Characterization of Compacted Myocardial Abnormalities by Cardiac Magnetic Resonance With Native T1 Mapping in Left Ventricular Non-Compaction Patients – A Comparison With Late Gadolinium Enhancement –

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**Background:** Native T1 mapping is an emerging cardiac magnetic resonance technique for quantitative evaluation of cardiomyopathies. This study aimed to investigate the usefulness of native T1 mapping in characterizing myocardial abnormalities in left ventricular non-compaction (LVNC) by comparing it with late gadolinium enhancement (LGE).

**Methods and Results:** The study group of 31 LVNC patients and 8 normal controls underwent cardiovascular magnetic resonance to acquire the native T1 maps and LGE images. Of the 31 LVNC patients, 14 had LGE. The mean native T1 value of the normal controls, LGE(−) and LGE(+) patients was 1,098.8±40.8 ms, 1,140.6±32.8 ms, and 1,181.4±53.7 ms, respectively. Significant differences were found in native T1 between any 2 groups (F=9.74, P<0.001). In discriminating the presence of LGE in LVNC patients, the odds ratio and corresponding 95% confidence interval (CI) of native T1 were, respectively, 2.966 (95% CI: 1.123–7.835, P=0.028) and 4.348 (95% CI: 1.155–16.363, P=0.030) before and after adjusting for confounding factors with an increment of 1 standard deviation.

**Conclusions:** The finding that LGE(−) patients had elevated native T1 compared with normal controls suggested native T1 mapping can be used earlier than LGE imaging to detect myocardial fibrosis in LVNC patients. Furthermore, higher native T1 values in LGE(+) patients than in the LGE(−) group suggested native T1 mapping is more sensitive than LGE imaging for identifying myocardial fibrosis in LVNC patients. (Circ J 2016; 80: 1210–1216)

**Key Words:** Cardiac magnetic resonance; Fibrosis; Left ventricular non-compaction; Late gadolinium enhancement; Native T1 mapping

Left ventricular non-compaction (LVNC) is a genetic cardiomyopathy characterized by prominent trabeculations and deep intertrabecular recesses in the left ventricle.1-3 The major clinical presentations of LVNC include progressive dysfunction, arrhythmia, and sudden death,1-3 which have been found to be associated with myocardial fibrosis.4-6 Recent studies have shown that fibrosis is an effective indicator of the severity and prognosis of LVNC.7-8 Therefore, early characterization of fibrosis in the myocardium of patients with LVNC prior to adverse outcomes is important for patient management.

As a widely accepted technique, late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) imaging has been used to detect myocardial fibrosis.4,9,10 However, LGE has difficulties in detecting early and small fibrotic lesions.11 In addition, LGE is limited in identification of diffuse fibrosis because there is no normal myocardium as a reference.11 Wan et al found that 60% of LVNC patients did not have LGE but showed a decline in left ventricular ejection fraction (LVEF), indicating the possibility of early or diffuse myocardial fibrosis that cannot be detected by traditional LGE techniques.4 This suggests that LGE may underestimate the extent of myocardial fibrosis in LVNC patients. Furthermore, the use of gadolinium contrast in the LGE technique also...
limits its use in patients with renal dysfunction.\textsuperscript{12} Recently, native T1 mapping has been demonstrated as a useful tool in quantitatively measuring myocardial tissue properties without administration of an exogenous contrast agent.\textsuperscript{13} It is reported that myocardial T1 values in patients with diffuse myocardial fibrosis correlate well with fibrosis confirmed by myocardial biopsy.\textsuperscript{14} Compared with LGE, native T1 mapping is superior in characterizing diffuse fibrosis and subtle focal lesions.\textsuperscript{11,13}

The aim of this study was to investigate the usefulness of native T1 mapping in the characterization of myocardial abnormalities in LVNC patients as compared with LGE.

Methods

Study Population

Patients with LVNC diagnosed by 2 senior cardiologists according to the Jenni echocardiographic criteria\textsuperscript{15} from December 2008 to June 2014 in Peking Union Medical College Hospital were included in this study. The CMR scanning was performed for all recruited LVNC patients. Patients with contraindications to CMR, history of other cardiomyopathies, including ischemic cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy etc, or pregnancy were excluded. In addition, 8 volunteers without cardiac disease or known risk factors for cardiac disease (diabetes mellitus, hypertension, and smoking) were enrolled as normal controls. The age and sex of the normal volunteers were matched with the LVNC patient group. Clinical information was collected from the medical record. The study protocol was approved by the local Institutional review board and written informed consent was given by all subjects.

