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Native T1 Relaxation Time and Extracellular Volume Fraction as Accurate Markers of Diffuse Myocardial Fibrosis in Heart Valve Disease

– Comparison With Targeted Left Ventricular Myocardial Biopsy –

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Background: The aim of our study was to investigate the relationship between the cardiac magnetic resonance (CMR)-derived native T1 relaxation time and myocardial extracellular volume (ECV) fraction and the extent of diffuse myocardial fibrosis (DMF) on targeted myocardial left ventricular (LV) biopsy.

Methods and Results: The study population consisted of 40 patients (age 63±8 years, 65% male) undergoing valve and/or ascending aorta surgery for severe aortic stenosis (77.5%), root dilatation (7.5%) or valve regurgitation (15%). The T1 relaxation time was assessed in the basal interventricular septum pre- and 10-min post-contrast administration using the modified Look-Locker Inversion recovery sequence prior to surgery. LV myocardial biopsy specimen was obtained during surgery from the basal interventricular septal segment matched with the T1 mapping assessment. The percentage of myocardial collagen was quantified using picrosirius red staining. The average percentage of myocardial collagen was 22.0±14.8%. Both native T1 relaxation time with cutoff value ≥1,010 ms (sensitivity=90%, specificity=73%, area under the curve=0.82) and ECV with cutoff value ≥0.32 (sensitivity=80%, specificity=90%, area under the curve=0.85) showed high accuracy to identify severe (>30%) DMF. The native T1 relaxation time showed significant correlation with LV mass (P<0.01).

Conclusions: Native T1 relaxation time and ECV at 10 min after contrast administration are accurate markers of DMF. (*Circ J* 2016; **80:** 1202–1209)

Key Words: Cardiac magnetic resonance imaging; Echocardiography; Fibrosis; Speckle tracking; Valvular disease

Myocardial fibrosis is a common feature of various cardiac pathologies with major impact on patient symptoms and survival.[1–5] Focal fibrosis (scar) is mostly associated with previous myocardial infarction or myocardial inflammatory process, and its extent has been shown to have an independent prognostic value.[1–3] In contrast, diffuse interstitial myocardial fibrosis (DMF) develops mostly in response to various stimuli (eg, left ventricular (LV) pressure or volume overload) and its clinical role remains to be defined.[6–8] It is noteworthy that LV hemodynamic overload is the hallmark of heart valve disease,[9,10] which suggests that DMF may play an important role in the pathophysiology of heart valve diseases and complications.[11–13]

Endomyocardial biopsy is the current reference standard for the assessment of myocardial fibrosis, but it is invasive and hence, not suitable for routine serial follow-up. Recently, a cardiac magnetic resonance (CMR)-derived T1 mapping technique has been shown to allow accurate detection and quantification of DMF.[14–17] The principle of T1 mapping is based on measurement of T1 longitudinal relaxation time in each myocardial voxel pre- or post-contrast administration.[15] DMF results in increased collagen content with expansion of the extracellular space and hence, alteration of the T1 relaxation time and extracellular volume (ECV) fraction compared with normal

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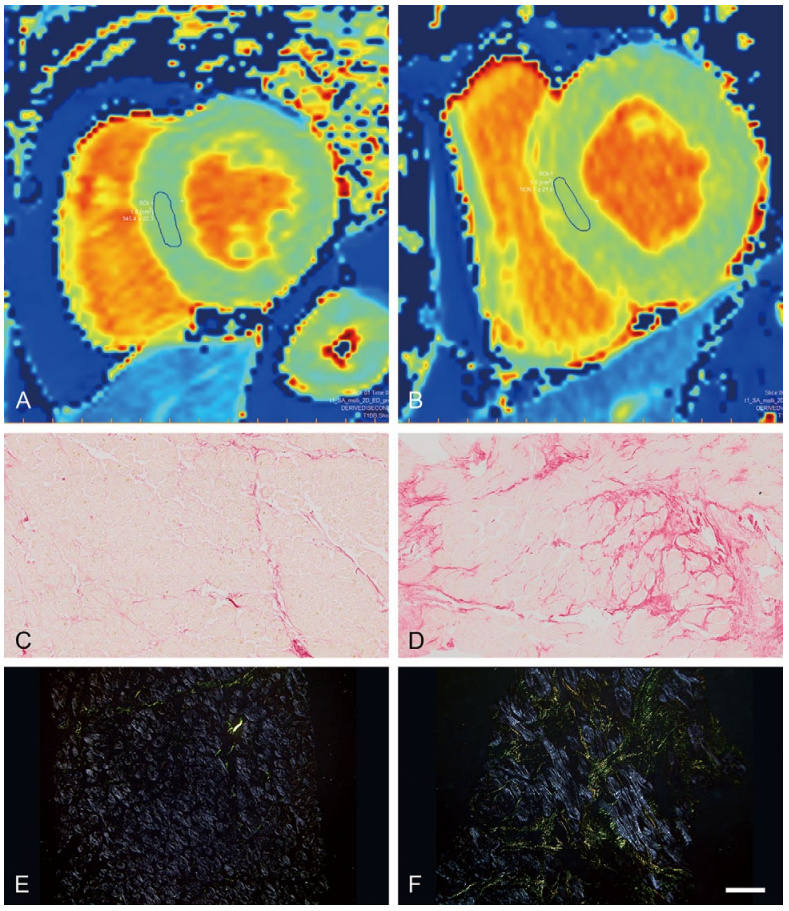

