Diffuse myocardial fibrosis is involved in the pathology of nonischemic cardiomyopathy (NIC). Recently, the application of native (noncontrast) myocardial T1 measurement has been proposed as a method for characterizing diffuse interstitial fibrosis. To determine the association of native T1 with myocardial structure and function, we prospectively studied 39 patients with NIC (defined as left ventricular ejection fraction (LVEF) ≤50% without cardiac magnetic resonance (CMR) evidence of previous infarction) and 27 subjects with normal LVEF without known overt cardiovascular disease. T1, T2, and extracellular volume fraction (ECV) were determined over 16 segments across the base, mid, and apical left ventricular (LV). NIC participants (57 ± 15 years) were predominantly men (74%), with a mean LVEF 34 ± 10%. Subjects with NIC had a greater native T1 (1,131 ± 51 vs 1,069 ± 29 ms; p < 0.0001), a greater ECV (0.28 ± 0.04 vs 0.25 ± 0.02, p = 0.002), and a longer myocardial T2 (52 ± 8 vs 47 ± 5 ms; p = 0.02). After multivariate adjustment, a lower global native T1 time in NIC was associated with a greater LVEF (β = −0.59, p = 0.0003), greater right ventricular ejection fraction (β = −0.47, p = 0.006), and smaller left atrial volume index (β = 0.51, p = 0.001). The regional distribution of native myocardial T1 was similar in patients with and without NIC. In NIC, native myocardial T1 is elevated in all myocardial segments, suggesting a global (not regional) abnormality of myocardial tissue composition. In conclusion, native T1 may represent a rapid, noncontrast alternative to ECV for delineating myocardial tissue remodeling in NIC. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;117:282–288)
previous symptoms, the history of cardiovascular disease, or on medications for hypertension or diabetes (as determined by self-reported questionnaire) and (2) 15 subjects recruited from clinically indicated CMR with normal LVEF by CMR and absence of ischemic LGE or the history of myocardial infarction. Of note, of the total 27 subjects without NIC, the 12 subjects enrolled as “normal volunteers” did not have assessment of cardiac structure or function by CMR. Our institutional review board approved the study, and all subjects provided written informed consent.

CMR was performed on a 1.5-T magnetic resonance imaging (MRI) system (Achieva; Philips Healthcare, Best, The Netherlands). All patients were in sinus rhythm at the time of CMR. Cine images were acquired for assessment of biventricular volumes, systolic function, and mass. Vertical and horizontal long-axis and a stack of LV short-axis cine images were acquired using a breath-hold steady-state free precession with retrospective electrocardiographic gating by standard society guidelines. Native T1 mapping was performed using a free-breathing slice-interleaved T1 (STONE) sequence (repetition time/echo time = 2.8/1.4 ms, flip angle = 70°, voxel size = 2.0 × 2.1 × 2.0 × 2.1 mm³, slice thickness = 8 mm, slice gap = 8 mm, number of phase-encoding lines = 70, linear ordering, 10 linear ramp-up pulses, SENSE factor = 2, and bandwidth = ~1,800 Hz/pixel). T2 mapping was performed using a free-breathing slice-interleaved T2 mapping sequence with the following parameters: repetition time/echo time = 2.2/1.1 ms, flip angle = 40°, voxel size = 2.5 × 2.5 × 2.5 mm³, slice thickness = 8 mm, acceleration factor = 2, acquisition window = 140 ms, multiple T2 prep echo times = 0, 25, 35, 45, 55, 65, 75, 85, 95, and infinite. A 4-second rest period after each image was used to allow for full spin relaxation. A 2-dimensional pencil-beam navigator positioned on the right hemidiaphragm was used for prospective slice tracking (with no gating) for free-breathing native T1 and T2 mapping. LGE imaging was performed using a 3-dimensional imaging protocol 15 to 20 minutes after injection of 0.1 mmol/kg of gadobenate dimeglumine (Multi-Hance; Bracco Diagnostic Inc., Princeton, New Jersey). The RV insertion point and both endocardial/epicardial borders of the myocardium were manually delineated on the 3 midventricular maps, and the 16 myocardial segments were automatically generated. Two reviewers (SR and RN) reviewed all images for image integrity and exclusion of artifacts. Both were blinded to clinical and cardiac structural information.

