Association Between Diffuse Myocardial Fibrosis by Cardiac Magnetic Resonance Contrast-Enhanced T1 Mapping and Subclinical Myocardial Dysfunction in Diabetic Patients
A Pilot Study

Arnold C.T. Ng, MBBS, PhD*; Dominique Auger, MD*; Victoria Delgado, MD, PhD; Saskia G.C. van Elderen, MD; Matteo Bertini, MD, PhD; Hans-Marc Siebelink, MD, PhD; Rob J. van der Geest, PhD; Cosimo Bonetti, PhD; Enno T. van der Velde, PhD; Albert de Roos, MD, PhD; Johannes W.A. Smit, MD, PhD; Dominic Y. Leung, MBBS, PhD; Jeroen J. Bax, MD, PhD; Hildo J. Lamb, MD, MSc, PhD

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

Methods and Results—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 healthy controls who were frequency matched in age, sex and body mass index. There were no significant differences in mean LV end-diastolic volume index, end-systolic volume index and LVEF between diabetic patients and healthy controls. Diabetic patients had significantly shorter global contrast-enhanced myocardial T1 time (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). Global contrast-enhanced myocardial T1 time was the strongest independent determinant of global longitudinal strain on multivariate analysis (standardized β=−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). Global contrast-enhanced myocardial T1 time was also the strongest independent determinant of septal E’ (standardized β=0.432, P<0.001).

Conclusions—A shorter global contrast-enhanced myocardial T1 time was associated with more impaired longitudinal myocardial systolic and diastolic function in diabetic patients. (Circ Cardiovasc Imaging. 2012;5:51-59.)

Key Words: diabetes mellitus ■ echocardiography ■ MRI ■ left ventricular fibrosis

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 More important, 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 accumulate and have increased washout times within these myocardial fibrous tissues because of the absence of viable myocytes and an increased volume of distribution.7 By using MRI T1 mapping sequences, the 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, a
shorter global contrast-enhanced myocardial $T_1$ time repre-
sents more interstitial fibrosis.\textsuperscript{8}

**Clinical Perspective on p 59**

Diabetic patients can develop subtle left ventricular (LV) myocardial dysfunction despite a normal LV ejection fraction (EF).\textsuperscript{9,10} Advanced echocardiographic techniques, such as tissue Doppler imaging and 2D speckle tracking, are highly sensitive for early detection of subclinical diabetic myocardial dysfunction.\textsuperscript{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 as follows: (1) to quantify and compare global contrast-enhanced myocardial $T_1$ time between diabetic patients with a normal LVEF and healthy controls and (2) to correlate global contrast-enhanced myocardial $T_1$ time with LV myocardial functional assessment using 2D speckle tracking analysis and tissue Doppler imaging.\textsuperscript{12}

**Methods**

**Patient Population and Study Protocol**

Sixty-five diabetic patients (35 with type 1 and 30 with type 2) were prospectively recruited into the present study. The inclusion criteria included diabetes mellitus diagnosed according to World Health Organization criteria.\textsuperscript{13} The exclusion criteria included aged <18 years, rhythm other than sinus rhythm, significant coronary artery disease, previous myocardial infarction, presence of segmental wall motion abnormalities or delayed contrast enhancement (DCE) on MRI indicative of macroscopic fibrosis/scar from previous myocardial infarction. LV EF <50%, and moderate or severe valvular stenosis or regurgitation. However, 15 patients with type 2 diabetes were excluded from the study because of the presence of DCE on MRI that was indicative of previous silent myocardial infarction. Thus, a total of 50 diabetic patients (35 with type 1 and 15 with 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 healthy control subjects were also included. The healthy controls were frequency matched against the diabetic patients for age, sex, and body mass index. All control subjects were clinically referred for evaluation of atypical chest pain, palpitations, history of diabetes mellitus, hypertension, previous myocardial infarction, presence of segmental wall motion abnormalities or DCE on MRI indicative of macroscopic myocardial scar/fibrosis.

**Cardiac MRI**

All patients underwent MRI examinations for the assessment of LV volumes, LVEF, global contrast-enhanced myocardial $T_1$ 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, 400×400 mm; and reconstructed matrix size, 256×256 pixels.

