis between myocardial ECV and each LV functional index for each group. In the HFpEF group, myocardial ECV was significantly correlated with EDV (r = 0.320, p = 0.011), ESV (r = 0.474, p < 0.001), EF (r = −0.539, p < 0.001), PER (r = 0.529, p < 0.001), PFR (r = −0.385, p = 0.002), and LV mass (r = 0.369, p = 0.003) (Figure 1). There was no significant correlation between myocardial ECV and LV functional indexes in the SHF group (EDV: r = 0.059, p = 0.717; ESV: r = 0.080, p = 0.622; EF: r = −0.107, p = 0.513; PER: r = −0.062, p = 0.703; PFR: r = 0.030, p = 0.856; LV mass: r = 0.096, p = 0.557) and non-HF group (EDV: r = 0.045, p = 0.842;

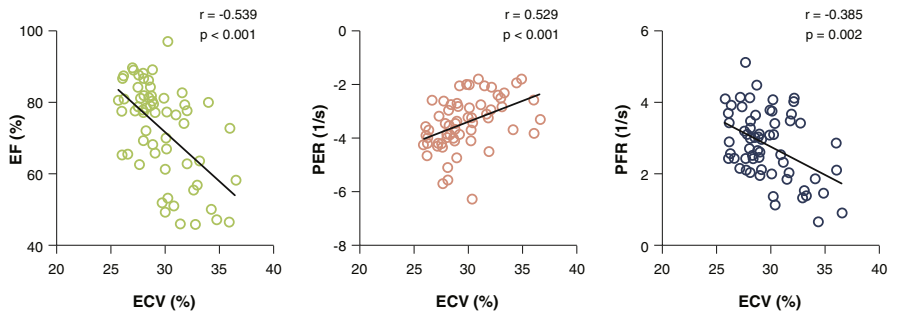

FIGURE 1 Correlation Between Myocardial ECV and Left Ventricular Functional Index

Correlations between myocardial extracellular volume fraction (ECV) with ejection fraction (EF), peak ejection rate (PER), and peak filling rate (PFR) in patients with heart failure with preserved EF.

ESV: $r = -0.015$, $p = 0.948$; EF: $r = 0.180$, $p = 0.422$; PER: $r = -0.233$, $p = 0.296$; PFR: $r = -0.238$, $p = 0.285$; LV mass: $r = -0.012$, $p = 0.956$). The differences in the correlation coefficients were significant among the 3 groups (ECV-ESV, $p = 0.022$; ECV-EF, $p = 0.008$; ECV-PER, $p < 0.001$; and ECV-PFR, $p = 0.025$). Post-hoc tests also showed that these correlations were significantly different between the HFpEF group and the other 2 groups (data not shown).

DISCUSSION

In this study, we used myocardial ECV to quantify diffuse myocardial fibrosis in patients with HF. As compared with patients without HF, myocardial ECV was increased in patients with HF. In patients with HF, ECV in SHF was higher than that in HFpEF, indicating that patients with SHF have a greater degree of diffuse myocardial fibrosis than patients with HFpEF. For the correlations between diffuse myocardial fibrosis and LV functional indexes, we found that among patients with HF, only patients with HFpEF had a significant correlation between ECV and diastolic function. Furthermore, myocardial ECV was significantly associated with apparently normal systolic functional indexes, such as EF and PER. These findings imply that diffuse myocardial fibrosis plays a unique role in patients with HFpEF, affecting both systolic and diastolic functions.

Myocardial fibrosis is defined as a significant increase in the collagen content in the myocardium, which has been considered the endpoint pathological process of the myocardium, leading to impaired ventricular function. Increased diffuse myocardial fibrosis has been reported to be a major determinant of altered diastolic filling and systolic pumping function of the LV (20). Once fibrosis develops, it increases myocardial stiffness and eventually deteriorates diastolic and systolic functions. The pathophysiology of accumulating collagen contents is diverse, depending on various cardiomyopathies (21). In general, 2 different types of myocardial fibrosis can be characterized on the basis of pathological results; 1 type shows increased collagen synthesis within the interstitium, and the other type shows replacement of myocytes with scarring (21). Diffuse myocardial fibrosis resulting from abnormal collagen accumulation within the interstitium is histologically different from the replacement fibrosis or scars resulting from previous myocyte death. Martos et al. (22) used biomarkers of serological fibrosis to investigate the myocardial collagen contents in patients with HFpEF and found elevated levels of serum fibrotic biomarkers, indicating increased collagen synthesis in patients with HFpEF. Borbely et al. (23) used endomyocardial biopsy to determine the extent of myocardial fibrosis in patients with HFpEF and reported a significantly higher collagen volume fraction in patients with HFpEF compared with patients without HF. In contrast to replacement or scarring fibrosis, which is often found in the infarcted myocardium, the predominant type of fibrosis in patients with HFpEF is interstitial fibrosis with a diffuse distribution surrounding the myocytes. Using the T1 mapping technique to quantify diffuse myocardial fibrosis in patients with HF, we found that diffuse myocardial fibrosis is indeed increased in both patients with SHF and patients with HFpEF. Interestingly, our results showed no significant association between ECV and ventricular functional indexes in patients with SHF. For patients with SHF, the prevalence of previous myocardial infarction is higher than that in HFpEF (40% vs. 12%). Infarcted myocardium is the result of

myocyte death, followed by replacement with scarring fibrosis. This type of fibrosis might affect LV function independently of diffuse myocardial fibrosis. Therefore, in patients with SHF, replacement fibrosis or scar may contribute more to ventricular dysfunction than diffuse myocardial fibrosis.

