Assessment of cardiac involvement in myotonic muscular dystrophy by T1 mapping on magnetic resonance imaging

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BACKGROUND Patients with myotonic muscular dystrophy (DM) are at risk for atrioventricular block and left ventricular (LV) dysfunction. Noninvasive detection of diffuse myocardial fibrosis may improve disease management in this population.

OBJECTIVE To define functional and postcontrast myocardial T1 time cardiac magnetic resonance characteristics in patients with DM.

METHODS Thirty-three patients with DM (24 with type 1 and 9 with type 2) and 13 healthy volunteers underwent cardiac magnetic resonance for the assessment of LV indices and the evaluation of diffuse myocardial fibrosis by T1 mapping. The association of myocardial T1 time with electrocardiogram abnormalities and LV indices was examined among patients with DM.

RESULTS Patients with DM had lower end-diastolic volume index (68.9 mL/m^2 vs 60.3 mL/m^2; $P = .045$) and cardiac index (2.7 L/min/m^2 vs 2.33 L/min/m^2; $P = .005$) and shorter myocardial T1 time (394.5 ms vs 441.4 ms; $P < .0001$) than did control subjects. Among patients with DM, there was a positive association between higher T1 time and LV mass index (2.2 ms longer per g/m^2; $P = .006$), LV end-diastolic volume index (1.3 ms longer per mL/m^2; $P = .026$), filtered QRS duration (1.2 ms longer per unit; $P = .005$), and low-amplitude (<40 mcV) late-potential duration (0.9 ms longer per unit; $P = .01$). Using multivariate random effects regression, each 10-ms increase in myocardial T1 time of patients with type 1 DM was independently associated with 1.3-ms increase in longitudinal PR and QRS intervals during follow-up.

CONCLUSIONS DM is associated with structural alterations on cardiac magnetic resonance. Postcontrast myocardial T1 time was shorter in patients with DM than in controls, likely reflecting the presence of diffuse myocardial fibrosis.

KEYWORDS Myotonic muscular dystrophy; MRI; T1 mapping; Ventricular function

ABBREVIATIONS **CMR** = cardiac magnetic resonance; **DM** = myotonic muscular dystrophy; **DM-1** = myotonic muscular dystrophy type 1 (Steinert's disease); **DM-2** = myotonic muscular dystrophy type 2 (proximal myotonic myopathy); **ECG** = electrocardiogram; **EF** = ejection fraction; **eGFR** = estimated glomerular filtration rate; **FOV** = field of view; **IR** = inversion recovery; **LV** = left ventricular; **MRI** = magnetic resonance imaging; **RA** = right atrial; **RV** = right ventricular; **TE** = echo time; **TR** = repetition time

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Introduction

Myotonic muscular dystrophy (DM) is a genetic multisystem disorder characterized by skeletal muscle weakness and myotonia. Two types of DM have been defined: type 1 (DM-1, Steinert's disease) and type 2 (DM-2, proximal myotonic myopathy). DM-1 is the most common adult-onset muscular dystrophy, whereas DM-2 is less frequent and tends to have a milder phenotype and later onset of symptoms.[1] Cardiac conduction deficits, mild to moderate ventricular dysfunction, and sudden death can occur in both DM-1 and DM-2.[2] Histopathologically, patchy interstitial fibrosis, myocyte hypertrophy and degeneration, fatty infiltration, and lymphocytes have been shown in myocardium, sinoatrial, and atrioventricular nodes of patients with DM.[3]

Cardiac magnetic resonance (CMR) imaging is a well-established method for the assessment of left ventricular (LV) function.[2] In addition, the contrast-enhanced CMR T1 mapping technique has been applied to noninvasively

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quantify diffuse interstitial fibrosis.[4] Postcontrast CMR images demonstrate retention of gadolinium and thus lower T1 times in the presence of fibrosis.[4,5] Other histopathologic processes such as edema and fatty infiltration, which coexist in patients with DM, can also influence myocardial T1 time. The relationship of myocardial T1 time with electrocardiogram (ECG) or structural abnormalities is unknown.

Thus, it is possible that detection of LV dysfunction and diffuse myocardial fibrosis may improve the quantification of cardiac involvement and prediction of arrhythmia risk in DM. We sought to define functional and postcontrast myocardial T1 time CMR characteristics in patients with DM.

