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PART II

MYOCARDIAL TISSUE CHARACTERIZATION AND LEFT VENTRICULAR MECHANICS IN DIABETIC PATIENTS

CHAPTER 7

ASSOCIATION BETWEEN DIFFUSE MYOCARDIAL FIBROSIS BY CARDIAC MAGNETIC RESONANCE CONTRAST-ENHANCED T1 MAPPING AND SUBCLINICAL MYOCARDIAL DYSFUNCTION IN DIABETIC PATIENTS: A PILOT STUDY.

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ABSTRACT

Diabetic patients have increased interstitial myocardial fibrosis on histology. Magnetic resonance imaging (MRI) T1 mapping is a previously validated imaging technique that can quantify the burden of global and regional interstitial fibrosis. However, association between MRI T1 mapping and subtle left ventricular (LV) dysfunction in diabetic patients is unknown.

Fifty diabetic patients with normal LV ejection fraction (EF) and no underlying coronary artery disease or regional macroscopic scar on MRI delayed enhancement were prospectively recruited. Diabetic patients were compared with 19 normal controls that were frequency matched in age, gender and body mass index. The burden of interstitial fibrosis using MRI T1 mapping was correlated with myocardial functional assessment by echocardiographic 2-dimensional speckle tracking global longitudinal strain analysis.

There were no significant differences in mean LV end-diastolic volume index, end-systolic volume index and LVEF between diabetic patients and normal controls. Diabetic patients had significantly shorter global contrast-enhanced myocardial T1 time compared to normal controls (425 ± 72 ms vs. 504 ± 34 ms, $p < 0.001$). There was no correlation between global contrast-enhanced myocardial T1 time and LVEF ($r = 0.14$, $p = 0.32$) in the diabetic patients. However, there was good correlation between global contrast-enhanced myocardial T1 time and global longitudinal strain ($r = -0.73$, $p < 0.001$). Multivariate analyses demonstrated that global contrast-enhanced myocardial T1 time was the strongest independent determinant of LV myocardial systolic function (standardized ß = -0.626, $p < 0.001$). Similarly, there was good correlation between global contrast-enhanced myocardial T1 time and septal E' ($r = 0.54$, $p < 0.001$). Multivariate analyses demonstrated that global contrast-enhanced myocardial T1 time was the strongest independent determinant of LV myocardial diastolic function (standardized ß = 0.432, $p < 0.001$).

A shorter global contrast-enhanced myocardial T1 time by MRI T1 mapping was associated with more impaired longitudinal myocardial systolic and diastolic function in diabetic patients.

INTRODUCTION

Diabetic patients can develop changes in cardiac structure and myocardial dysfunction that are independent of hypertension and coronary artery disease.[1-3] Although the underlying pathogenesis is likely to be multifactorial[1-4], there is eventually accelerated cellular apoptosis and necrosis resulting in increased perivascular and diffuse interstitial fibrosis within the myocardium.[2] Importantly, previous studies have demonstrated histological evidence of increased diffuse microscopic fibrosis in the myocardium of diabetic patients.[5, 6] In magnetic resonance imaging (MRI), gadolinium-based contrast agents accumulates and have increased wash-out times within these myocardial fibrous tissues due to the absence of viable myocytes and increased volume of distribution.[7] Using MRI T1 mapping sequences, global contrast-enhanced T1 relaxation time can detect and quantify the extent of diffuse interstitial myocardial fibrosis. A recent independent study has histologically validated and demonstrated an inverse linear relationship between global contrast-enhanced myocardial T1 time and the burden of myocardial interstitial fibrosis.[8] Thus, shorter global contrast-enhanced myocardial T1 time represent more interstitial fibrosis.[8]

Diabetic patients can develop subtle left ventricular (LV) myocardial dysfunction despite normal LV ejection fraction (EF).[9, 10] Advanced echocardiographic techniques such as tissue Doppler imaging and 2-dimensional (2D) speckle tracking are highly sensitive for early detection of subclinical diabetic myocardial dysfunction.[10, 11] Therefore, increased interstitial fibrosis within the diabetic myocardium may result in subtle LV dysfunction which can be detected by these sophisticated echocardiographic techniques. Thus, the aims of the present study were:

1) to quantify and compare global contrast-enhanced myocardial T1 time between diabetic patients with normal LVEF and normal controls, and

2) to correlate global contrast-enhanced myocardial T1 time with LV myocardial functional assessment using global longitudinal strain by 2D speckle tracking analysis.[12]

METHODS

Patient population and study protocol

Sixty-five diabetic patients (35 type 1 and 30 type 2) were prospectively recruited in the present study. Inclusion criteria included diabetes mellitus diagnosed according to World Health Organization criteria.[13] Exclusion criteria included age < 18 years, rhythm other than sinus rhythm, significant coronary artery disease, previous myocardial infarction, presence of segmental wall motion abnormalities or presence of delayed contrast enhancement (DCE) on MRI indicative of macroscopic fibrosis/scar from previous myocardial infarction, LVEF < 50%, and moderate or severe valvular stenosis or regurgitation. However, 15 type 2 diabetic patients were excluded from the study due to the presence of DCE on MRI that was indicative of previous silent myocardial infarction. Thus, a total of 50 diabetic patients (35 type 1 and 15 type 2) were included in the final analysis. The study was approved by the local institutional ethics committee and written informed consent was obtained.