Hypertension is a major risk factor for developing HF (24). Enhanced collagen synthesis and increased collagen volume fraction in the hypertensive myocardium have been reported in postmortem autopsies (20,25) and endomyocardial biopsy specimens of human hearts (26,27). Patients with HFpEF have a higher prevalence rate of hypertension as compared with those with SHF (2). Because diffuse myocardial fibrosis may be increased in patients with hypertension, we enrolled subjects without HF but with a prevalence of hypertension, similar to the HFpEF group, as controls to control the effect of hypertension on diffuse myocardial fibrosis. In fact, the effect of hypertension on diffuse myocardial fibrosis was examined by Querejeta et al. (28) by using serum fibrosis markers and endomyocardial biopsy specimens. They found that hypertensive patients with HF have significantly more diffuse interstitial fibrotic depositions than those without HF. By comparing the HFpEF and non-HF groups, which had a comparable prevalence of hypertension, this study further supports that diffuse myocardial fibrosis is indeed increased in patients with HF besides the presence of hypertension.

Myocardial T1 time is a measure of the longitudinal relaxation rate of magnetization, and it can be performed before and after gadolinium-based contrast administration. Several studies have used post-contrast myocardial T1 time to quantify diffuse myocardial fibrosis in patients with various cardiomyopathies (21,29,30). However, post-contrast myocardial T1 time is affected by several factors, such as magnetic field strength, the timing of post-contrast MOLLI acquisition, the type of MOLLI scheme, the amount of contrast injected, and the renal function of patients (31). In contrast, myocardial ECV is measured by normalization of myocardial T1 time with blood T1 time, which is theoretically less affected by these factors. Lee et al. (32) compared different post-contrast scanning times and different types of MOLLI schemes to estimate myocardial ECV and T1 time at 1.5-T and 3.0-T. They reported that myocardial ECV appears to be more stable and should not be affected by these variables. Recent studies have proved that increased ECV is associated with the severity of diffuse myocardial fibrosis in histology (10,12). Therefore, myocardial ECV is more favorable than post-contrast myocardial T1 time to estimate extracellular matrix expansion such as diffuse myocardial fibrosis.

SHF and HFpEF are fundamentally different disease entities and have different manifestations of LV geometric remodeling. The disparate patterns of LV remodeling have been widely recognized; patients with SHF present with eccentric LV remodeling with low MVR, and patients with HFpEF manifest concentric LV remodeling with high MVR (33,34). Sanderson (35) emphasized the importance of the remodeling process in determining whether a patient has SHF or HFpEF (35). Compared with patients without HF, we found significantly higher ventricular volume and larger LV mass in patients with SHF, leading to significantly lower MVR. In contrast, patients with HFpEF had normal ventricular volume and larger LV mass, resulting in significantly higher MVR. This geometric remodeling is consistent with previous results measured from echocardiography (34), suggesting that CMR is feasible to discriminate the changes in structure and function of the LV for patients with HF.

STUDY LIMITATIONS. First, this study has no histological evidence to validate the results regarding the changes in myocardial ECV because all subjects had no indication for endomyocardial biopsy. Second, the values of myocardial ECV were mainly measured from the LV septum, but some were measured from non-septal areas if there were hyperenhanced scars in the LV septum. Although a previous study showed that there is no regional difference of ECV in healthy subjects (36), there is still a possibility of bias. Third, because the temporal resolution of cine CMR is inferior to echocardiography, the LV function assessed by CMR might not be accurate. One study has already shown that CMR-derived indexes such as PFR are a sensitive indicator to detect LV diastolic dysfunction (37). Therefore, we believe that cine CMR is a valid method to assess LV diastolic function.

CONCLUSIONS

In this study, we showed that diffuse myocardial fibrosis is increased in patients with HF. The increased myocardial fibrosis is associated with ventricular functional indexes in patients with HFpEF. For patients with SHF, the diffuse myocardial fibrosis is more severe than that in patients with HFpEF, but the degree of diffuse myocardial fibrosis seems unrelated to the impairment of ventricular function. These data support that diffuse myocardial fibrosis is a key factor in the pathophysiology of HFpEF and may play a unique role leading to diastolic dysfunction in patients with HFpEF.

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KEY WORDS cardiac magnetic resonance, extracellular volume fraction, heart failure with preserved ejection fraction