Materials and methods

Patients and controls

The protocol was reviewed and approved by the Johns Hopkins Institutional Review Board. The patient population included 33 patients with DM (24 with type 1 and 9 with type 2) diagnosed by genetic testing (55%) or by clinical examination in subjects who had a first-degree family member with genetically proven DM (45%). Patients with clinical findings of DM but negative genotype were not included. All consecutive patients with DM who were referred to the electrophysiology service for arrhythmia risk stratification, without history of atrioventricular block, resuscitated sudden death, or contraindications to CMR, were enrolled in the study. All patients underwent CMR and standard 12-lead ECG. Standard ECG was repeated during routine and symptom-prompted follow-up visits. The median follow-up time was 705.5 days (interquartile range: 408.8–1124.5 days), and the median number of follow-up visits was 2 (interquartile range: 1–5.3 visits/patient). Twenty-three of the 33 patients with DM underwent signal-averaged ECG with Frank orthogonal leads at a sampling rate of 1 kHz/channel and enough QRS complexes to reduce the noise level to <1 mcV (PC ECG 1200; Norav Medical Ltd, Thornhill, Ontario, Canada). Thirteen healthy volunteers underwent CMR as a control group under a separate protocol approved by the Institutional Review Board and after providing informed consent. None of the volunteers had a history of cardiovascular and/or other systemic disease. Estimated glomerular filtration rate (eGFR) was determined from serum creatinine by using the Modification of Diet in Renal Disease Study Equation.

CMR imaging

CMR was performed with a 1.5-T magnetic resonance scanner (Avanto; Siemens Medical Systems, Erlangen, Germany) by using anterior and posterior surface coils for signal reception. Cine images were acquired in 2-chamber (2ch), 4-chamber (4ch), and short-axis planes during breath holding by using an ECG-triggered steady-state free precession pulse sequence (repetition time (TR)/echo time (TE): 2.5–3.8 ms/1.1–1.2 ms; flip angle: 60°–81°; spatial resolution: $<1.56 \times 1.56 \times 8$ mm; slice gap: 2 mm; temporal resolution: 20–45 ms). Patients and healthy volunteers then received 0.15–0.2 mmol/kg intravenous gadopentetate dimeglumine (n = 29) (Magnevist; Bayer Healthcare Pharmaceuticals, Montville, NJ) or gadodiamide (n = 17) (Omniscan; Amersham Health/General Electric Healthcare, Waukesha, WI). To measure T1 time, an inversion recovery (IR)-prepared look-locker steady-state free precession pulse sequence was acquired 7–15 minutes after gadolinium injection in the 4ch plane (field of view (FOV) = 380 × 262–326 mm; matrix size = 192 × 72–90; slice thickness = 8 mm; TR/TE = 2.5/1.1 ms; phase interval = 23–25 ms; flip angle = 50°; 14–56 phases acquired every other R-R interval). Delayed gadolinium-enhanced images were acquired immediately after the look-locker sequence with an ECG-triggered, IR-prepared segmented spoiled gradient recalled echo pulse sequence (TR/TE: $\leq$6.9/$\leq$4.1 ms; flip angle: 25°; spatial resolution: better than 2.1 × 2.1 × 8 mm; slice gap: 2 mm) with images obtained in the short axis, 2ch, and 4ch planes. Inversion time was individually adjusted to null the signal from normal myocardium.

Image analysis

CMR studies were evaluated and quantified by a single reader who was blinded to the subjects' ECG and other clinical information. LV mass, volumes, functional parameters, and right ventricular (RV) volumes and ejection fraction (EF) were determined from short-axis cine images covering the heart from the base to the apex throughout the cardiac cycle by using the MASS research software (MASS V2010-EXP, Leiden University Medical Center, Leiden, The Netherlands). LV endocardial and epicardial contours and RV endocardial contours were traced manually at both end-diastole and end-systole. Papillary muscles were included in the LV and RV volume and excluded from LV mass measurements. LV mass and volumes were indexed to body surface area. LV EF was calculated as LV stroke volume divided by LV end-diastolic volume multiplied by 100.

Left atrial and right atrial (RA) area and length measurements were done at atrial diastole by using 2ch and 4ch cine images according to published methods to obtain atrial volumes.[6] Left atrial volume was calculated by using biplane area-length formula: Volume = $0.848 \times (\text{area}_{4ch} \times \text{area}_{2ch})/[(\text{length}_{4ch} + \text{length}_{2ch})/2]$. RA volume was calculated by using the monoplane area-length formula: Volume = $0.848 \times (\text{area}_{4ch})^2/\text{length}_{4ch}$.