In addition, 19 normal control subjects were also included. The normal controls were frequency matched against the diabetic patients for age, gender and body mass index. All control subjects were clinically referred for evaluation of atypical chest pain, palpitations or syncope without murmur and had normal MRI examinations. Exclusion criteria for the control subjects included history of diabetes mellitus, hypertension, previous myocardial infarction, presence of segmental wall motion abnormalities or presence of DCE on MRI, LVEF < 50%, and moderate or severe valvular stenosis or regurgitation.

All subjects underwent a comprehensive MRI examination (including administration of gadolinium-based contrast for DCE and quantification of global contrast-enhanced myocardial T1 time).

All diabetic patients underwent a complete transthoracic echocardiographic examination including assessment of myocardial systolic and diastolic function by 2D speckle tracking strain and tissue Doppler septal E' analyses respectively. Baseline clinical variables recorded included diabetic complications (including diabetic retinopathy, neuropathy and nephropathy), cardiac risk factors, and glomerular filtration rates (GFR) calculated by the Modification of Diet in Renal Disease formula as recommended by the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative Guidelines.[14]

LV volumes, EF and mass were quantified in all the patients using MRI as gold standard. In addition, global contrast-enhanced myocardial T1 time was also quantified, with a shorter T1 time suggestive of more fibrosis.[8] Previous study has demonstrated that the assessment of global longitudinal strain by 2D speckle tracking echocardiography is the most sensitive marker of myocardial systolic function in diabetic patients compared to circumferential or radial strain.[10] Thus, to evaluate the effects of increasing interstitial fibrosis on LV systolic function, the linear correlations between global contrast-enhanced myocardial T1 time, LVEF and global longitudinal strain were explored. Similarly, the linear correlation between global contrast-enhanced myocardial T1 time and septal E' was also determined. Finally, the independent effect of global contrast-enhanced myocardial T1 time on global longitudinal strain (marker of myocardial systolic function) and septal E' (marker of myocardial diastolic function) were determined in a multivariate analysis corrected for clinical and MRI covariates.

Cardiac magnetic resonance imaging

All patients underwent MRI examinations for assessment of LV volumes, LVEF, global contrast-enhanced myocardial T1 time and DCE with a 1.5-T whole-body MRI scanner (Gyroscan ACS/NT15; Philips, Best, the Netherlands). LV volumes and EF were assessed by imaging the entire heart in the short-axis orientation with ECG-gated breath-hold balanced steady state free-precession imaging. Cine imaging parameters included the following: echo time = 1.7 ms, repetition time = 3.4 ms, flip-angle = 35°, slice thickness = 10 mm with a gap of 0 mm, field of view = 400 x 400 mm, reconstructed matrix size = 256 x 256 pixels.

DCE images were acquired 15 minutes after bolus injection of gadolinium diethylenetriamine penta-acetic acid (Magnevist, Schering, Berlin, Germany; 0.15 mmol/kg) with an inversion recovery gradient echo sequence with parallel imaging (SENSE, acceleration factor 2). Inversion time was determined by real-time plan scan (Look-Locker sequence) to null normal myocardium signal. DCE images of the heart were acquired in 1 breath-hold using 20 – 24 short-axis slices (depending on the heart size). DCE imaging parameters were: echo time = 1.06 ms, repetition time = 3.7 ms, flip-angle = 15°, slice thickness = 5 mm, field of view = 400 x 400 mm, reconstructed matrix size = 256 x 256 pixels. All subjects included in the present study had no evidence of DCE suggestive of macroscopic myocardial scar/fibrosis.

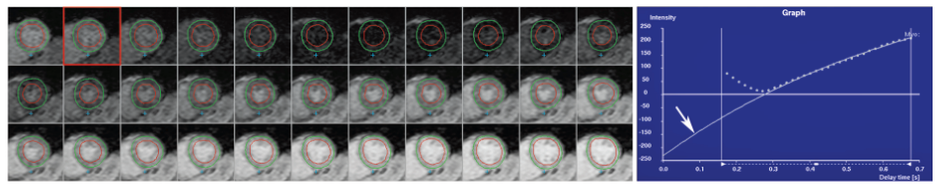
Contrast-enhanced myocardial T1 mapping with the Look-Locker sequence was used to cycle through images over a range of inversion times.[15] The sequence consisted of an ECG-gated, inversion recovery gradient echo sequence with parallel imaging (SENSE, acceleration factor 1.8). Thirty-three images were acquired sequentially at increasing inversion times 10 minutes after bolus injection of gadolinium diethylenetriamine penta-acetic acid in 1 breath-hold. The Look-Locker sequence imaging parameters were: echo time = 1.0 ms, repetition time = 3.79 ms, flip-angle = 8°, inversion time 150 ms, slice thickness = 10 mm, field of view = 370 x 370 mm, reconstructed matrix size = 256 x 256 pixels. These images were then processed with a curve fitting technique to generate T1 maps as described below.

Evaluation of LV mass, volumes and function. All MRI images were digitally stored on hard disks and analyzed offline using dedicated quantitative software (MASS, Medis, Leiden, The Netherlands). LV endocardial and epicardial borders were outlined on the short-axis cine images. Papillary muscles were considered as part of the LV cavity, and epicardial fat was excluded. LV end-diastolic mass index, LV end-diastolic volume index (EDVI) and LV end-systolic volume index (ESVI) were measured and corrected for body surface area.[16] LVEF was calculated and expressed as a percentage. Stroke volume was calculated as the difference between LV end-diastolic and end-systolic volumes, and cardiac output was calculated as the product of stroke volume and heart rate.