Figure 1. Individual examples of native T1 relaxation time-derived parametric maps and corresponding histology in patient with mild (**A**,**C**,**E**) vs. severe (**B**,**D**,**F**) DMF. Native T1 relaxation time was assessed using manual contouring in the midwall of the basal interventricular septum while avoiding epicardial structures and blood (**A**,**B**). The first patient showed mild DMF of 9% of the PSR-stained area using an Olympus slide scanner (**C**) and polarized light (**E**). Corresponding native T1 relaxation time and ECV at 10 min post-contrast administration (**A**) were 945 ms and 0.22, respectively. In contrast, the other patient showed severe DMF of 36% (**D**,**F**) with corresponding native T1 relaxation time and ECV of 1,042 ms and 0.41, respectively. Scale bar=100 μm. It is noteworthy that both patients had similar color aspects of the myocardium on parametric maps despite a great difference in the extent of DMF and T1 mapping indices. Therefore, the presence and extent DMF, in contrast to focal scar, cannot be assessed using simple "eye balling". DMF, diffuse myocardial fibrosis; PSR, picrosirius red staining.

myocardium.[15] Of the several different T1 mapping sequences that have been introduced, the modified Look-Locker inversion (MOLLI) recovery sequence seems to be the most robust technique for routine clinical use.[15] Recent studies have shown high reproducibility and test-retest stability of the MOLLI sequence, both with phantoms and in different clinical settings.[15,16,18–20] There is increasing evidence of the accuracy of the MOLLI-derived T1 mapping indices in relation to the gold standard represented by LV myocardial histology.[21,22] Therefore, the aim of the present study was to investigate the relationship between the CMR MOLLI-derived native T1 relaxation time, ECV and the extent of DMF on targeted LV myocardial biopsy in patients with severe heart valve disease undergoing valve or aortic root surgery.

Methods

Patients

We prospectively enrolled 40 patients (age 63±8 years, 65% male) with severe aortic stenosis (AS: 77.5%), severe aortic or mitral regurgitation (AR/MR: 15%) or severe aortic root dilatation (7.5%) scheduled for valve or aortic root surgery in a single institution during a 1-year period in 2014. Patients younger than 18 years, with post-myocardial revascularization or infarction, other than sinus rhythm, severe renal insufficiency with creatinine clearance <30 ml/min/1.73 m^2, and contraindication to CMR were excluded. Informed consent was given by each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Study Protocol

During the 1 month prior to cardiac surgery, all patients underwent CMR-derived T1 mapping and transthoracic echocardiography. Hematocrit level was assessed within 24 h of CMR study. Fasting blood samples were collected 1 day before surgery to assess levels of hemoglobin, creatinine, B-type natriuretic peptide (BNP), galectin-1 and galectin-3. Multiple LV myocardial needle biopsies were performed during surgery under visual control from the basal interventricular septal segment concordant with the T1 mapping assessment.

CMR CMR examinations were performed using a 1.5-Tesla scanner (Magnetom Avanto, Siemens). The scanning protocol included pilot, T2-weighted dark blood, cine in short-axis and 2-, 3- and 4-chamber planes covering the entire end-diastolic ventricular length, late gadolinium enhancement (LGE), and pre-and post-contrast MOLLI sequence. All sequences were acquired during a breath-hold of 10–20 s. LV volume, mass, and ejection fraction (EF) were assessed using steady-state free precession cine imaging in a short-axis stack (slice thickness 8 mm, slice spacing 0) with correction for the valve position in the long-axis planes. The endocardial border was semi-automatically contoured with manual correction using the Segment software (Medviso, Sweden). LV papillary muscles were included in the LV mass. The T2-weighted dark blood

Table 1. Baseline Clinical and Imaging Characteristics of the Study Patients With Heart Valve Disease