Delayed enhancement images were visually evaluated for possible gadolinium enhancement. For evaluation of diffuse fibrosis with myocardial T1 mapping, LV endocardial and epicardial borders were traced semiautomatically for all phases in the look-locker sequence. Pixel by pixel fit was performed to a 3-parameter model ($A - B\exp[-TI/T_1^*]$) to obtain myocardial T1 as $T_1 = (B/A - 1)T_1^*$. Only those pixels where the χ^2 test for goodness of fit[7] was significant with the level of significance $\alpha = .05$ were included in the average myocardial T1 value. Mean average myocardial T1 values from patients with DM and control

subjects were corrected to obtain the equivalent T1 value based on standard relaxation rates of gadopentetate dimeglumine and gadodiamide and normalized to a contrast dose of 0.2 mmol/kg, postcontrast delay time of 11 minutes, and eGFR of ≅90 mL/min/1.73 m^2 as previously described.[8] As an alternative indexation method, we obtained skeletal muscle T1 values and calculated the myocardial to skeletal muscle T1 ratio.

Interreader variability of postcontrast myocardial T1 values was examined by reading 10% of the cases (n = 6) by 2 readers, and intraclass correlation was 0.997 (95% confidence interval: 0.980–0.999). Those magnetic resonance imagings (MRIs) were also reread by 1 reader with an intrareader intraclass correlation of 0.999 (95% confidence interval: 0.994–0.999). The mean difference was 0.74 ms (95% confidence interval: 12.1 to −10.6 ms) and 2.15 ms (8.1 to −3.83 ms) for inter- and intrareader in Bland-Altman analysis.

Statistics

Continuous variables are summarized as mean ± standard deviation. Categorical and dichotomous variables are presented as percentages. The unpaired Student's *t* test was used to compare continuous variables, and the χ^2 test was used for categorical variables. Univariate linear regression models were used to evaluate the association of average myocardial T1 time with LV indices, CTG repeats size, and standard and signal-averaged ECG findings. Multivariate random effects regression models of panel data clustered by patient and adjusted for heart rate and other potential confounders were used to measure the association of myocardial T1 time with time-dependent surface ECG PR and QRS interval progression in patients with DM-1. Statistical analyses were performed by using Stata 9.0 for Windows (StataCorp, College Station, TX).

Results

Comparison of CMR results between patients and controls

Baseline characteristics

Baseline characteristics of patients with DM (n = 24 DM-1; n = 9 DM-2) and control subjects (n = 13) are presented in Table 1. The mean age of patients with DM was 46.3 years, 46% of the patients were men, 72.7% had DM-1, and 27.3% had DM-2. The mean body mass index was 25 kg/m^2, and mean eGFR was 106.5 mL/min/1.73 m^2. Among patients with DM, QRS duration was 113.9 ± 29.9 on standard ECG and 110.6 ± 23.5 on signal-averaged ECG. Baseline characteristics of patients with DM-1 were similar to those of patients with DM-2 with the exception of the following: patients with DM-1 were younger (42 years old vs 57 years old; $P = .007$) and had lower cardiac index (2.2 L/min/m^2 vs 2.6 L/min/m^2; $P = .02$) than did patients with DM-2. The mean age of control subjects was 38.1 years, 54% of whom were men. Patients with DM-2 were older than control subjects (57 vs 46 years old). There was no significant difference in sex, body mass index, or eGFR between either type of patients with DM and control subjects.

Cine CMR

Thirty-one of the 33 patients with DM had technically adequate quality on cine CMR images. The LV mass index and end-diastolic volume index were 58.6 ± 12.9 g/m^2 and 60.3 ± 17.6 mL/m^2, respectively. The mean stroke volume index was 35.8 ± 8.4 mL/m^2, the cardiac index was 2.33 ± 0.6 L/min/m^2, and the EF was 60.2% ± 7.9%. Eight of the 33 (26%) patients with DM had an EF lower than 55% (Table 1). Compared with control subjects, patients with DM-1 had significantly lower end-diastolic volume index, stroke volume index, and cardiac index. LV mass, volumes, and EF of patients with DM-2 were similar to those of control subjects. Mass to volume ratio, an index of ventricular remodeling, tended to be greater in both patients with DM-1 and patients with DM-2. There were no significant differences between patients with DM and control subjects for LV mass index and LV end-systolic volume index. Although the mean EF was not significantly different between patients with DM and controls, the number of patients with low EF (<55%) was significantly higher in the DM-1 group (Table 1).