Evaluation of T1 mapping. T1 recovery is a basic fundamental parameter of magnetic resonance imaging and refers to the recovery of "longitudinal magnetization" of protons along the main magnetic field in the z-axis. The rate of this recovery can be described by the exponential equation: $MZ(t) = MZ(t=\infty)[1 - e\text{-}t/T1]$, where MZ(t) is the sample magnetization observed at time = t = inversion time for an inversion recovery experiment, and $MZ(t=\infty)$ denotes the equilibrium magnetization in the z-axis. To quantify contrast-enhanced myocardial T1 time, LV endocardial and epicardial borders were outlined from a single mid-ventricular short-axis Look-Locker sequence of varying inversion times using MASS research software (MASS V2010-EXP, Leiden University Medical Center, Leiden, The Netherlands) (***Figure 1***). As the different inversion recovery times fall into different cardiac phases during the Look-Locker sequence, it resulted in movement of the left ventricle. Thus, the endo- and epicardial contours were manually drawn in each image (total of 33 images) to ensure the inclusion of only myocardium and the exclusion of blood pool/epicardial fat. The software then permits automatic pixel-by-pixel quantification of contrast-enhanced

myocardial T1 time by fitting data acquired at the various inversion times.[17] The location of a pixel position within the myocardium can be described by its relative position across the local wall thickness (relative distance to the endocardial and epicardial contour) and its relative position along the length of the defined myocardial contours (for short-axis images, the longitudinal location is defined by the angular position relative to the posterior junction of the RV free wall with the LV). Following this definition, signal intensity curves of matching pixels were reconstructed and used for T1 fitting. Prior to fitting, the signal intensity of initial phases was inverted. The best fit for T1 value (corresponding to the smallest fitting error) was determined iteratively by inverting initial phases up to a time corresponding to the zero crossing of the longest possible T1 value and performing a fit for each case. The Levenberg-Marquardt algorithm was used to perform a nonlinear fit of the model to the measured data. Only pixels where the X^2 test for goodness of fit was significant with level of significance $\alpha = 0.05$ were included in the final average T1 value.

Figure 1. **Example of myocardial T1 mapping using the Look-Locker sequence with increasing inversion times.**
Left ventricular endocardial and epicardial borders were outlined for all 33 images (*left panel*). The software then automatically determines the myocardial signal intensity for every individual pixel from each image. The individual pixel intensities within the myocardium (y-axis) were subsequently plotted against the inversion time (x-axis) (*right panel*). Finally, the global contrast-enhanced myocardial T1 time was automatically calculated by the software which performed curve-fitting of the data points to an exponential recovery curve (arrow) representing the recovery of myocardial longitudinal magnetization. Therefore, a short global contrast-enhanced myocardial T1 time indicate a higher burden of interstitial fibrosis due to a greater concentration of gadolinium within the fibrous tissues, and vice versa.



A global contrast-enhanced myocardial T1 time was subsequently automatically calculated as the average of all the individual contrast-enhanced myocardial T1 time from each pixel. As the function of gadolinium-based contrast agents normally shortens T1 time, and its wash-out time increases within myocardial fibrous tissues due to increased volume of distribution[7], a shorter global contrast-enhanced myocardial T1 time consequently is suggestive of more interstitial fibrosis.[8] The derived

global contrast-enhanced myocardial T1 time is generally expected to be shorter than the true T1 time of myocardium due to the multiple readout gradients from the Look-Locker sequence and the presence of gadolinium-based contrast agents.

Transthoracic echocardiography

Transthoracic echocardiography was performed with the diabetic patients at rest using commercially available ultrasound transducer and equipment (M4S probe, Vivid 7, GE-Vingmed, Horten, Norway). All images were digitally stored on hard disks for offline analysis (EchoPAC version 108.1.5, GE-Vingmed, Horten, Norway). A complete 2D, color, pulsed and continuous-wave Doppler echocardiogram was performed according to standard techniques.[18, 19]

Transmitral and pulmonary venous flow velocities were recorded using conventional pulsed-wave Doppler echocardiography in the apical 4 chamber view using a 2 mm sample volume. Transmitral early (E wave) and late (A wave) diastolic velocities as well as deceleration time were recorded at the mitral leaflet tips. The pulmonary venous peak systolic (S) and diastolic (D) velocities were recorded with the sample volume positioned 1 cm below the orifice of the right superior pulmonary vein in the left atrium.

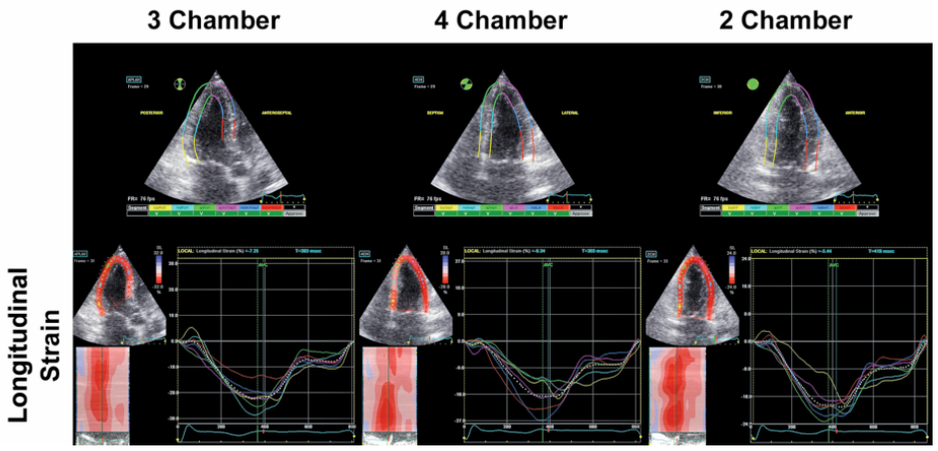
Evaluation of myocardial systolic function. Quantification of myocardial systolic function was performed using 2D speckle tracking echocardiography.[12] Briefly, 2D speckle tracking is a commercial software (EchoPAC version 108.1.5, GE-Vingmed, Horten, Norway) that performs semi-automated frame-by-frame tracking of natural acoustic markers within the myocardium seen on standard 2D gray-scale echocardiographic images, and it permits direct quantification of global longitudinal myocardial function. Previous study has demonstrated that the assessment of global longitudinal strain and strain rate by 2D speckle tracking echocardiography is the most sensitive marker of myocardial systolic function in diabetic patients and is superior to LVEF, circumferential and radial strain/strain rate.[10]