Categorical and continuous covariates were expressed as number (percentage) or mean ± SD, as specified. We compared native T1, T2, and ECV between our non-NIC (hereafter referred to as “normal”) population and subjects with NIC using appropriate t tests. To measure association between native T1 and important indexes of cardiac structure and function, we estimated general univariate and multivariable linear models for association between native T1 with LV and RV ejection fraction (RVEF) and volumes and left atrial volumes and function (a surrogate for LV diastolic function and chronicity of LV end-diastolic pressure elevation). Multivariable models were adjusted for age, gender, and beta-blocker use (a surrogate for optimal heart failure therapy). Finally, we examined the segmental variation in native T1 across all subjects, stratified by NIC status, using repeated measures analysis of variance. For linear regressions, dependent and independent variables were standardized. A 2-sided p value <0.05 was considered significant. MedCalc 12.5.0 (http://www.medcalc.org) and SAS 9.3 (SAS Institute, Cary, North Carolina) were used for data analysis.

Results

Demographic, clinical, and biochemical characteristics of 39 patients with NIC are summarized in Table 1. Subjects with NIC were predominantly middle-aged men (age 57 ±
15 years; 74% men) with well-controlled blood pressure on an optimal heart failure medical regimen. Twenty-one patients with NIC (54%) had a first diagnosis of LV dysfunction noted within 1 year of CMR. Patients had well-controlled symptoms at the time of CMR (predominantly New York Heart Association functional class I to II). Overall, the population without NIC (n = 27) was younger (38 ± 15 years; 59% men). Of the 15 control participants enrolled from clinically indicated CMR scans, referral indications included evaluation of suspected cardiomyopathy (LV noncompaction, LV end-diastolic volume index (ml/m^3)), LV mass index (gm/m^3), RV ejection fraction (%), RV end-diastolic volume (ml/m^3), Maximal left atrial volume indexed (ml/m^3; NIC, N=38; normal, N=15), Total left atrial emptying fraction (%; NIC, N=33; normal N=15), Global native myocardial T1 time (msec), Global myocardial T2 time (msec; NIC, N=35; normal, N=21), ECV (NIC, N=33; normal, N=20), Presence of LGE. ECV = extracellular volume fraction; LGE = late gadolinium enhancement; LV = left ventricular; RV = right ventricular.

* Only 15 control subjects (those clinically referred for CMR) had LV, RV, and left atrial function/volumes assessed in addition to parametric tissue mapping. One patient did not receive contrast because of prohibitive glomerular filtration rate.

<table>
<thead>
<tr>
<th>Cardiac structure/function*</th>
<th>NIC</th>
<th>Control*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction (%)</td>
<td>34 ± 10</td>
<td>59 ± 3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic volume index (ml/m^3)</td>
<td>125 ± 39</td>
<td>84 ± 11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass index (gm/m^3)</td>
<td>68 ± 20</td>
<td>49 ± 11</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV ejection fraction (%)</td>
<td>53 ± 12</td>
<td>59 ± 5</td>
<td>0.01</td>
</tr>
<tr>
<td>RV end-diastolic volume (ml/m^3)</td>
<td>76 ± 26</td>
<td>82 ± 12</td>
<td>0.31</td>
</tr>
<tr>
<td>Maximal left atrial volume indexed (ml/m^3; NIC, N=38; normal, N=15)</td>
<td>53 ± 23</td>
<td>44 ± 17</td>
<td>0.21</td>
</tr>
<tr>
<td>Total left atrial emptying fraction (%; NIC, N=33; normal N=15)</td>
<td>45 ± 14</td>
<td>55 ± 8</td>
<td>0.003</td>
</tr>
<tr>
<td>Global native myocardial T1 time (msec)</td>
<td>1131 ± 51</td>
<td>1069 ± 29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Global myocardial T2 time (msec; NIC, N=35; normal, N=21)</td>
<td>52 ± 8</td>
<td>47 ± 5</td>
<td>0.02</td>
</tr>
<tr>
<td>ECV (NIC, N=33; normal, N=20)</td>
<td>0.28 ± 0.04</td>
<td>0.25 ± 0.02</td>
<td>0.002</td>
</tr>
<tr>
<td>Presence of LGE</td>
<td>10 (26%)</td>
<td>0 (0%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 1. Parametric CMR tissue characterization in 2 patients with NIC using navigated, free-breathing acquisitions. (A) Images from a 47-year-old woman with moderate reduction in LV function (LVEF 30%). (B) Images from a 39-year-old man with normal LV function. Parametric maps to the right in each panel demonstrate full ventricular coverage (based on a 16-segment model).
RV dysplasia, myocarditis, or hemochromatosis, n = 10); origin of ventricular arrhythmia (n = 3); and aortic valve disease (n = 2; neither had significant disease). Within our control cohort (n = 27), 15 subjects recruited from clinical CMR scans were older (47 ± 13 vs 27 ± 9 years, p = 0.0001), with a trend for greater weight (81.1 ± 19.7 vs 70.5 ± 9.1 kg, p = 0.08) and higher hypertension prevalence (27% vs 0%, p = 0.052) relative to 12 control subjects without self-reported cardiovascular disease; there was no statistical difference in gender (50% vs 67% men, in clinical vs self-reported cohort) or diabetes (0 in both).