In patients with DM, the RV end-diastolic volume index and stroke volume index were 65.8 ± 14.0 and 35.8 ± 8.3 mL/m^2, respectively. RV EF was 54.6% ± 6.8%. Left atrial and RA volume indexes were 32.3 ± 9.6 and 26.0 ± 9.1 mL/m^2. Compared with control subjects, patients with DM-1 had significantly lower RV end-diastolic volume index, RV stroke volume index, and RA volume index (Table 1).

Delayed gadolinium-enhanced CMR and myocardial T1 time

There was no evidence of focal late gadolinium-enhanced scar in either patients with DM or control subjects. However, the mean myocardial T1 time of patients with DM was significantly shorter than that of control subjects (394.5 ± 57.6 ms vs 441.4 ± 32.0 ms, respectively; $P < .0001$) (Figure 1). In addition, the myocardium/skeletal muscle T1 ratio was shorter in patients with DM than in controls (0.67 ± 0.08 vs 0.76 ± 0.08, respectively; $P = .002$). This suggests greater accumulation of gadolinium in the myocardium relative to skeletal muscle.

Univariate association of myocardial T1 time with LV indices, CTG repeats size, and measures of conduction abnormalities in patients with DM

LV indices

The mean myocardial T1 time was on average 2.2 ms longer per each 1-g/m^2 increase in LV mass index ($P = .006$) and 1.3 ms longer per each 1-mL/m^2 increase in LV end-diastolic volume index ($P = .026$) (Figures 2A and 2B). There was no significant association between the

Table 1 Baseline characteristics and left ventricular cine MRI results of DM patients and controls

	Mean ± SD or % (n)			
	DM-1 (n = 24)	DM-2 (n = 9)	Whole DM patients (n = 33*)	Healthy volunteers (n = 13†)
Demographics				
Age (y)	**42.2 ± 14.4**‡	**57.2 ± 9.2**§	46.3 ± 14.7	38.1 ± 11.1
Sex (male)	50 (12)	67 (6)	46 (15)	54 (7)
BMI (kg/m^2)	25.0 ± 5.7	24.9 ± 3.4	25.0 ± 5.1	27.8 ± 5.5
GFR (mL/min/1.73 m^2)	106.5 ± 33.1	107.0 ± 7.1	106.5 ± 31.3	99.0 ± 32.7
LV parameters				
LV mass index (g/m^2)	56.8 ± 12.8	62.7 ± 12.9	58.6 ± 12.9	58.9 ± 5.4
LV end-diastolic volume index (mL/m^2)	**58.1 ± 17.8**‖	65.7 ± 16.6	**60.3 ± 17.6**¶	68.9 ± 9.7
LV end-systolic volume index (mL/m^2)	23.9 ± 11.9	26.0 ± 11.5	24.5 ± 11.7	25.7 ± 5.9
Mass/volume ratio	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.87 ± 0.2
Stroke volume index (mL/m^2)	**34.2 ± 8.9**‖	39.7 ± 6.1	**35.8 ± 8.4**¶	43.2 ± 5.2
Cardiac index (L/min/m^2)	**2.2 ± 0.6**‡‖	2.6 ± 0.3	**2.33 ± 0.6**¶	2.7 ± 0.3
Ejection fraction (%)	59.6 ± 8.4	61.7 ± 6.6	60.2 ± 7.9	63.0 ± 5.1
Ejection fraction <55% (yes)	**31.8 (7)**‖	11.1 (1)	**25.8 (8)**¶	0 (0)
RV parameters				
RV end-diastolic volume index (mL/m^2)	**62.9 ± 12.9**‖	72.8 ± 14.9	65.8 ± 14.0	72.0 ± 9.7
RV end-systolic volume index (mL/m^2)	28.7 ± 7.3	33.0 ± 10.8	29.9 ± 8.5	30.6 ± 4.6
RV stroke volume index (mL/m^2)	**34.2 ± 8.6**‖	39.8 ± 6.4	**35.8 ± 8.3**¶	41.4 ± 5.9
RV ejection fraction (%)	54.3 ± 7.3	55.4 ± 5.8	54.6 ± 6.8	57.5 ± 3.0
Atrial volumes				
Left atrial volume index (mL/m^2)	29.9 ± 6.7	38.1 ± 13.2	32.3 ± 9.6	34.1 ± 4.9
Right atrial volume index (mL/m^2)	**23.4 ± 6.5**‖	32.9 ± 11.5	**26.0 ± 9.1**¶	34.9 ± 7.5
ECG				
Standard ECG QRS duration (ms)	114.8 ± 30.6	111.6 ± 29.4	113.9 ± 29.9	94.5 ± 17.8
Digital ECG filtered QRS duration (ms)	110.7 ± 21.2	114.4 ± 35.1	110.6 ± 23.5	NA
Terminal (40 ms) root mean square voltage (mcV)	26.6 ± 21.7	34.4 ± 32.8	33.3 ± 26.6	NA
Low-amplitude (<40 mcV) late-potential duration (ms)	40.4 ± 20.0	56.6 ± 47.7	41.9 ± 30.3	NA