To obtain global longitudinal strain/strain rate, 2D speckle tracking analyses were performed on grey scale images of the LV obtained in the 3 apical (3-, 4- and 2-chamber) views (***Figure 2***). During analysis, the endocardial border was manually traced at end-systole and the region of interest width adjusted to include the entire myocardium. The software then automatically tracks and accepts segments of good tracking quality and rejects poorly tracked segments, while allowing the observer to manually override its decisions based on visual

assessments of tracking quality. From the 3 individual apical views, myocardial systolic function was calculated as the average of the 3 peak global longitudinal strain.[10] All strain measurements were exported to a spreadsheet (Microsoft ® Excel 2002, Microsoft Corporation, Redmond, WA).

Figure 2. **Quantification of longitudinal myocardial function by 2-dimensional speckle tracking echocardiography.**

Longitudinal strain was quantified from the 3 apical (3-, 4- and 2 chamber) views. The 2-dimensional speckle tracking software then automatically displays the respective segmental (colored lines) and global (single white dotted line) longitudinal strain curves. Longitudinal myocardial function was then calculated as the mean of the 3 individual peak global longitudinal strain values, and expressed as a percentage. Longitudinal strain is normally expressed as a negative percentage, indicating percentage shortening of the myocardium.



Evaluation of myocardial diastolic function. Quantification of myocardial diastolic function was performed using septal E' and E/e' ratio by tissue Doppler imaging.[20] Color-coded tissue Doppler images of the left ventricle was obtained in apical 4-chamber view acquired at the highest possible frame rates (> 150 frames/s) during end-expiration and stored for off-line analysis. Peak early diastolic myocardial velocities (E') was measured in the basal septal mitral annulus, and the ratio of peak transmitral E wave to septal E' was calculated (septal E/e' ratio).[20]

Variability analysis

To determine intra- and inter-observer variabilities for global contrast-enhanced myocardial T1 time, measurements were repeated in 10 randomly

selected patients. The intra- and inter-observer variabilities for global contrast-enhanced myocardial T1 time expressed as mean absolute differences ± 1 standard deviation were 12.6 ± 12.7 ms and 12.4 ± 10.0 ms respectively.

Previous work from our laboratory has reported the intra- and inter-observer variabilities for mean global longitudinal strain as mean absolute differences ± 1 standard deviation of 1.2 ± 0.5% and 0.9 ± 1.0% respectively.[10]

Statistical analysis

All continuous variables were presented as mean ± 1 SD unless otherwise stated. Categorical variables were presented as frequencies and percentages. Comparisons between diabetic and control patients were performed using Mann-Whitney U test and Chi square test for continuous and categorical variables respectively. Pearson correlation was employed to examine the linear association between 2 continuous variables. Multiple linear regression analyses were then performed to identify independent clinical and echocardiographic determinants of global longitudinal strain and septal E' for diabetic patients. All univariable predictors with $p < 0.20$ were simultaneously entered into the multiple linear regression models. Validity of the multiple linear regression models were established by confirming the residuals to be normally distributed. A 2-tailed p value of < 0.05 was considered significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago), version 17.

RESULTS

Table 1 summarizes the baseline clinical characteristics of the 50 diabetic patients and 19 control subjects. There were no differences in age, gender, blood pressure, hemoglobin and GFR between the diabetic patients and control subjects. A total of 28 (56%) diabetic patients were treated for hypertension. A respective 31 (62.0%), 12 (24.0%) and 7 (14.0%) diabetic patients had evidence of diabetic retinopathy, peripheral neuropathy and nephropathy respectively. However, no diabetic patients had a history of previous myocardial infarction or underlying significant coronary artery disease by virtue of the study exclusion criteria.

Table 1. Clinical and biochemical characteristics of diabetic patients and normal controls

Variable	Diabetic patients (n = 50)	Controls (n = 19)	p value*
Demographics			
Age (years)	51 ± 10	45 ± 15	0.15
Male gender (%)	54.0	63.2	0.49
Body mass index (kg/m2)	26.3 ± 3.7	26.1 ± 4.4	0.84
Medical history			
Retinopathy (%)	62.0	-	-
Neuropathy (%)	24.0	-	-
Nephropathy (%)	14.0	-	-
Systolic blood pressure (mmHg)	129 ± 10	123 ± 14	0.08
Diastolic blood pressure (mmHg)	76 ± 7	73 ± 8	0.14
Laboratory			
Hemoglobin (g/dL)	14.2 ± 1.3	14.1 ± 1.1	0.76
GFR (mL/min/1.73m2)	92.8 ± 18.9	97.9 ± 18.8	0.26
HbA1c (%)	8.0 ± 1.4	-	-

*p value by Mann-Whitney U test and Chi square test for continuous and categorical variables respectively. GFR = glomerular filtration rate; HbA1c = glycated hemoglobin level.