	Patients (n=40)
Age, years	63±8
Female sex, n (%)	14 (35)
Ischemic heart disease, n (%)	10 (25.0)
Diabetes mellitus, n (%)	12 (30.0)
Hypertension, n (%)	29 (72.5)
Symptoms	
Asymptomatic, n (%)	6 (15.0)
NYHA class I, n (%)	4 (10.0)
NYHA class II, n (%)	18 (45.0)
NYHA class III, n (%)	12 (30.0)
Medications	
ACEI/ARB, n (%)	24 (60.0)
Spironolactone, n (%)	5 (12.5)
Biochemistry	
BNP, pg/ml	237±303
Galectin-1, ng/ml	2.63±0.78
Galectin-3, ng/ml	6.21±2.27
CMR parameters	
LV end-diastolic volume, ml	150±52
LV end-systolic volume, ml	63±33
LVEF, %	59±12
LVM, g	209±75
LVMI, g/m^2	102±33
Stroke volume, ml	88±28
Heart rate, beats/min	63±11
Cardiac output, L/min	5.54±1.75
Native T1 relaxation time, ms	1010±48
ECV at 10 min post contrast,%	0.29±0.05
ECV at 20 min post contrast,%	0.29±0.05
Echocardiography (n=31 with AS)	
Aortic valve area, cm^2	0.80±0.23
Transaortic P mean, mmHg	57±19
LV myocardial histology	
Diffuse myocardial fibrosis,%	22.01±14.76

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; BNP, B-type natriuretic peptide; ECV, extracellular volume fraction; LV, left ventricular; LVM, LV mass; LVMI, LVM index; NYHA, New York Heart Association; Transaortic P, transaortic pressure.

sequences with and without fat saturation in the short-axis and 4-chamber planes were used to assess for the presence of myocardial edema. LGE images were acquired using the single breath-hold ECG-triggered phase-sensitive inversion recovery (PSIR) gradient echo sequence in the short-axis and 2- and 4-chamber planes (slice thickness 8 mm, slice spacing 0) at 8–15 min after administration of the average 0.19 ml/kg (15 ml for 80 kg patient weight and for each ±5 kg additional ±1 ml of Gadobutrol) of a 1-molar gadolinium-based contrast agent (Gadobutrol, GadovistW, Bayer, Germany).

T1 Mapping The native T1 relaxation time and ECV were analyzed using the MOLLI sequence pre-, 10 and 20 min after contrast administration by an operator blinded to the results of LV biopsy. In brief, the MOLLI sequence is an ECG-prospective triggered steady-state free precession sequence with single-shot read out. It consists of 11 images (3 images obtained after the first inversion pulse, 3 images after the second inversion pulse and 5 images after the third inversion pulse) acquired with different inversion times during 17 cardiac cycles within 1 breath-hold.[15,16] Parameters of the MOLLI sequence were as follows: field of view 340 mm, field of view phase 228 mm, matrix 128×192, slice thickness 8 mm, voxel size 2.1×1.8×8 mm, TE 1.0 ms, TR 2.2 ms, flip angle 35°, bandwidth 1090 Hz/pixel. The scan with the MOLLI sequence was performed in the basal short-axis slice. The T1 relaxation time was analyzed in the midwall region of the basal interventricular septum between the anterior and inferior septal segments (**Figure 1**). The selection of the slice and region of interest (ROI) for the T1 relaxation time analysis were based on our previous experience with postmortem heart specimens (unpublished data). The midwall of the basal interventricular septum matches precisely with the segment where the perioperative biopsy specimen via the LV outflow tract is taken. The analysis of the T1 relaxation time was performed using the V1.4, MRmap software (https://sourceforge.net/projects/mrmap) with manual registration of source images and T1 Look-Locker correction.[23] In brief, on parametric maps the ROI was drawn manually on the midwall of the basal interventricular segment matching the region of subsequent perioperative biopsy (**Figure 1**). Great care was exercised to exclude epicardial structures and blood from the contours. Standard size of the ROI was 1 cm^2 in all patients. T1 relaxation time was measured pre (native), 10 and 20 min post-contrast administration. ECV was calculated according to the following equation:[24]

$$\mathrm{ECV}=(1-\mathrm{hematocrit})\times\frac{(1\div\mathrm{T1})_{\mathrm{myo,post}}-(1\div\mathrm{T1})_{\mathrm{myo,pre}}}{(1\div\mathrm{T1})_{\mathrm{blood,post}}-(1\div\mathrm{T1})_{\mathrm{blood,pre}}}$$

T1 value of the blood pool was measured using manual drawing of a ROI in the LV cavity, excluding papillary muscles. Blood samples were taken 1–4 h prior to CMR to determine the hematocrit and creatinine.