Parameters of biventricular structure, function, and parametric tissue mapping are provided in Table 2, stratified by NIC status. By definition, relative to the normal population, study participants with NIC had a decreased LVEF (p < 0.0001) and a more dilated LV (LV end-diastolic volume index; p < 0.0001), with greater LV mass index (p = 0.0001). Although the RVEF was slightly lower in NIC participants (p = 0.01), RV volumes were similar. Maximal left atrial volumes were similar between NIC and normal population although left atrial emptying fraction was lower in subjects with NIC (p = 0.003). Global native T1 (an average T1 across all available myocardial segments) was significantly higher in subjects with NIC (p < 0.0001). T2 time was slightly greater in NIC (p = 0.02) and global ECV was greater in subjects with NIC (p = 0.002).

An example of an STONE acquisition is shown in Figure 1. For native T1 mapping in NIC, 56 segments (9%; of 624 segments) were excluded because of imaging artifact. For T2 mapping acquisitions, 4 patients (10%) did not have interpretable T2 data because of image artifacts. In the remaining 35 patients, 13 segments (2% of 560 segments) were excluded because of imaging artifact. A total of 33
patients had ECV data; 6 patients did not have ECV because of technical error (n = 1) or lack of postcontrast acquisition (n = 5). For these 33 patients, 44 segments (8% of 528 segments) were excluded because of poor image quality.

Ten subjects with NIC (26%) had focal LGE in a non-subendocardial distribution. Global native T1 was similar in patients with NIC with (1,160 ± 71 ms) or without focal LGE (1,121 ± 38 ms; p = 0.13). We measured the association between clinically relevant parameters of atrial and ventricular remodeling with native T1 in regression models with NIC (Table 3). In subjects with NIC, after multivariate adjustment, a greater global native T1 was associated with lower LVEF (p = 0.0003), greater LV end-diastolic volume index (p = 0.0007), lower RVEF (p = 0.006), greater RV end-diastolic volume index (p = 0.002), and greater maximal left atrial volume index (p = 0.001). Global native T1 was also associated with T2 time (r = 0.39, p = 0.02) and with ECV (r = 0.54, p = 0.001). There was no difference in native T1, T2, or myocardial ECV between subjects with “new onset” (LV dysfunction diagnosis within 1 year of CMR) versus chronic NIC.

To examine the heterogeneity in native T1 time across segments of the myocardium using STONE, we measured native T1 across all myocardial segments in both NIC and normal cohorts (Figure 2). We used a repeated measures analysis of variance to test within-subject heterogeneity in T1 was also associated with T2 time (r = 0.39, p = 0.02) and with ECV (r = 0.54, p = 0.001). There was no difference in native T1, T2, or myocardial ECV between subjects with “new onset” (LV dysfunction diagnosis within 1 year of CMR) versus chronic NIC.