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

**Evaluation of LV Mass, Volumes, and Function**

All MRIs were digitally stored on hard disks and analyzed off-line using dedicated quantitative software (MASS V2010-EXP; Leiden University Medical Center, Leiden, the Netherlands). LV endocar-dial 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 (EDV1), and LV end-systolic volume index were measured and corrected for body surface area.\textsuperscript{14} 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 $T_1$ Mapping**

$T_1$ recovery is a basic fundamental parameter of MRI 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: $M_z(t) = M_{ZF} = \frac{M_0}{1 - e^{-rt}}$. 

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where $M_x(t)$ is the sample magnetization observed at time $t$, $\tau$—inversion time for an inversion recovery experiment and $M_{eq}(t)$ denotes the equilibrium magnetization in the $z$ axis. To quantify the contrast-enhanced myocardial $T_1$ time, LV endocardial and epicardial borders were outlined from a single midventricular short-axis Look-Locker sequence of varying inversion times using MASS research software (MASS V2010-EXP, Leiden University Medical Center; Leiden) (Figure 1). The different inversion recovery times that fell into different cardiac phases during the Look-Locker sequence resulted in movement of the left ventricle. Thus, the endocardial and epicardial contours were manually drawn in each image (a 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 $T_1$ time by fitting data acquired at the various inversion times. 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 right ventricular free wall with the LV). Following this definition, signal intensity curves of matching pixels were reconstructed and used for $T_1$ fitting. Before fitting, the signal intensity of the initial phases was inverted. The best fit for $T_1$ value (corresponding to the smallest-fitting error) was determined iteratively by inverting initial signal intensity curves of matching pixels were reconstructed 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 $\chi^2$ test for goodness of fit was significant, with a level of significance of $\alpha=0.05$, were included in the final average $T_1$ value.

A global contrast-enhanced myocardial $T_1$ time was subsequently automatically calculated as the average of all the individual contrast-enhanced myocardial $T_1$ times from each pixel. Because the function of gadolinium-based contrast agents normally shortens the $T_1$ time, and its washout time increases within myocardial fibrous tissues because of an increased volume of distribution, a shorter global contrast-enhanced myocardial $T_1$ time consequently is suggestive of more interstitial fibrosis. The derived global contrast-enhanced myocardial $T_1$ time is generally expected to be shorter than the true $T_1$ time of the myocardium because of 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 a commercially available ultrasonographic transducer and equipment (M4S probe, Vivid 7, GE-Vingmed; Horten, Norway). All images were digitally stored on hard disks for off-line analysis (EchoPAC version 108.1.5, GE-Vingmed). A complete 2D, color, pulsed and continuous-wave Doppler echocardiogram was obtained according to standard techniques. Transmural 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. Transmural early (E-wave) and late (A-wave) diastolic velocities and 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. Briefly, 2D speckle tracking is a commercial software (EchoPAC version 108.1.5, GE-Vingmed) that performs semiautomated 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. A previous study 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 and circumferential and radial strain/strain rate.

To obtain global longitudinal strain/strain rate, 2D speckle tracking analyses were performed on gray-scale images of the LV obtained in the 3 apical (2-, 3-, and 4-chamber) views (Figure 2). During analysis, the endocardial border was manually traced at end systole, and the region-of-interest width was 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, the myocardial systolic function was calculated as the average of the 3 peak global longitudinal strain. All strain measurements were exported to a spreadsheet (Microsoft Excel 2002, Microsoft Corporation; Redmond, WA).

**Variability Analysis**

To determine intraobserver and interobserver variabilities for global contrast-enhanced myocardial $T_1$ time, measurements were repeated in 10 randomly selected patients. The intraobserver and interobserver variabilities for global contrast-enhanced myocardial $T_1$ time, ex-
pressed as mean absolute differences ± 1 SD, were 12.6 ± 12.7 and 12.4 ± 10.0 ms, respectively.