Echocardiography All echocardiography examinations were performed using a commercially available system (Vivid E9, GE Medical Systems, Horten, Norway). All acquired images were stored digitally for offline analysis. The mean of at least 3 consecutive beats was taken for each measurement. Standard assessment of LV dimensions, volumes and EF (bi-apical Simpson's method) was performed according to the current recommendations. The aortic valve area was assessed using the continuity equation.

Myocardial Biopsy and Histology Perioperative LV myocardial specimens were obtained from the basal interventricular septum via the LV outflow tract using a deep myocardial needle (SuperCore™ Semi-Automatic Biopsy Instrument 16G×9 cm). The CMR operator was present in the operation room to assure segmental concordance between the biopsy and the CMR assessment. The myocardial sample was immediately immersed in 10% buffered formalin, embedded in paraffin blocks and later sectioned into 3-μm thick slices. Parallel sections were stained with picrosirius red (PSR) for 1 h using a standard protocol. PSR is a collagen-specific stain for collagen quantification using both normal and polarized light.[25,26] Samples were digitized using a ×20 objective lens on an Olympus slide scanner (resolution: 3 pixels/μm). For quantitative analysis, regions including almost the entire sample were exported with a resolution of 1.5 pixels/μm to achieve a maximally representative sample. The percentage of myocardial fibrosis was calculated as the ratio of the PSR-positive area over the total area using Image J software with differential thresholding.[27] Several different samples per biopsy specimen were analyzed separately by observers blinded to the T1 mapping and clinical

Table 2. Correlation Between DMF, T1-Mapping, Imaging and Laboratory Parameters in the Study Patients With Heart Valve Disease

	DMF,%	Native T1 relaxation time, ms	LVMI, g/m²
Native T1 relaxation time, ms	0.39, P=0.01	NA	0.53, P<0.01
ECV at 10 min after contrast	0.32, P=0.04	0.56, P<0.001	NS
LV mass, g	0.33, P=0.04	0.49, P<0.01	NA
LV mass index, g/m²	0.32, P=0.05	0.53, P<0.01	NA
BNP, pg/ml	0.13, P=0.45	0.29, P=0.07	0.43, P<0.01

Data presented with Spearman's correlation coefficient and P value. BNP, brain natriuretic peptide; DMF, diffuse myocardial fibrosis; ECV, extracellular volume fraction; LVMI, left ventricular mass index; NA, not applicable.

data. The final percentage of myocardial collagen was calculated as an average from all analyzed samples.

Statistical Analysis

Data are presented as mean±SD for continuous variables and as percentages for categorical variables. The unpaired Student's t-test and the Pearson or Spearman's correlation coefficient were used as appropriate. Fisher's exact test was used to compare categorical variables in 2×2 contingency tables. Receiver-operating characteristics curves were constructed to assess optimal cutoff value for the native T1 relaxation time and ECV to predict high extent (>30%) of DMF. Statistical analysis was performed by statistical software Stata release 9.2 (Stata Corp, College Station, TX, USA). For all tests, P<0.05 was considered significant.

Results

All the CMR scans were classified as of a sufficient quality for further analysis. No patient showed the presence of myocardial edema on the T2-weighted images or focal fibrosis in chronic myocardial infarction on the LGE images.

Baseline Characteristics

Table 1 and Table S1 shows the baseline clinical and imaging characteristics of the patients. The majority of patients had severe AS (77.5%) with symptoms (90%) and preserved LVEF (59±12%). Mean aortic valve area and mean transaortic pressure gradient were 0.94±0.55 cm² and 52±22 mmHg, respectively, in the total cohort, and 0.80±0.23 cm² and 57±19 mmHg, respectively, in 31 patients with severe AS. The average amount of myocardial fibrosis was 22.01±14.76%, ranging from 4.69% to 61.25%.

Myocardial Fibrosis vs. Clinical Characteristics

Patients with valve regurgitation had a significantly larger extent of DMF than the patients with valve stenosis (32.11±15.27% vs. 19.58±12.5%, P=0.037). In contrast, the amount of DMF did not show significant associations with sex, history of ischemic heart disease, presence of diabetes or hypertension or medical therapy (all P=NS).

Myocardial Fibrosis vs. LV Morphology and Function

Of the CMR-derived parameters, only LV mass (r=0.33, P=0.04) and LV mass index (r=0.32, P=0.05) were significantly related to the extent of DMF (Table 2). In contrast, LV volume and EF did not show significant correlation with the extent of DMF (both P=NS). None of the echocardiography-derived variable showed significant association with the degree of DMF (all P=NS) (Table 2).