P value is based on the χ^2 test for categorical variables and *t* test for continuous variables. Values in bold text are statistically significantly different among patient groups.

BMI = body mass index; DM = myotonic muscular dystrophy; DM-1 = myotonic muscular dystrophy type 1; DM-2 = myotonic muscular dystrophy type 2; ECG = electrocardiogram; GFR = glomerular filtration rate; LA = left atrial; LV = left ventricular; MRI = magnetic resonance imaging; RA = right atrial; RV = right ventricular.

*Of 33 patients with myotonic muscular dystrophy, 13 had GFR value (n = 17 in DM-1 and n = 2 in DM-2), 31 had technically adequate MRI data for LV and RV function (n = 22 in DM-1 and n = 9 in DM-2), 27 had technically adequate MRI data for LA volume measurement (n = 19 in DM-1 and n = 8 in DM-2), and 29 had technically adequate MRI data for RA volume measurement (n = 21 in DM-1 and n = 8 in DM-2).

†Of 13 healthy volunteers, 8 had standard ECG.

‡*P* <.05, patients with DM-1 vs patients with DM-2.

‖*P* <.05, patients with DM-1 vs healthy volunteers.

§*P* <.05, patients with DM-2 vs healthy volunteers.

¶*P* <.05, patients with whole DM vs healthy volunteers.

mean myocardial T1 time and stroke volume index, cardiac index, and EF (*P* = .14, .80, and .08, respectively) (Table 2).

CTG repeats size

There was no significant association between the mean myocardial T1 time and CTG repeats size in patients with DM-1 (*P* = .20).

Measures of conduction abnormalities

Signal-averaged filtered QRS duration and low-amplitude (<40 mcV) late-potential duration showed positive associations with mean myocardial T1 time (1.2 ms longer, *P* = .005, and 0.9 ms longer, *P* =0.01, respectively) (Figures 2C and 2D). The mean myocardial T1 time was not significantly associated with terminal (40 ms) root mean square voltage on signal-averaged ECG (*P* = .08) (Table 2).

Multivariate analysis of the association of myocardial T1 time with longitudinal changes in PR and QRS duration

Time-dependent surface ECG progression in PR and QRS intervals of patients with DM-1 was derived from repeat surface ECG measures with a median follow-up duration of 385 days (interquartile range: 16–979 days). Table 3 lists predictor variables in the random effects linear regression model of time-dependent changes in PR and QRS intervals. Patient age, number of CTG repeats, and paroxysmal atrial flutter or fibrillation were independently associated with PR and QRS prolongation during follow-up. Decreased LV EF was associated

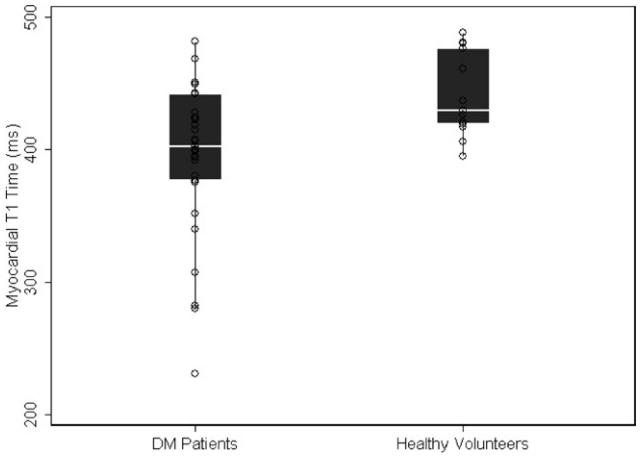

Figure 1 Scatter and box-plot overlay diagram showing variation in the postcontrast myocardial T1 time between healthy volunteers and patients with myotonic dystrophy. The box-plots display the median and the 25th to 75th percentile range (*center white line and solid black box*), the lower and upper adjacent values (*thin lines*), and data points (*dots*). DM = myotonic muscular dystrophy.

with greater QRS (but not PR) prolongation during follow-up. After adjustment for the above covariates, myocardial T1 time remained independently associated with both PR and QRS interval progression during long-term follow-up.