Previous work from our laboratory has reported the intraobserver and interobserver variabilities for mean global longitudinal strain as mean absolute differences ± 1 SD 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 the Mann-Whitney U-test and the \( \chi^2 \) test for continuous and categorical variables, respectively. Pearson correlation was used 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. The validity of the multiple linear regression models was established by confirming the residuals to be normally distributed. A 2-tailed \( P < 0.05 \) was considered significant. All statistical analyses were performed using SPSS for Windows, version 17 (SPSS Inc; Chicago, IL).

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

MRI and Echocardiography
Table 2 summarizes the baseline MRI and echocardiographic characteristics of the diabetic patients and healthy controls. There were no significant differences in LVEDVI (79.1 ± 14.4 versus 79.8 ± 17.1 mL/m²; \( P = 0.60 \)), LV end-systolic volume index (33.3 ± 7.6 versus 34.7 ± 7.5 mL/m²; \( P = 0.23 \)), LV mass index (49.0 ± 7.6 versus 50.9 ± 8.7 g/m²; \( P = 0.24 \)), and LVEF (58.1 ± 4.6% versus 56.2 ± 3.8%; \( P = 0.10 \)) between the diabetic patients and control subjects. No pa-
patients had evidence of regional DCE suggestive of focal macroscopic scar/fibrosis by virtue of the study exclusion criteria. However, diabetic patients had a significantly shorter global contrast-enhanced myocardial T1 time (425 ± 72 versus 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 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 versus 429 ± 52 ms; P = 0.74).

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 LV mass index (r = 0.24, P = 0.55). Furthermore, there was no significant correlation between global contrast-enhanced myocardial T1 time and different LV functional parameters. However, there was a positive correlation between global contrast-enhanced myocardial T1 time and left ventricular ejection fraction (r = 0.47, P < 0.001). This suggests that a shorter global contrast-enhanced myocardial T1 time was associated with more impaired myocardial systolic and diastolic function, respectively.

Determinants of Myocardial Systolic Function in Diabetic Patients

The mean global longitudinal strain for the diabetic patients was −16.1 ± 1.4%. Patients with type 2 diabetes (−16.4 ± 1.4% versus −15.3 ± 1.2%; P = 0.009). Women had significantly more preserved global longitudinal strain than men (−16.6 ± 1.5% versus −15.6 ± 1.2%; P = 0.017). Table 4 outlines the univariate Pearson correlations for global longitudinal strain.

To identify independent determinants of global longitudinal strain for the diabetic patients, univariable predictors with P < 0.20 (including sex, 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, with type 2 diabetes (−16.4 ± 1.4% versus −15.3 ± 1.2%; P = 0.009). Women had significantly more preserved global longitudinal strain than men (−16.6 ± 1.5% versus −15.6 ± 1.2%; P = 0.017). Table 4 outlines the univariate Pearson correlations for global longitudinal strain.

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**Table 2. The MRI and Echocardiographic Characteristics of Diabetic Patients**

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

LV indicates left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; E/A, xxx; S/D, xxx.

*Obtained by Mann-Whitney U test.

**Table 3. Univariate Pearson Correlation Coefficients Between Global Contrast-Enhanced Myocardial T1 Time and LV Volume and Functional Parameters in Diabetic Patients and Healthy Controls**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0.02</td>
<td>0.87</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.07</td>
<td>0.55</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>0.15</td>
<td>0.22</td>
</tr>
<tr>
<td>LVESVI</td>
<td>0.09</td>
<td>0.47</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.04</td>
<td>0.76</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>0.32</td>
<td>0.01</td>
</tr>
<tr>
<td>Transmirtal E/A ratio</td>
<td>−0.10</td>
<td>0.44</td>
</tr>
<tr>
<td>Deceleration time</td>
<td>0.36</td>
<td>0.003</td>
</tr>
<tr>
<td>Pulmonary S/D ratio</td>
<td>−0.03</td>
<td>0.83</td>
</tr>
<tr>
<td>Global longitudinal strain</td>
<td>−0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal E’</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal E/e’ ratio</td>
<td>−0.33</td>
<td>0.007</td>
</tr>
</tbody>
</table>

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global contrast-enhanced myocardial \( T_1 \) time was the strongest determinant of myocardial systolic function (standardized coefficient \( \beta = -0.626, \ p < 0.001 \)). There were no significant interactions between global contrast-enhanced myocardial \( T_1 \) 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 \( T_1 \) time with a corresponding normal and impaired global longitudinal strain, respectively.