Myocardial Fibrosis vs. Native T1 Relaxation Time and ECV

The average native T1 relaxation time, ECV at 10 min and ECV at 20 min post-contrast administration were 1,010±48 ms, 0.29±0.05 and 0.29±0.05, respectively (Table 2). For comparison, the native T1 relaxation time in healthy volunteers was 962±37 ms on the same MRI scanner. Figure 1 shows an example of the native T1 parametric maps derived using the MOLLI sequence and corresponding histology in patients with mild vs. severe DMF. Both the native T1 relaxation time and ECV at 10 min post-contrast administration showed significant correlation with the extent of DMF (Table 2). Both these parameters also correlated significantly with each other (r=0.56, P<0.001). In contrast, ECV at 20 min post-contrast administration did not show a significant relationship with the extent of DMF (r=0.23, P=0.16). Native T1 relaxation time was significantly associated with LV mass and its index, and tended to correlate with BNP (Table 2). In contrast, ECV at 10 min post-contrast administration did not have significant relationships with these parameters (all P=NS).

Predictors of Severe DMF

In this study cohort, 10 patients (25%) had severe (>30%) DMF. Patients with severe DMF showed significantly higher native T1 relaxation time (1,054±16 ms vs. 995±7 ms, P<0.001), ECV at 10 min post-contrast administration (0.35±0.02 vs. 0.27±0.01 ms, P<0.001) and BNP (450±177 pg/ml vs. 173±29 pg/ml, P=0.014). All the remaining clinical and imaging parameters, including NYHA class, indices of LV remodeling, aortic valve area or transaortic gradients, galectin-1 and galectin-3 levels, were similar (all P=NS) between patients with severe vs. mild DMF. Native T1 relaxation time with a cutoff value ≥1,010 ms (sensitivity=90%, specificity=73%, area under the curve=0.82) and ECV at 10 min post-contrast with cutoff value ≥0.32 (sensitivity=80%, specificity=90%, area under the curve=0.85) showed the highest accuracy to identify severe DMF (Figures 2,3). LV mass index with cutoff value ≥100 g/m² (sensitivity=70%, specificity=67%, area under the curve=0.68) and ECV at 20 min with cutoff value also ≥0.32 (sensitivity=80%, specificity=87%, area under the curve=0.83) were also relevant (Figures 4,5).

Reproducibility

Reproducibility for native T1 relaxation time was assessed in 10 randomly selected patients from recorded scans. The trace-retrace intra- and interobserver variabilities were both <1%.

Discussion

The present study investigated the relationship between the CMR T1 mapping-derived native T1 relaxation time, ECV

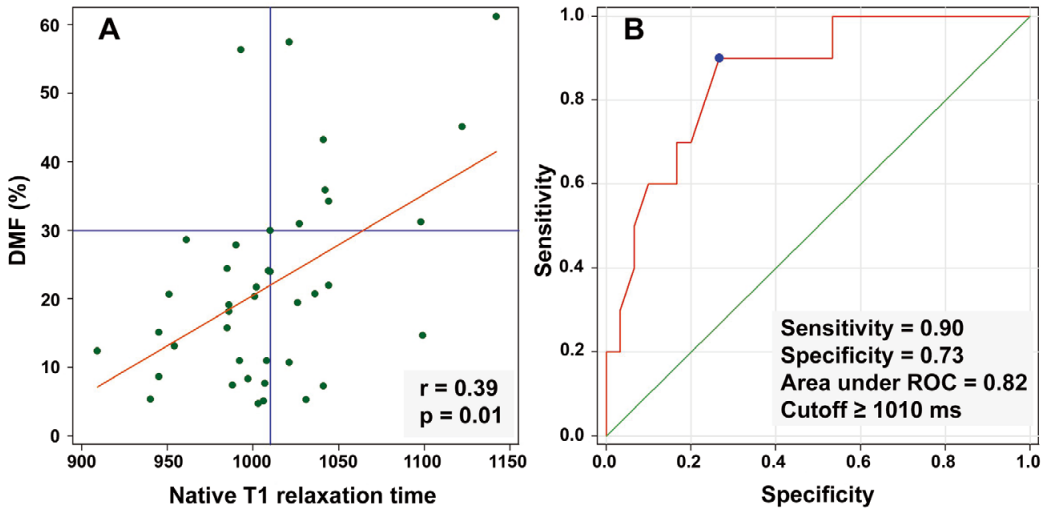

Figure 2. Correlation between native T1 relaxation time and DMF at perioperative biopsy (**A**), and the area under the curve to identify severe (>30%) DMF (**B**). DMF, diffuse myocardial fibrosis; ROC, receiver-operating characteristic.