Discussion

To the best of our knowledge, the current study is the first to assess diffuse myocardial fibrosis in patients with DM. Postcontrast myocardial T1 values of patients with DM were significantly lower than those of control subjects, suggesting the presence of diffuse myocardial fibrosis. The current study also demonstrated that LV end-diastolic volume index, stroke volume index, and cardiac index were significantly lower in patients with DM than in controls.

Macroscopic cardiac structure and function

Alterations in cardiac structure and function of patients with DM have been previously reported by using echocardiography[9–11] and MRI.[12] LV hypertrophy,[9,10,12] wall motion abnormality,[9,11] LV dilatation,[9,10] and systolic dysfunction[9,11,12] were observed in prior studies. However, 2 recent studies did not observe a difference in LV mass, end-diastolic and end-systolic volume, and EF of patients with DM compared with control subjects.[13,14] Such discrepancies may be due to variations in disease severity among study samples. The current study was in line with previous studies by showing no significant difference in LV mass and EF in patients with DM compared with control subjects. In contrast to previous studies, however, LV volumes (end-diastolic and end-systolic and stroke volume) and cardiac

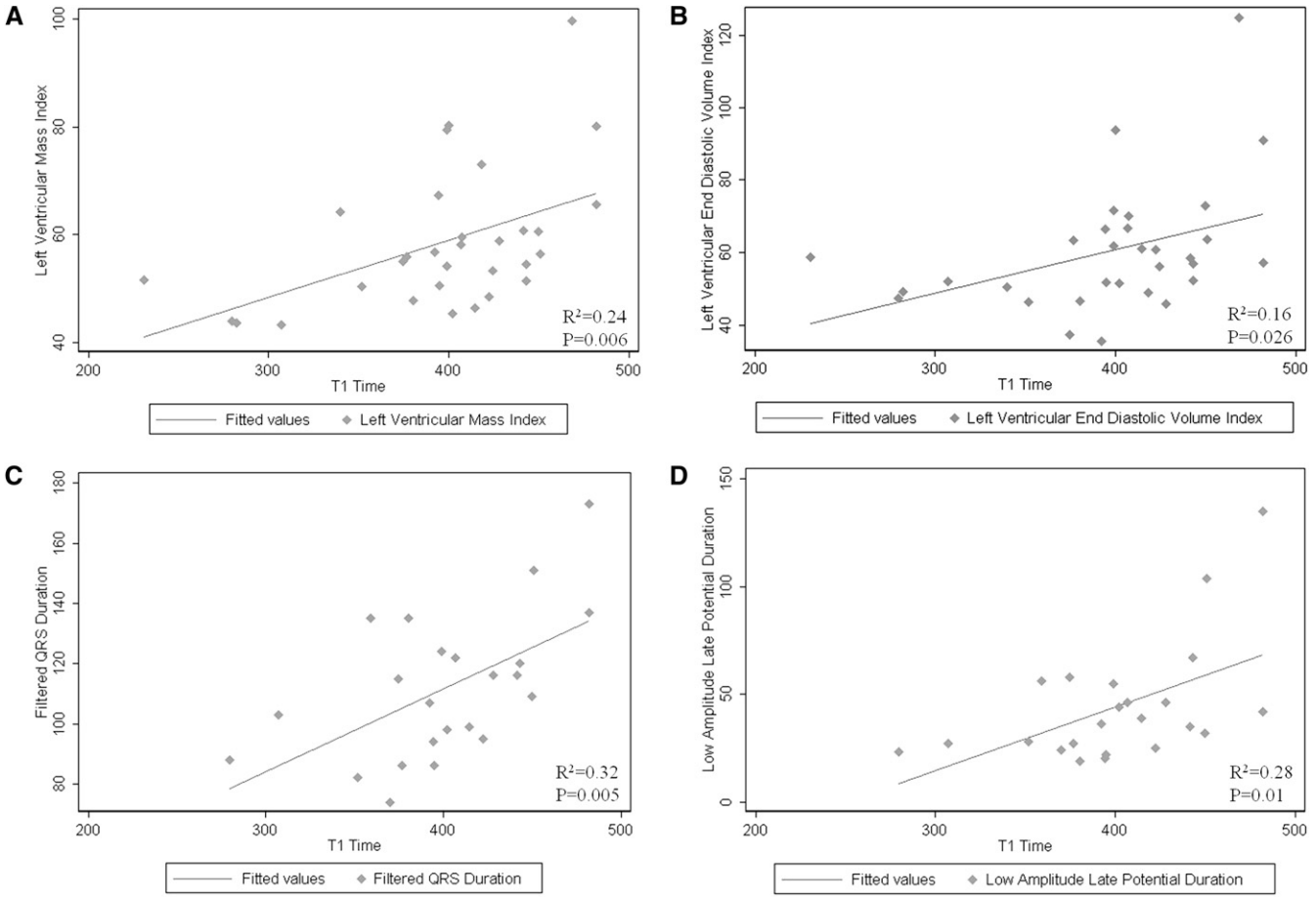

Figure 2 **A–D:** Associations of postcontrast myocardial T1 time with LV end-diastolic mass index **(A)**, end-diastolic volume index **(B)**, digital ECG filtered QRS duration **(C)**, and low-amplitude (<40 mcV) late-potential duration **(D)**. ECG = electrocardiogram; LV = left ventricular.

Table 2 Univariate linear regression models showing associations of mean myocardial T1 time

Variable	R^2	Regression coefficient (ms)	95% CI	*P*
CTG repeats (yes vs no)	0.10	−0.09	−0.2 to 0.1	.196
Digital ECG filtered QRS duration (per 1 ms)	0.32	1.2	0.4–1.9	**.005**
Terminal (40 ms) root mean square voltage (per 1 mcV)	0.14	−0.8	−1.6 to 0.1	.079
Low-amplitude (<40 mcV) late-potential duration (per 1 ms)	0.28	0.9	0.3–1.6	**.01**
LV mass index (per 1 g/m^2)	0.24	2.2	0.7–3.7	**.006**
LV end-diastolic volume index (per 1 mL/m^2)	0.16	1.3	0.2–2.5	**.026**
Stroke volume index (per 1 mL/m^2)	0.07	1.9	−0.6 to 4.5	.138
Cardiac index (per 1 L/min/m^2)	0.01	−4.9	−45.4 to 35.5	.803
Ejection fraction (%)	0.11	−2.4	−5.1 to 0.3	.075

CI = confidence interval; ECG = electrocardiogram; LV = left ventricular. Statistically significant *P* values have been highlighted in bold text.