Discussion

In this prospective study of patients with NIC, we found that native T1 was increased and was associated with markers of cardiac structure, including larger LV and RV volumes and reduced systolic ventricular function, larger left atrial volumes, and abnormal tissue characteristics (including edema [higher T2 time] and interstitial expansion [higher ECV]). In addition, native T1 exhibited segmental LV variation with a similar pattern in both NIC and non-NIC study subjects. Collectively, these results suggest that native T1 is a physiologically relevant disease biomarker associated with greater cardiac remodeling, dysfunction, and markers of interstitial matrix expansion and tissue inflammation.

Elevation in native T1 has been demonstrated in numerous cardiomyopathies, including ischemic cardiomyopathy,6-7 aortic stenosis,8,18 and myocarditis.19 In 27 subjects with NIC, Puntmann et al first reported the use of modified Look-Locker inversion recovery to demonstrate a greater native midwall septal T1 in patients with NIC (1,239 ± 57 ms) relative to healthy controls (1,070 ± 55 ms). As in our study, native T1 was similar in patients with and without LGE.10 In a follow-up study using similar method in an NIC population, these investigators reported a greater native T1 (1,145 ± 37 ms) in NIC, demonstrating associations with arterial stiffness and LV structural parameters. Despite previous reports of variability in segmental T1 measurements in other diseases,3,9 the study on multislice LV mapping to define heterogeneity in T1 with more precise sequences in NIC is lacking. In addition, despite the well-recognized dependence of modified Look-Locker inversion recovery T1 on T2 effects, data regarding T2 mapping in NIC to address the relations between T1, T2, and ECV have been lacking.

In this context, our report provides several important insights in native T1 mapping in NIC. We observed modest associations of native T1 with ECV and T2 time, both markers of tissue structural changes. In addition, patterns of segmental variability in native T1 were similar in individuals with and without NIC, suggesting that while elevated native T1 is a hallmark of NIC, the segmental variation in T1 may be dependent on technical (sequence-dependent) factors not necessarily related to underlying disease biology. Given the importance of regional tissue characteristics (e.g., fibrosis) on response to therapy (e.g., resynchronization therapy20,21),...
investigations of native T1 (a more generalizable, non-contrast marker of myocardial disease) as an integrated index of myocardial physiology are warranted.

The limitations of our study should be viewed in light of its design. Although we recognize that native T1 is not synonymous with fibrosis (and could reflect increased myocardial water content from other processes), the relation between native T1 and ECV, in conjunction with previous work demonstrating a link between ECV and fibrosis, is suggestive. Our control population derived from self-reported healthy volunteers without cardiovascular disease and subjects clinically referred for CMR with normal LV function, which were slightly different in co-morbidity; however, we would expect these differences would bias differences in native T1 toward the null, not consistent with the significant differences we observed. We did not perform functional or morphologic imaging in all control participants, given that our focus was native T1; larger studies could validate the associations between native T1 and cardiac structure we observed in NIC in a healthier population. Furthermore, we recognize that the segmental heterogeneity in T1 may be a sequence-specific effect, as patterns of T1 heterogeneity were similar in subjects with and without NIC. We were careful to use a careful cardiac shim to avoid significant off-resonance effects that might interfere with T1 measurements. Partial volume effects in NIC may limit the generalizability of these techniques to thinned-wall LVs although we carefully examined and excluded those segments where manual contouring could not separate blood pool from the LV wall. In addition, although we used a protein bound gadolinium contrast agent to measure ECV (leading to potential underestimation), the primary hypothesis of this work to examine functional significance and distribution of native T1, for which the sequence used has a high precision and accuracy. Finally, standardization of T1 mapping sequences and field strength, both of which can affect T1, is important in the generalizability of these results. Future studies longitudinally measuring native T1 and changes in regional distribution of T1 with therapy will be important to dissect what specific components of tissue architecture myocardial T1 reflects in vivo.

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Disclosures

The authors have no conflicts of interest to disclose that are relevant to the content of this manuscript.