Magnetic resonance imaging and echocardiography

Table 2 summarizes the baseline MRI and echocardiographic characteristics of the diabetic patients and normal controls. There were no significant differences in LVEDVI (79.1 ± 14.4 vs. 79.8 ± 17.2 mL/m^2, p = 0.60), LVESVI (33.3 ± 7.6 vs. 34.7 ± 7.5 mL/m^2, p = 0.23), LV mass index (49.0 ± 7.6 vs. 50.9 ± 8.7 g/m^2, p = 0.24) and LVEF (58.1 ± 4.6 vs. 56.2 ± 3.8%, p = 0.10) between the diabetic patients and control subjects. No patients had evidence of regional DCE suggestive of focal macroscopic scar/fibrosis by virtue of the study exclusion criteria. However, diabetic patients had significantly shorter global contrast-enhanced myocardial T1 time (425 ± 72 vs. 504 ± 34 ms, $p < 0.001$). Furthermore, there was a wide range of global contrast-enhanced myocardial T1 time in diabetic patients ranging from 271 ms to 604 ms. There was no difference in the global contrast-enhanced myocardial T1 time in diabetic patients with and without a history of hypertension (422 ± 83 vs. 429 ± 52 ms, p = 0.74).

Table 2. Magnetic resonance imaging and echocardiographic characteristics of diabetic patients

Variable	Diabetic patients (n = 50)	Controls (n = 19)	p value*
Magnetic resonance imaging			
LV mass index (g/m2)	49.0 ± 7.6	50.9 ± 8.7	0.24
LVEDVI (mL/m2)	79.1 ± 14.4	79.8 ± 17.1	0.60
LVESVI (mL/m2)	33.3 ± 7.6	34.7 ± 7.5	0.23
LVEF (%)	58.1 ± 4.6	56.2 ± 3.8	0.10
Cardiac output (L/min)	6.5 ± 1.3	6.2 ± 2.2	0.44
Global contrast-enhanced myocardial T1 time (ms)	425 ± 72	504 ± 34	< 0.001
Echocardiography			
Heart rate (beats/min)	74 ± 12	67 ± 12	0.10
Transmitral E/A ratio	1.13 ± 0.34	1.19 ± 0.52	0.97
Deceleration time (ms)	194 ± 44	266 ± 68	< 0.001
Pulmonary S/D ratio	1.31 ± 0.28	1.22 ± 0.22	0.20
Global longitudinal strain (%)	-16.1 ± 1.4	-20.2 ± 1.0	< 0.001
Septal E' (cm/s)	7.3 ± 1.1	8.7 ± 1.8	0.005
Septal E/e' ratio	10.0 ± 3.3	8.4 ± 2.0	0.03

*p value by Mann-Whitney U test. EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; LV = left ventricular.

Global contrast-enhanced myocardial T1 time and LV function

Table 3 outlines the univariate Pearson correlations between global contrast-enhanced myocardial T1 time and different parameters of LV function for the entire study population. There was no significant correlation between global contrast-enhanced myocardial T1 time and LVEF (r = 0.04, p = 0.76; ***Figure 3***).

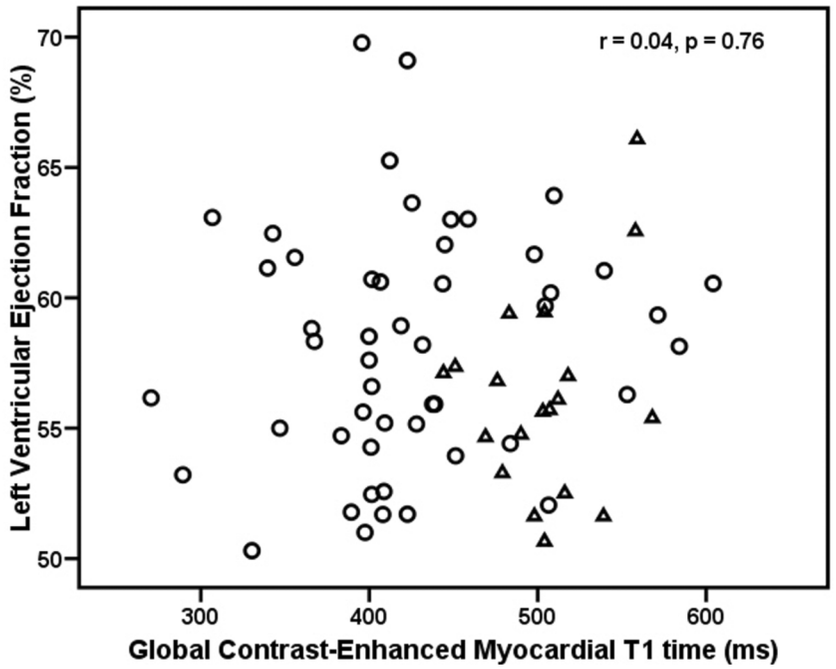
Table 3. Univariate Pearson correlation coefficients between global contrast-enhanced myocardial T1 time and left ventricular volume and functional parameters in diabetic patients and normal controls

Variable	Correlation coefficient	p value
Heart rate	0.02	0.87
LV mass index	0.07	0.55
LVEDVI	0.15	0.22
LVESVI	0.09	0.47
LVEF	0.04	0.76
Cardiac output	0.32	0.01
Transmitral E/A ratio	-0.10	0.44
Deceleration time	0.36	0.003
Pulmonary S/D ratio	-0.03	0.83
Global longitudinal strain	-0.71	< 0.001
Septal E'	0.47	< 0.001
Septal E/e' ratio	-0.33	0.007

EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; LV = left ventricular

Figure 3. **Scatterplot showing no correlation between global contrast-enhanced myocardial T1 time and LVEF in diabetic patients (circles) and control subjects (triangles).**

Thus, LVEF may not accurately reflect the burden of diffuse interstitial fibrosis as represented by the global contrast-enhanced myocardial T1 time.