output were lower in patients with DM than in control subjects. In addition, patients with DM-1 had significantly lower RA and RV end-diastolic volumes and reduced RV stroke volume compared with controls. Many of our patients had evidence of cardiac involvement by ECG (PR intervals > 200 ms and QRS intervals > 120 ms). The severity of cardiac involvement, however, was usually mild. Only 8 of the 33 patients (25%) had an EF of <55%, and none had clinical symptoms of heart failure.

Diffuse fibrosis

The pathologic features underlying cardiac findings in patients with DM appear to involve myocyte hypertrophy, interstitial fibrosis, lymphocytes, and/or fatty infiltration of the conduction system and myocardium.[15] Invasive electroanatomic voltage mapping has revealed widespread reduced electrogram voltage amplitude involving the interatrial septum, anterolateral atrial wall, and RV outflow tracts of patients with DM-1.[16] A prior MRI study has also revealed evidence of fatty infiltration and edema/inflammation in addition to fibrosis in patients with DM with severe disease and advanced conduction disturbance.[12] Late gadolinium-enhanced MRI is a well-established technique to assess focal myocardial scar (dense myocardial fibrosis). In this technique, normal myocardial signal is suppressed by an IR pulse and focal myocardial scar is seen as hyperintense areas due to gadolinium retention.[17] The IR technique, however, may suppress diffuse myocardial fibrosis despite substantial retention of gadolinium, because the signal intensity variation compared with normal tissue is minimal in these areas. The myocardial T1 mapping technique can detect diffuse myocardial fibrosis noninvasively by quantitating the variability in myocardial T1 times. Diffuse myocardial fibrosis causes shortening in T1 times because of the retention of gadolinium-based contrast in increased interstitial spaces. Previous studies have utilized T1 mapping to quantify diffuse fibrosis in patients with heart failure, aortic regurgitation, adult congenital heart disease, and nonischemic cardiomyopathy.[4,5,18,19] Importantly, the postcontrast myocardial T1 time is sensitive to MRI acquisition parameters (ie, contrast dose, delay time of MRI scan) and physiologic parameters (ie, eGFR). However, those factors can be corrected to a standardized value of dose, MRI delay time, and eGFR value for interpatient comparison as performed in the current study.[8] Histopathologic processes other than diffuse myocardial fibrosis such as fatty infiltration, edema, amyloid protein deposition, and iron deposition also influence the myocardial T1 time.