CMR Protocol

The CMR imaging was performed with a 3.0-T MR system (Achieva TX, Philips Healthcare, Best, The Netherlands) using a 32-channel phased array heart coil (InVivo, Gainesville, FL, USA). The cine, phase-sensitive inversion recovery (PSIR), and modified look-locker inversion recovery (MOLLI) image sequences were acquired.\textsuperscript{16} The ECG-gated balanced steady-state free precession (bSSFP) cine images of the long- and short-axis (SAX) images covering the whole LV were acquired with the following parameters: TR/TE 2.7/1.3 ms with 30 heart phases; voxel size 1.8×1.5×8.0 mm\textsuperscript{3}; slice thickness 8 mm; and slice spacing 2 mm. The PSIR sequence was acquired 15±5 min after the injection of 0.2 mmol/kg of gadolinium-DTPA (Magnevist, Bayer Schering Pharma, Guangzhou, China) with flow rate of 3 ml/s and 20 ml saline for flushing. The LGE images were obtained during mid-diastole in the same SAX orientations as cine, covering the whole LV, with the following imaging

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**Figure 1.** Example of the measurement of the ratio of the thickness of non-compacted to compacted myocardium (NC/C). (A–C) Diastolic horizontal long-axis (4-chamber view), short-axis (2-chamber view), and the diastolic horizontal long-axis (4-chamber view) images from a LVNC patient. The maximum NC/C was 4.7 at end-diastole (D).
parameters: TR/TE 5.3/2.6 ms, voxel size 1.25×1.4×8.0 mm³. The MOLLI imaging sequence was acquired to measure the native T1 at 8 inversion times over an 11-heart-beat breath-hold with 2 inversions using a 5(3)3 scheme. Native T1 values were obtained from 3 SAX slices with 20 mm gap, covering 50 mm of the mid-ventricular cavity. Typical imaging parameters for MOLLI were as follows: bSSFP single shot read out; TR/TE 2.5/1.1 ms; field of view 300×150 mm²; voxel size 1.5×1.5×10.0 mm³; flip angle 35°.

CMR Analysis
All CMR data were analyzed using MATLAB (MathWorks, Natick, MA, USA). The end-diastolic volume (EDV), end-systolic volume (ESV), compacted myocardial mass and LVEF were measured on the SAX cine images. As previously described, the papillary muscles were not included in compacted myocardium because of the difficulty in differentiating papillary muscles from dense trabeculations. The ratio of the thickness of non-compacted to compacted myocardium (NC:C) in diastole was calculated (Figure 1). The maximum value of NC:C and the corresponding wall thickness among all myocardial segments were determined for each subject. The presence or absence of LGE was identified in each segment of compacted myocardium by consensus of 2 observers with 5 years’ experience in CMR. The myocardium was divided into 17 segments using the standard AHA model. The boundaries for endocardium and epicardium of compacted myocardium were manually outlined to measure the T1 values of myocardium. The averaged T1 values over 3 slices per patient were determined.

Statistical Analysis
The patients were divided into 2 groups: with (LGE(+)) and without (LGE(−)) LGE. All continuous variables are described as mean±SD. The quantitative measurements were compared among the LGE(−) and LGE(+) LVNC patient groups and normal controls using 1-way ANOVA analysis with post-hoc Student-Newman-Keuls correction. Logistic regression was conducted to calculate the odds ratio (OR) and corresponding 95% confidence interval (CI) of native T1 in discriminating the presence of LGE in LVNC patients. Chi-square test was used to compare the non-compaction segments distribution between LGE(−) and LGE(+) patients. P<0.05 was considered statistically significant. All statistical analysis was performed using SPSS Version 20.0 (SPSS, Chicago, IL, USA).