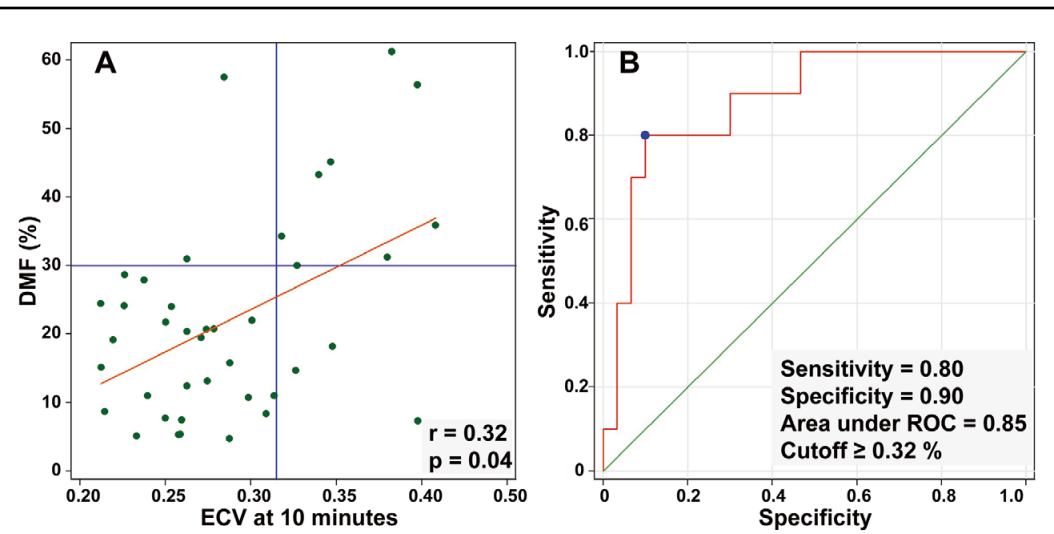

Figure 3. Correlation between ECV at 10 min post-contrast administration and DMF at perioperative biopsy (**A**), and the area under the curve to identify severe (>30%) DMF (**B**). DMF, diffuse myocardial fibrosis; ECV, extracellular volume; ROC, receiver-operating characteristic.

and the extent of DMF in targeted LV myocardial biopsy from patients with severe heart valve disease, mainly AS, undergoing valve or aortic root surgery. This is to our knowledge the largest study so far to compare the MOLLI-derived T1 mapping indices with LV myocardial histology in heart valve disease. Moreover, great care was exercised to achieve precise matching between the region where the perioperative biopsy was taken, and the region of the CMR-derived T1 relaxation time assessment.

The findings of the present study can be summarized as follows. First, the degree of DMF showed great interindividual variability over a wide range of values, with larger extent of in patients with greater LV mass. A higher degree of DMF was present in patients with AR, but this finding has limited value and might be coincidence because only 6 patients had severe AR. Second, the assessment of native T1 relaxation time and ECV at 10 min using the MOLLI sequence was highly feasible and reproducible. We assume that the absence of a significant relationship of ECV at 10 min with the extent of DMF might be explained by a certain degree of myocardial signal inhomogeneity leading to non-systematic error of a single measurement. Another source of error might be the slow decline of the signal-to-noise ratio in time on 1.5-T scanners. Third, both native T1 relaxation time and ECV at 10 min