Similarly, there was no significant correlation between global contrast-enhanced myocardial T1 time and transmitral E/A ratio (r = -0.10, p = 0.44). However, there was a good correlation with global longitudinal strain (r = -0.71, p < 0.001; ***Figure 4***) and septal E' (r = 0.47, p < 0.001; ***Figure 5***), suggesting that a shorter global contrast-enhanced myocardial T1 time was associated with more impaired myocardial systolic and diastolic function respectively.

Figure 4. **Scatterplot showing correlation between global contrast-enhanced myocardial T1 time and global longitudinal strain for diabetic patients (circles) and control subjects (triangles).**

Thus, a higher burden of interstitial myocardial fibrosis (represented by shorter global contrast-enhanced myocardial T1 time) was associated with more impaired myocardial systolic function (represented by global longitudinal strain).

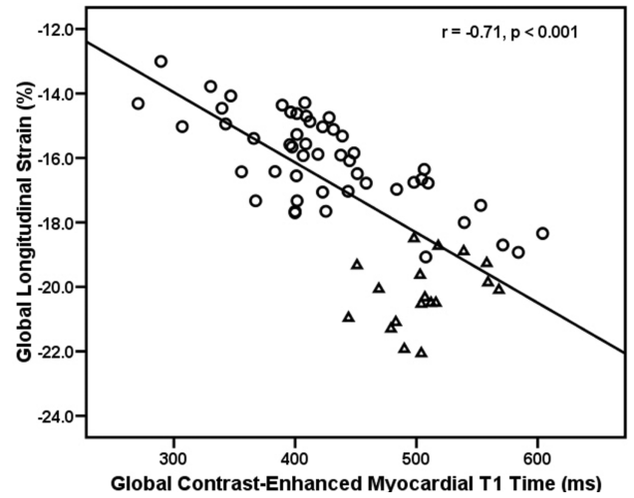
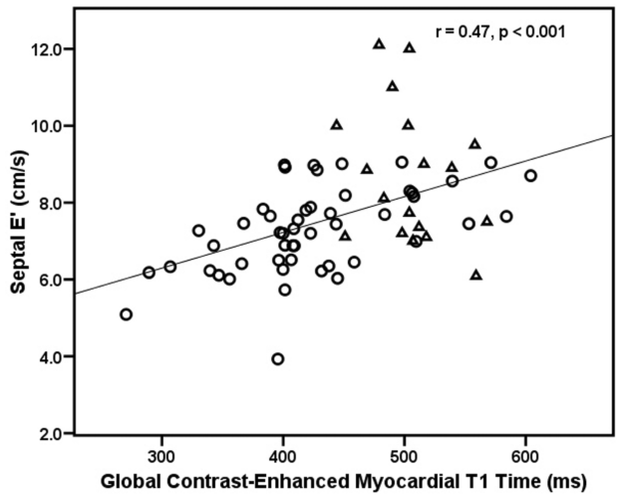


Figure 5. **Scatterplot showing correlation between global contrast-enhanced myocardial T1 time and septal E' for diabetic patients (circles) and control subjects (triangles).**

Thus, a higher burden of interstitial myocardial fibrosis (represented by shorter global contrast-enhanced myocardial T1 time) was associated with more impaired myocardial diastolic function (represented by septal E').



Determinants of myocardial systolic function in diabetic patients

The mean global longitudinal strain for the diabetic patients was -16.1 ± 1.4%. Type 1 diabetic patients had significantly more preserved global longitudinal strain than type 2 diabetic patients (-16.4 ± 1.4 vs. -15.3 ± 1.2%, p = 0.009). Women had significantly more preserved global longitudinal strain than men (-16.6 ± 1.5 vs. -15.6 ± 1.2%, p = 0.017). ***Table 4*** outlines the univariate Pearson correlations for global longitudinal strain.

Table 4. Univariate Pearson correlation coefficients for global longitudinal strain and septal E' in diabetic patients

	Global longitudinal strain		Septal E'	
Variable	Correlation coefficient	p value	Correlation coefficient	p value
Age	0.14	0.32	-0.55	< 0.001
Body mass index	0.06	0.69	0.04	0.80
Systolic blood pressure	0.24	0.10	-0.17	0.23
Diastolic blood pressure	0.08	0.60	0.01	0.95
Heart rate	-0.15	0.30	0.03	0.82
LV mass index	0.20	0.17	0.18	0.20
LVEDVI	-0.21	0.15	0.45	0.001
LVESVI	0.03	0.86	0.37	0.009
Transmitral E/A ratio	-0.03	0.84	0.25	0.08
Deceleration time	-0.21	0.15	-0.08	0.58
Pulmonary S/D ratio	-0.02	0.89	-0.32	0.03
Global contrast-enhanced myocardial T1 time	-0.73	< 0.001	0.54	< 0.001

EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; LV = left ventricular

To identify independent determinants of global longitudinal strain for the diabetic patients, univariable predictors with p < 0.20 (including gender, type of diabetes, systolic blood pressure, deceleration time, LV mass index, LVEDVI and global contrast-enhanced myocardial T1 time) were all entered into a multiple linear regression model as covariates (***Table 5***). On multivariable analysis, the contrast-enhanced myocardial T1 time was an independent determinant of global longitudinal strain (model R = 0.82, p < 0.001). Furthermore, global contrast-enhanced myocardial T1 time was the strongest determinant of myocardial systolic function (standardized ß= -0.626, p < 0.001). There were no significant interactions between global contrast-enhanced myocardial T1 time and the other significant covariates in the model. ***Figure 6*** shows examples of 2 diabetic patients with high and low global contrast-enhanced myocardial T1 time with a corresponding normal and impaired global longitudinal strain respectively.