### Results
#### Clinical Characteristics
In total, 31 LVNC patients (mean age: 40.8±15.1 years; 19 males) were recruited in this study, of whom 14 (45%) had LGE(+) in compacted myocardium. Three pedigrees with 9 family members were found in this study population. The clinical characteristics of this study population are summarized in Table 1. There were no significant differences in age, sex, body surface area (BSA), and systemic thromboembolism, and cardiovascular risk factors (smoking, hypertension, and diabetes) among the LGE(−) LVNC patients, LGE(+) LVNC patient, and normal controls. Of the 31 LVNC patients, 9 (29%) had a family history of LVNC. All the LGE(+) LVNC patients and 50% of the LGE(−) LVNC patients showed abnormal ECG. Significant difference were found in New York Heart Association (NYHA) functional class and ECG changes between LGE(−) and LGE(+) LVNC patient groups (both with P<0.001).

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of the Study Population of Patients With LVNC</th>
<th>Normal control (n=8)</th>
<th>LGE(−) group (n=17)</th>
<th>LGE(+) group (n=14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49.8±17.8</td>
<td>37.2±16.3</td>
<td>45.1±12.9</td>
<td>0.139</td>
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<tr>
<td>Sex, male</td>
<td>6/8 (75)</td>
<td>10/17 (59)</td>
<td>7/14 (50)</td>
<td>0.539</td>
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<tr>
<td>BSA, m²</td>
<td>1.9±0.2</td>
<td>1.9±0.2</td>
<td>1.8±0.2</td>
<td>0.342</td>
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<tr>
<td>Family history</td>
<td>0</td>
<td>8/17 (47)</td>
<td>1/14 (7)</td>
<td>0.005</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1</td>
<td>1.7±0.7</td>
<td>2.5±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest pain/chest distress</td>
<td>0</td>
<td>10/17 (59)</td>
<td>14/14 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0</td>
<td>3 (19)</td>
<td>7/14 (47)</td>
<td>0.019</td>
</tr>
<tr>
<td>STE</td>
<td>0</td>
<td>1/17 (6)</td>
<td>1/14 (7)</td>
<td>0.768</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>0</td>
<td>9/17 (53)</td>
<td>14/14 (100)</td>
<td>&lt;0.001</td>
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<td>Smoker</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0.442</td>
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<tr>
<td>Hypertension</td>
<td>0</td>
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<td>1</td>
<td>0.329</td>
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<tr>
<td>Diabetes</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.449</td>
</tr>
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</table>

Values are mean±SD. *P<0.05 for LGE(−) group vs. LGE(+) group; †P<0.05 for LGE(−) group vs. normal control; ‡P<0.05 for LGE(+) group vs. normal control. BSA, body surface area; LGE, late gadolinium enhancement; LVNC, left ventricular non-compaction; NYHA, New York Heart Association; STE, systemic thromboembolism.
Native T1 Mapping Evaluates Myocardium Abnormality

Measurement of LGE and Native T1
The distribution of non-compaction and compaction segments with LGE was different. There were 227 non-compaction segments in the 31 LVNC patients. In the LGE(−) group, 107 NC segments were observed in 289 segments in 17 patients, and 110 NC segments were found in a total of 238 segments from 14 LGE(+) patients. Compared with the LGE(−) group, the LGE(+) group showed more NC segments (P=0.041) (Figure 2A,B). These results indicated that the more NC segments, the more likely the patient might have LGE(+). In addition, of all 31 LVNC patients, 14 (45%) had LGE in the myocardium in 96 (40%) compacted segments (Figure 2C). Of the 9 family members of the 3 pedigrees, 1 had myocardial LGE. The LGE lesions were found to most likely involve in the basal antero-septal segments, followed by apical anterior and basal inferoseptal segments.

Association Between LGE and Native T1
The mean native T1 value of normal controls, LGE(−) LVNC patients and LGE(+) patients was 1,098.8±40.8 ms, 1,140±32.8 ms, and 1,181.4±53.7 ms, respectively. The 1-way ANOVA with post-hoc Student-Newman-Keuls analysis showed significant differences in native T1 between any 2 groups (F=9.7, P<0.001, Figure 4). In discriminating the presence of LGE in LVNC patients, logistic regression showed the OR of native T1 was, respectively, 2.966 (95% CI: 1.123–7.835, P=0.028) and 4.348 (95% CI: 1.155–16.363, P=0.030) before and after adjusting for age, sex, BSA, and the NC:C with an increment of 1 standard deviation (SD) of the native T1 value.