In contrast to patients with Becker and Duchenne muscular dystrophy, those with DM-1 and DM-2 tend not to have cohesive myocardial fibrosis.[20] In the current study, patients with DM had no focal myocardial scar in late gadolinium-enhanced MRI images. However, T1 mapping revealed significantly shorter values in patients with DM than in control subjects. This observation is most likely due to the presence of diffuse myocardial fibrosis in patients with DM. On the other hand, within the group of patients with DM, those with evidence of more severe cardiac involvement (higher LV end-diastolic mass, volume, or conduction delays on filtered ECG) had

Table 3 Predictors of longitudinal PR and QRS interval changes (after adjusting for heart rate) in the multivariate random effects regression model

	PR interval		QRS interval	
Variable (unit)	Regression coefficient	*P*	Regression coefficient	*P*
Time	+4.8 ms/1000 d	.029		NS
Age	+6.5 ms/10 y	.015	+5.9 ms/10 y	.008
Number of CTG repeats	+5.3 ms/100 repeats	.002	+8.3 ms/100 repeats	<.001
Paroxysmal atrial fibrillation or flutter	+65.1 ms	<.001	+34.8 ms	<.001
Left ventricular ejection fraction		NS	−14.3 ms/10% increase	.001
Myocardial T1 time	+1.3 ms/10 ms	.035	+1.3 ms/10 ms	.007

NS = not significant.

longer myocardial T1 times. Fatty infiltration, myocardial edema, and inflammation in patients with DM may lengthen myocardial T1 times. We have measured T1 values of subcutaneous fat in patients with DM and observed that it shows a large variation from 266 to 568 ms; fat T1 values can be higher than postcontrast myocardial T1 values in some cases. The amount of fatty infiltration is also important. In pathology specimens of patients with DM, fatty infiltration was reported to be approximately 5%. We expect that 5% fatty infiltration can increase the postcontrast myocardial T1 value by approximately 10 ms. However, the presence of fatty infiltration in patients with DM with evidence of more severe cardiac involvement is unlikely to fully explain the observed increase in postcontrast myocardial T1 times of those with greater conduction disease. We speculate that similar to patients with acute myocardial infarction,[21] myocardial edema and/or inflammation may also contribute to longer myocardial T1 times in patients with severe DM.[22] De Ambroggi et al[12] have shown myocardial T2 hyperintensities in patients with DM, which suggests the presence of edema/inflammation. Unfortunately, T2-weighted images were not included in our study protocol. This finding needs to be assessed in further studies.

Limitations

The average myocardial T1 values were obtained from a single plane assuming that diffuse fibrosis/fibro-fatty infiltration affects the whole myocardium evenly. This assumption seems reasonable since fibrosis was diffuse in histopathologic specimens obtained from patients with DM.[15] Because of associated complications, myocardial biopsies could not ethically be obtained to confirm the presence of fibro-fatty myocardial infiltration in our cases. A more recent modified lock-locker sequence is likely to provide more consistent and reproducible results for T1 mapping.[23] This sequence was not available at the time of CMR scans of the current study. However, our experience shows an excellent correlation between the 2 sequences. We cannot clearly establish, at present, whether changes in myocardial T1 time might be predictive of specific clinical outcomes. In addition, because of lack of standard or signal-averaged ECG data in healthy volunteers, the association of T1 time with QRS duration and late potentials could not be assessed in that subset.

Conclusions

LV end-diastolic volume, stroke volume, and cardiac output were significantly lower in patients with DM than in controls. Postcontrast myocardial T1 times of patients with DM were significantly shorter than those of control subjects. On the other hand, patients with DM with evidence of more severe cardiac involvement had longer myocardial T1 times. These findings suggest (a) the early presence of diffuse myocardial fibrosis in patients with DM and (b) greater fat deposition, edema, and/or inflammatory infiltration in advanced disease states. Based on our results, the T1 mapping technique will likely be useful for the assessment of cardiac involvement in patients with DM, rather than for diagnosis or for ruling out DM in normal subjects. The utility of our findings for risk stratification is unknown and warrants further study.

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