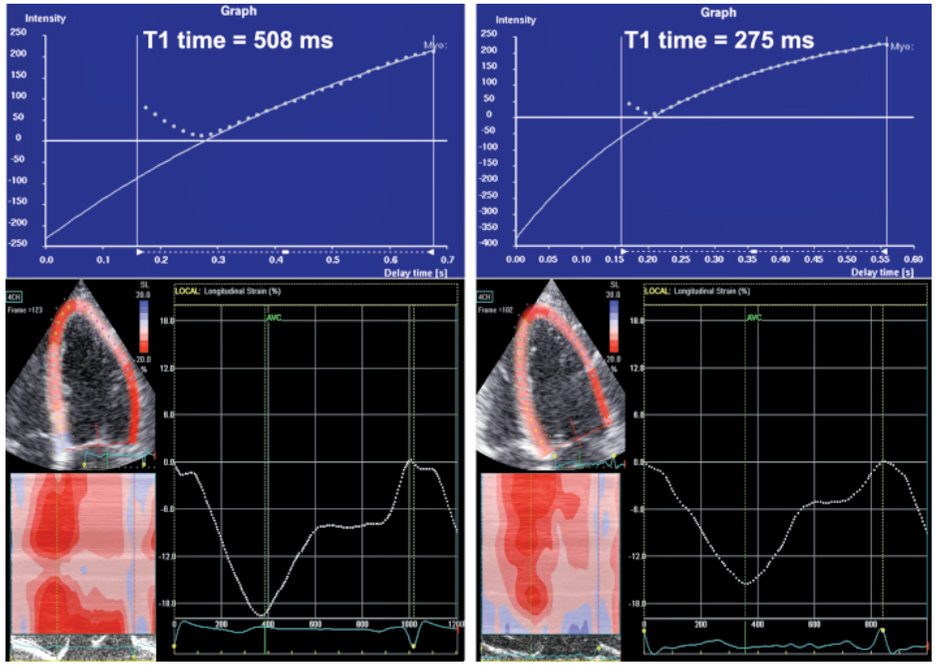
Table 5. Independent determinants of left ventricular global longitudinal strain in diabetic patients

Variable	Global longitudinal strain		
	Unstandardized β	Standardized β	p value
Gender	0.494	0.177	0.16
Type of diabetes	0.834	0.266	0.02
Systolic blood pressure	0.020	0.142	0.14
LV mass index	0.026	0.142	0.31
LVEDVI	0.001	t0.015	0.91
Deceleration time	-0.001	-0.028	0.77
Global myocardial T1 time	-0.012	-0.626	< 0.001

EDVI = end-diastolic volume index; LV = left ventricular

Figure 6. **Example of a diabetic patient with high global contrast-enhanced myocardial T1 time (508 ms) suggesting less interstitial fibrosis, and a corresponding global longitudinal strain of -19.0% (*left panel*).**

In contrast, another diabetic patient with a low global contrast-enhanced myocardial T1 time (275 ms) suggesting more interstitial fibrosis, and a reduced global longitudinal strain of -14.3% (*right panel*). Their respective LVEF on MRI were 59% and 57%.



Determinants of myocardial diastolic function in diabetic patients

The mean septal E' for the diabetic patients was 7.3 ± 1.1 cm/s. Similarly, type 1 diabetic patients had more preserved septal E' compared to type 2 diabetic patients (7.6 ± 1.0 vs. 6.5 ± 0.9 cm/s, p < 0.001). There was no difference in the septal E' between men and women (7.3 ± 0.9 vs. 7.2 ± 1.4 cm/s, p = 0.64). ***Table 5*** outlines the univariate Pearson correlations for septal E'.

To identify independent determinants of septal E' for the diabetic patients, univariable predictors with p < 0.20 (including age, type of diabetes, LVEDVI, transmitral E/A ratio, pulmonary S/D ratio and global contrast-enhanced myocardial T1 time) were all entered into a multiple linear regression model as covariates (***Table 6***). On multivariable analysis, the contrast-enhanced myocardial T1 time was an independent determinant of septal E' (model R = 0.78, p < 0.001). Similarly, global contrast-enhanced myocardial T1 time was the strongest determinant of myocardial function (standardized ß = 0.432, p < 0.001). There were no

significant interactions between global contrast-enhanced myocardial T1 time and the other significant covariates in the model.

Table 6. Independent determinants of left ventricular septal E' in diabetic patients

Variable	Septal E'		
	Unstandardized β	Standardized β	p value
Age	-0.036	-0.288	0.02
Type of diabetes	-0.587	-0.231	0.06
LVEDVI	0.005	0.069	0.60
Transmitral E/A ratio	0.225	0.067	0.57
Pulmonary S/D ratio	-0.569	-0.140	0.27
Global myocardial T1 time	0.007	0.432	< 0.001

EDVI = end-diastolic volume index; LV = left ventricular

DISCUSSION

Using MRI, the present study demonstrated that diabetic patients had a significantly shorter global contrast-enhanced myocardial T1 time compared to normal controls. Despite normal LVEF and no evidence of previous myocardial infarction, diabetic patients had a wide range of global contrast-enhanced myocardial T1 time. Furthermore, global contrast-enhanced myocardial T1 time was independently associated with and was the strongest determinant of both myocardial systolic and diastolic function.