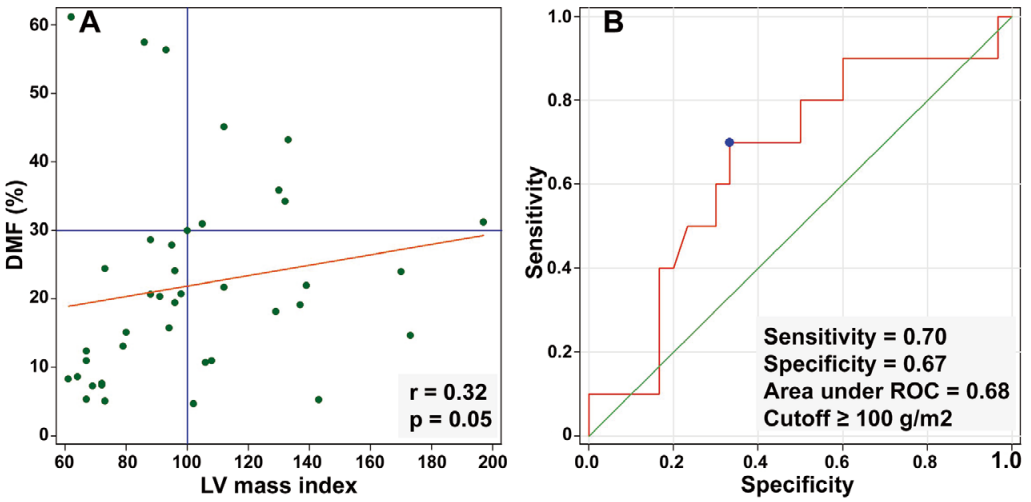

Figure 4. Correlation between CMR-derived LV mass index and DMF at perioperative biopsy (**A**), and the area under curve to identify severe (>30%) DMF (**B**). DMF, diffuse myocardial fibrosis; LV mass index, left ventricular mass indexed to body surface area; ROC, receiver-operating characteristic.

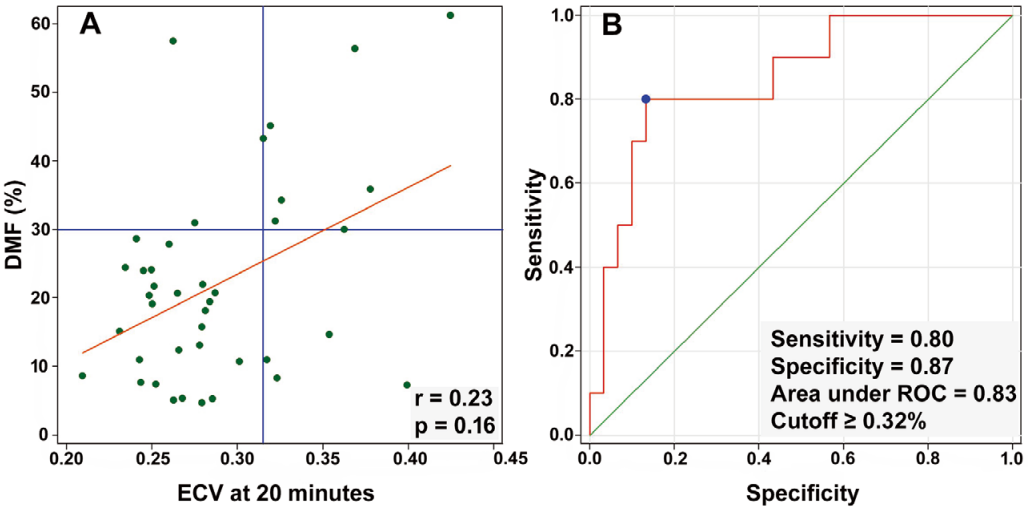

Figure 5. Correlation between ECV at 20 min post-contrast administration and DMF at perioperative biopsy (**A**), and the area under the curve to identify severe (>30%) DMF (**B**). DMF, diffuse myocardial fibrosis; ECV, extracellular volume; ROC, receiver-operating characteristic.

post-contrast administration showed high accuracy to identify patients with severe DMF. Native T1 relaxation time and ECV at 10 min were superior to LV mass index by cine MRI in predicting the extent of DMF.

Diffuse Myocardial Fibrosis in Heart Valve Disease

The volume and pressure overload associated with heart valve diseases induces LV remodeling accompanied by initially interstitial and later focal myocardial fibrosis.[11,28–31] In the present study, both the patients with valve regurgitation and those with valve stenosis showed great interindividual variability in the amount of DMF. Yet, the patients with valve regurgitation had a significantly larger extent of DMF than patients with valve stenosis. This finding should be, however, validated in a larger patient population because only a few patients had severe valve regurgitation in the present study. In contrast to previous studies, we did not observe a significant relationship between aortic valve area, symptomatic status and DMF.[31] This may be explained by the fact that the present study enrolled mainly patients with severe symptomatic AS, whereas the population of the study by Bull et al[31] also involved asymptomatic patients with moderate to severe AS. Several authors

have observed a significant relationship between the extent of DMF and LV dysfunction, heart failure, exercise intolerance and symptoms.[11–13,31–33] Azevedo et al have shown significantly worse long-term survival and LV functional improvement after aortic valve surgery for severe AS or AR in patients with ≥30% myocardial fibrosis measured by histopathology.[34] Corroborating those results, the present study demonstrated a significant correlation between DMF and LV mass.[12,31,32,35] Patients with severe DMF also showed higher BNP levels than the patients with milder degrees of DMF. This suggests that DMF may be one of the critical mechanisms underlying progression of heart valve diseases with an unfavorable clinical course. It is noteworthy that DMF does not regress after aortic valve replacement despite the reduction in LV hypertrophy.[32,36] This emphasizes the clinical need for a non-invasive technique to assess DMF early in the disease course before its progression to the irreversible stage.[37,38]