**Determinants of Myocardial Diastolic Function in Diabetic Patients**

The mean septal \( E' \) for the diabetic patients was 7.3 ± 1.1 cm/s. Similarly, patients with type 1 diabetes had more preserved septal \( E' \) compared with patients with type 2 diabetes (7.6 ± 1.0 versus 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 versus 7.2 ± 1.4 cm/s; \( p = 0.64 \)). Table 5 outlines the univariate Pearson correlations for septal \( E' \).

To identify the 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 \( T_1 \) time) were all entered into a multiple linear regression model as covariates (Table 5). On multivariable analysis, the contrast-enhanced myocardial \( T_1 \) time was an independent determinant of septal \( E' \) (model \( R = 0.78, p < 0.001 \)). Similarly, global contrast-enhanced myocardial \( T_1 \) time was the strongest determinant of myocardial function (standardized coefficient \( \beta = 0.432, p < 0.001 \)). There were no significant interactions between global contrast-enhanced myocardial \( T_1 \) time and the other significant covariates in the model.

### Table 4. Univariate Pearson Correlation Coefficients for Global Longitudinal Strain and Septal \( E' \) in Diabetic Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Global Longitudinal Strain</th>
<th>Septal ( E' )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation Coefficient</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>Age</td>
<td>0.14</td>
<td>0.32</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.06</td>
<td>0.69</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>0.24</td>
<td>0.10</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.08</td>
<td>0.60</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.15</td>
<td>0.30</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.20</td>
<td>0.17</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>-0.21</td>
<td>0.15</td>
</tr>
<tr>
<td>LVESVI</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>Transmitral ( E/A ) ratio</td>
<td>-0.03</td>
<td>0.84</td>
</tr>
<tr>
<td>Deceleration time</td>
<td>-0.21</td>
<td>0.15</td>
</tr>
<tr>
<td>Pulmonary ( S/D ) ratio</td>
<td>-0.02</td>
<td>0.89</td>
</tr>
<tr>
<td>Global contrast-enhanced myocardial ( T_1 ) time</td>
<td>-0.73</td>
<td>( &lt;0.001 )</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; \( E/A, xxx; S/D, xxx. \)

### Table 5. Independent Determinants of LV Global Longitudinal Strain and Septal \( E' \) in Diabetic Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized ( \beta )</th>
<th>Standardized ( \beta )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global longitudinal strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of diabetes</td>
<td>0.834</td>
<td>0.266</td>
<td>0.02</td>
</tr>
<tr>
<td>Global myocardial ( T_1 ) time</td>
<td>-0.012</td>
<td>-0.626</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>Septal ( E' )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.036</td>
<td>-0.288</td>
<td>0.02</td>
</tr>
<tr>
<td>Type of diabetes</td>
<td>-0.587</td>
<td>-0.231</td>
<td>0.06</td>
</tr>
<tr>
<td>Global myocardial ( T_1 ) time</td>
<td>0.007</td>
<td>0.432</td>
<td>( &lt;0.001 )</td>
</tr>
</tbody>
</table>
Discussion

By using MRI, the present study demonstrated that diabetic patients had a significantly shorter global contrast-enhanced myocardial T1 time compared with healthy controls. Despite a 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 coworkers has histologically validated and demonstrated the ability of MRI T1 mapping to quantify diffuse interstitial myocardial fibrosis in patients with chronic heart failure. 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 biopsy specimens. When compared with healthy control subjects, patients with chronic heart failure had a significantly shorter global contrast-enhanced myocardial T1 time because of an increased burden of interstitial fibrosis. More important, there was also a significant relationship between interstitial fibrosis and LV diastolic function, whereby patients with a progressively worse LV diastolic function had an increasingly shorter global contrast-enhanced myocardial T1 time.