Quantification of interstitial myocardial fibrosis by T1 mapping

A recent study by Iles and co-workers has histologically validated and demonstrated the ability of MRI T1 mapping to quantify diffuse interstitial myocardial fibrosis in chronic heart failure patients.[8] The authors showed that the global contrast-enhanced myocardial T1 time by MRI T1 mapping was inversely correlated to the myocardial collagen content on endomyocardial biopsies.[8] When compared to normal control subjects, chronic heart failure patients had significantly shorter global contrast-enhanced myocardial T1 time due to an increased burden of interstitial fibrosis. Importantly, there was also a significant relationship between interstitial fibrosis and LV diastolic function, whereby patients with progressively worse LV diastolic function had increasingly shorter global contrast-enhanced myocardial T1 time.[8]

Interstitial myocardial fibrosis in diabetic patients

Although the pathogenesis of diabetic heart disease is likely to be multifactorial, the final common pathway is the activation of the renin-angiotensin-aldosterone system resulting in myocyte necrosis and deposition of collagen in the interstitial, perivascular and sub-endocardial regions.[2] The deposited collagen interacts with glucose to eventually form advanced glycation end-products, which is thought to contribute to myocardial stiffness, endothelial dysfunction and atherosclerosis.[2] In diabetic patients, the milieu of hyperglycemia, increased free fatty acid availability with altered metabolism, activation of renin-angiotensin-aldosterone system, and increased oxidative stress with endothelial dysfunction, all contribute to the subsequent development of replacement fibrosis, myocardial dysfunction and diabetic heart disease.[1, 2, 21, 22] In the present study, global contrast-enhanced myocardial T1 time using MRI T1 mapping was utilized as a surrogate marker of the burden of interstitial myocardial fibrosis. Consistent with previous studies, diabetic patients demonstrated evidence of interstitial myocardial fibrosis.[5, 6] Furthermore, there was a significant association between global contrast-enhanced myocardial T1 time and longitudinal myocardial systolic and diastolic function.

Global contrast-enhanced myocardial T1 time and myocardial dysfunction

Although quantification of LV systolic function by LVEF is easy to perform, it is relatively insensitive in detecting subtle myocardial dysfunction.[10, 23] This was reflected in the present study where there was a lack of relationship between LVEF and global contrast-enhanced myocardial T1 time. In contrast, advanced echocardiographic techniques such as global longitudinal strain analysis by 2D speckle tracking are more sensitive markers of myocardial systolic function.[10] Recently, Ng and co-workers demonstrated impaired global longitudinal systolic and diastolic function indicative of early subtle myocardial dysfunction in asymptomatic diabetic patients with normal LVEF.[10] By quantifying both global contrast-enhanced myocardial T1 time, global longitudinal strain and septal E', the present study demonstrated the independent association between global contrast-enhanced myocardial T1 time and associated myocardial systolic and diastolic dysfunction in diabetic patients, thereby contributing to the understanding of the pathogenesis of diabetic heart disease.

Clinical implications

Contrast-enhanced myocardial T1 mapping may non-invasively quantify diffuse interstitial myocardial fibrosis in diabetic patients. The present study demonstrated a linear and independent relationship between global contrast-enhanced myocardial T1 time and myocardial systolic and diastolic dysfunction. Early diagnosis of diabetic heart disease by contrast-enhanced myocardial T1 mapping and 2D speckle tracking analyses may permit identification of patients at risk of subsequent development of clinical heart failure. Furthermore, a number of therapies have been postulated to inhibit the progression of heart failure, principally through the inhibition of the renin-angiotensin-aldosterone system and subsequent reduction of myocardial fibrosis.[10, 24-26] Similarly, recent studies have demonstrated the role of diffuse interstitial myocardial fibrosis in hypertensive heart disease.[27, 28] Thus, contrast-enhanced myocardial T1 mapping may permit non-invasive monitoring of the effectiveness of these anti-fibrotic therapies targeted at patients with diabetic or hypertensive heart disease.

Study limitations

The present study initially recruited approximately equal proportions of type 1 and 2 diabetic patients. However, 15 patients were excluded due to the unexpected presence of DCE indicative of previous myocardial infarction, resulting in disproportionally less type 2 diabetic patients. This could have influenced the multivariable analysis demonstrating a small but significantly different relationship between type of diabetes, global contrast-enhanced myocardial T1 time and global longitudinal strain. Therefore, the presence of underlying significant but undiagnosed coronary artery disease could have affected the results. Future larger studies will be needed to compare interstitial myocardial fibrosis in type 1 versus type 2 diabetes. Furthermore, although previous studies have validated global contrast-enhanced myocardial T1 time with interstitial fibrosis on histopathology[8, 29], the presence of myocardial inflammation may also have potentially confounded the present results.

There are currently several different MRI inversion pulse sequences that are available for generating contrast-enhanced myocardial T1 maps.[8, 30, 31] Furthermore, T1 recovery time naturally increases with higher MRI field strength, and is influenced by the dosage and type of contrast agent used, the timing of T1 map acquisition from time of injection, and cardiac output (which influences gadolinium wash-out

rate from the myocardium). Thus, the derived global myocardial T1 time from one study is not directly comparable across different studies that use different protocols.

CONCLUSIONS

A shorter global contrast-enhanced myocardial T1 time (suggestive of a higher burden of interstitial myocardial fibrosis) in diabetic patients is independently associated with more impaired longitudinal myocardial systolic and diastolic function. Future larger studies are needed to confirm the present findings.

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