T1 Mapping vs. Diffuse Myocardial Fibrosis

Endomyocardial biopsy has been the only available approach so far to assess DMF. However, myocardial biopsy is an invasive procedure and therefore can be associated with serious complications,[39] which hampers the potential of myocardial biopsy for routine clinical use. CMR-derived assessment of LGE is currently the method of choice to assess focal fibrotic scar.[40,41] In patients with AS, recent studies have shown a significant correlation between the extent of focal scar on LGE, NYHA class and indices of systolic function.[41] However, DMF is not characteristic of AS and if it occurs, then it is late in the disease course.[1–3,11,28–31] Corroborating those findings, in the present study none of the patients showed focal fibrotic scar on LGE despite severe symptoms and Class I indication for cardiac surgery. In contrast, DMF occurs early in the course of pressure overload and hence, it may represent a more suitable diagnostic target than focal scar.[11,28–31] Unfortunately, the LGE technique misses DMF, which is by definition diffusely spread within the myocardium and therefore not distinguishable on LGE images. The CMR-derived T1 mapping technique has been introduced recently to quantify DMF[15,16] and several methods to assess native T1 relaxation time and post-contrast ECV have been proposed.[15] Of them, the MOLLI sequence introduced by Messroghli et al[16] seems to be the most suitable for clinical use. Recent studies have demonstrated excellent precision, reproducibility and test-retest stability of the MOLLI sequence.[15,16,18–20] Corroborating those results, we observed negligible trace-retrace intra- and interobserver variability for the T1 relaxation time. In the previous studies, the MOLLI sequence was tested in different settings involving phantoms, healthy volunteers, different cardiomyopathies, myocarditis and ischemic heart disease.[15,16,18–20] However, there is only limited and somewhat conflicting evidence of its accuracy in relation to LV myocardial histology and of its potential role in heart valve diseases. Bull et al have shown a moderate but significant correlation between the native T1 relaxation time and DMF in 19 patients with severe symptomatic AS using the ShMOLLI (a shortened MOLLI) sequence with a 1.5-T scanner.[31] Lee et al have even shown a strong correlation between the native T1 relaxation time and DMF in 20 patients with severe AS using a 3-T scanner and the MOLLI sequence.[21] De Meester de Ravenstein et al[22] have shown the opposite result. All 31 of their patients with valvular heart disease (severe AS or severe AR or severe MR) underwent CMR using a 3-T scanner and the MOLLI sequence and the authors reported no correlation between the native T1 relaxation time and DMF and a close correlation of ECV and DMF.[22] Flett et al also observed a strong correlation between ECV and DMF in 18 patients with severe symptomatic AS.[14,32] However, the present findings may be hampered by the use of a multi-breath-hold LGE sequence for the T1 relaxation time assessment with stepwise increments of inversion time per breath-hold. Corroborating these results, in the present study we observed a significant correlation between both native T1 relaxation time and ECV at 10 min post-contrast administration, and DMF using the MOLLI sequence on a 1.5-T scanner. Moreover, both parameters showed high accuracy in identifying severe DMF, which may have clinical importance.[41–43] The native (pre-contrast) T1 relaxation time appears to be more robust and a clinically more useful technique for DMF assessment than ECV, because it is based only on 1 measurement, does not require contrast administration and it is less dependent on renal function,[7] the amount of myocardial fibrosis or hemodynamic status.[15,17,31] All these factors might influence the time when myocardial blood equilibrium status is achieved.

Study Limitations

The cutoff values for the T1 relaxation time defining normality and pathology may not correspond between different T1 mapping methods. In the present study, the MOLLI sequence was used. The MOLLI sequence is widely available and seems to be the most robust technique for clinical use with excellent precision, reproducibility and test-retest stability.[15] The other sequences are more artifact-prone or show less precision than the MOLLI sequence.[15]

Conclusions and Clinical Implications

The timing of valve replacement in asymptomatic patients with preserved LVEF is challenging. The search for predictors of early unfavorable course is ongoing. The results of the previous and present studies suggest that DMF may be an underlying mechanism of progression of heart valve disease and its complications. Recent advances in CMR have provided a non-invasive tool (ie, T1 mapping technique) for the assessment of DMF. In the present study, both the native T1 relaxation time and ECV at 10 min post-contrast administration showed excellent accuracy to detect severe DMF when compared with LV myocardial histology. The potential clinical significance of these findings remains to be defined in a larger prospective trial.

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Supplementary Files

Supplementary File 1

Table S1. Imaging parameters of all 40 patients included in the study

Please find supplementary file(s);
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