Discussion
This study investigated the usefulness of native T1 for characterization of compacted myocardial abnormality in patients.
with LVNC as compared with LGE CMR. In this study, the LVNC patients with LGE showed the highest native T1 value, followed by LVNC patients without LGE, and then the normal controls. We found the native T1 value was significantly associated with LGE before and after adjusting for confounding factors, suggesting that native T1 might be an independent indicator of LGE. The finding of LVNC patients without LGE exhibiting elevated native T1 values in compacted myocardium suggested that the native T1 mapping might be a useful tool for early detection of myocardial fibrosis. LGE(+) patients having a higher native T1 value than LGE(−) patients may indicate that native T1 mapping is more sensitive than LGE imaging for identifying myocardial fibrosis in LVNC patients.

In this study, the LGE was most likely located in the basal anteroseptal segments of the myocardium in LVNC patients. Our findings are consistent with previous LVNC studies and a DCM study. The histopathology of an explanted LVNC heart showed diffused myocardial fibrosis including the septal wall. However, the segments of non-compaction are rarely located in the basal and septal wall, which suggests that the distribution of LGE lesions might not correspond to the segments of non-compacted myocardium in LVNC patients.

The native T1 values in myocardium are associated with those pathologies that affect the water content, such as edema.

**Figure 3.** (A–I) Examples of cardiac magnetic resonance images from a normal control (case 1), LVNC patient with LGE(−) (case 2) and LVNC patient with LGE(+) (case 3). The CINE (LAX) images are end-diastolic frames of cine long-axis images. The contours in yellow are the regions of non-compacted myocardium. The LGE lesions (K, yellow arrows) can be found in the interventricular septum of case 3. The corresponding native T1 maps indicate an increasing trend of native T1 values of compacted myocardium from normal control (D) to LVNC patient without LGE (H) and LVNC patient with LGE (L). LGE, late gadolinium enhancement; LVNC, left ventricular non-compaction.

**Figure 4.** Mean native T1 values in normal controls, LVNC patients with LGE(−) and LGE(+) are presented. The error bars indicate±1 SD. One-way ANOVA with post-hoc Student-Newman-Keuls analysis shows significant differences in native T1 between any 2 groups (F=9.7, P<0.001). LGE, late gadolinium enhancement; LVNC, left ventricular non-compaction.
Native T1 Mapping Evaluates Myocardium Abnormality

Conclusions

The finding of LGE(−) patients having elevated native T1 values with and without LGE were significantly higher than in the normal controls (1178±13 ms) (all $P<0.05$). These findings indicate that fibrosis may still exist in myocardium without LGE in many cardiomyopathies. It has been shown that, except for scar, LGE imaging techniques appear insensitive to diffuse or small patches of fibrosis determined by histology. Our finding of elevated T1 values in the myocardium of LVNC patients without LGE suggests that the native T1 value might be a more useful indicator of early-stage myocardial fibrosis in LVNC patients than LGE imaging.

In this study, LVNC patients with LGE showed higher native T1 values than patients without LGE, and there was a significant association between native T1 and LGE. The relationship between native T1 and LGE has been found in patients with HCM and HCM and acute myocardial infarction in previous studies. Dass et al reported that patients with HCM and LGE showed higher native T1 values than those without LGE (all $P<0.01$), and native T1 was related to LGE ($r=0.35$, $P<0.001$). Dall’Armellina et al showed that native T1 correlated with LGE in acute myocardial infarction ($r=0.71$, $P<0.001$). Our findings also showed a relationship between native T1 and LGE in LVNC patients, which could be a reliable and sensitive indicator of myocardial fibrosis.

Study Limitations

First, the sample size was small. Future studies with larger sample size are warranted. Second, other than myocardial fibrosis, some physiological parameters including heart rate and hemoglobin may also affect the native T1 value. To normalize these parameters might improve the accuracy of native T1 measurement. Third, there were no clinical follow-up data and the relationship between native T1 and prognostic information cannot be determined. Finally, the native T1 values reflect a composite signal of both interstitium and myocytes. Therefore, it cannot distinguish the intracellular from extracellular compartment. Post-contrast T1 mapping and extracellular volume imaging are suggested to be conducted in future studies.

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Disclosures

None of authors has a commercial interest, financial interest, and/or other relationship with manufacturers of pharmaceuticals, laboratory supplies, and/or medical devices or with commercial providers of medically related services.

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