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 subendocardial regions. The deposited collagen interacts with glucose to eventually form advanced glycation end products, which are thought to contribute to myocardial stiffness, endothelial dysfunction, and atherosclerosis. 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. In the present study, global contrast-enhanced
myocardial T1 time using MRI T1 mapping was used 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, whereby 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, in asymptomatic diabetic patients with normal LVEF, impaired global longitudinal systolic and diastolic function is indicative of early subtle myocardial dysfunction.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 noninvasively 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, several therapies may 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 noninvasive monitoring of the effectiveness of these antifibrotic therapies targeted at patients with diabetic or hypertensive heart disease.

Study Limitations
The present study initially recruited approximately equal proportions of patients with type 1 and 2 diabetes. However, 15 patients were excluded because of the unexpected presence of DCE, indicative of previous myocardial infarction, resulting in disproportionately fewer patients with type 2 diabetes. 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 histopathologic examination,9–20 the presence of myocardial inflammation may also have potentially confounded the present results.

There are 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 the gadolinium washout 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. Furthermore, precontrast T1 maps were not acquired during the present study.

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.

Disclosures
V.D. received consulting fees from St Jude Medical; and the department of Cardiology, Leiden University Medical Center, The Netherlands, received grants from Biotronik, Medtronic, Boston Scientific Corporation, Lantheus Medical Imaging, St Jude Medical, GE Healthcare, and Edwards Lifesciences.

References
Diabetic patients have increased interstitial myocardial fibrosis, and magnetic resonance imaging (MRI) T1 mapping can quantify the burden of global and interstitial fibrosis. However, the relation between MRI T1 mapping and left ventricular (LV) myocardial function is unknown. The present study demonstrated that diabetic patients had significantly shorter MRI T1 time compared to controls, suggestive of a higher burden of interstitial fibrosis. Furthermore, there were good correlations between MRI T1 time and global longitudinal strain by 2-dimensional speckle tracking, and between MRI T1 time and septal E’ by tissue Doppler. Multivariable analyses demonstrated that MRI T1 time was independently associated with global longitudinal strain and septal E’. Thus, a shorter MRI T1 time was associated with more impaired myocardial systolic and diastolic function in diabetic patients. Future studies assessing the effectiveness of antifibrotic therapy in diabetic patients may include quantification of myocardial fibrosis by MRI T1 mapping and assessment of myocardial function by speckle tracking and tissue Doppler echocardiography.
Association Between Diffuse Myocardial Fibrosis by Cardiac Magnetic Resonance Contrast-Enhanced T₁ Mapping and Subclinical Myocardial Dysfunction in Diabetic Patients: A Pilot Study

Arnold C.T. Ng, Dominique Auger, Victoria Delgado, Saskia G.C. van Elderen, Matteo Bertini, Hans-Marc Siebelink, Rob J. van der Geest, Cosimo Bonetti, Enno T. van der Velde, Albert de Roos, Johannes W.A. Smit, Dominic Y. Leung, Jeroen J. Bax and Hildo J. Lamb

*Circ Cardiovasc Imaging*, 2012;5:51-59; originally published online December 1, 2011; doi: 10.1161/CIRCIMAGING.111.965608

*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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/content/5/2/e25.full.pdf

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In the article by Ng et al, “Association Between Diffuse Myocardial Fibrosis by Cardiac Magnetic
Resonance Contrast-Enhanced T1 Mapping and Subclinical Myocardial Dysfunction in Diabetic
Patients: A Pilot Study,” which appeared in the January 2012 issue of the journal (Circulation:
Cardiovascular Imaging 2012;5:51-59), the following corrections should be made to the legends
for Tables 2–4:

The Table 2 legend should read: LV indicates left ventricular; LVEDVI, left ventricular
diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left
ventricular ejection fraction.

The Table 3 legend should read: LV indicates left ventricular; LVEDVI, left ventricular
diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left
ventricular ejection fraction.

The Table 4 legend should read: LV indicates left ventricular; LVEDVI, left ventricular
diastolic volume index; LVESVI, left ventricular end-systolic volume index.

The online version of the article has been corrected.

DOI: 10.1161/HCI.0b013e31824f9007