T1 Mapping in Discrimination of Hypertrophic Phenotypes: Hypertensive Heart Disease and Hypertrophic Cardiomyopathy

Findings From the International T1 Multicenter Cardiovascular Magnetic Resonance Study

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Background—The differential diagnosis of left ventricular (LV) hypertrophy remains challenging in clinical practice, in particular, between hypertrophic cardiomyopathy (HCM) and increased LV wall thickness because of systemic hypertension. Diffuse myocardial disease is a characteristic feature in HCM, and an early manifestation of sarcomere-gene mutations in subexpressed family members (G+P− subjects). This study aimed to investigate whether detecting diffuse myocardial disease by T1 mapping can discriminate between HCM versus hypertensive heart disease as well as to detect genetically driven interstitial changes in the G+P− subjects.

Methods and Results—Patients with diagnoses of HCM or hypertension (HCM, n=95; hypertension, n=69) and G+P− subjects (n=23) underwent a clinical cardiovascular magnetic resonance protocol (3 tesla) for cardiac volumes, function, and scar imaging. T1 mapping was performed before and >20 minutes after administration of 0.2 mmol/kg of gadobutrol. Native T1 and extracellular volume fraction were significantly higher in HCM compared with patients with hypertension (P <0.0001), including in subgroup comparisons of HCM subjects without evidence of late gadolinium enhancement, as well as of hypertensive patients LV wall thickness of >15 mm (P <0.0001). Compared with controls, native T1 was significantly higher in G+P− subjects (P<0.0001) and 65% of G+P− subjects had a native T1 value >2 SD above the mean of the normal range. Native T1 was an independent discriminator between HCM and hypertension, over and above extracellular volume fraction, LV wall thickness and indexed LV mass. Native T1 was also useful in separating G+P− subjects from controls.

Conclusions—Native T1 may be applied to discriminate between HCM and hypertensive heart disease and detect early changes in G+P− subjects. (Circ Cardiovasc Imaging. 2015;8:e003285. DOI: 10.1161/CIRCIMAGING.115.003285.)

Key Words: cardiac magnetic resonance ■ hypertension ■ hypertrophic cardiomyopathy ■ left ventricular hypertrophy ■ T1 mapping

Differential diagnosis of left ventricular (LV) hypertrophy (LVH) remains challenging in clinical practice, in particular between hypertrophic cardiomyopathy (HCM) and increased LV wall thickness (LVWT) because of systemic hypertension. Reactive LVH that develops in response to an extrinsic increase in cardiac work, such as in hypertension, is distinguished from LVH because of familial HCM, in which the stimulus for increase in LVWT is intrinsic to the genetically altered cardiomyocyte.1 HCM is characterized by diffuse myocardial disease, defined by structurally dysmorphic myocytes, architectural loss of parallel arrangement, and disarray of fibers and fascicles, as well as genetically driven alterations of extracellular matrix with accumulation of interstitial fibrosis.1-9 Cardiovascular magnetic resonance (CMR) provides means of phenotyping the complex

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Received February 23, 2015; accepted October 27, 2015.

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Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org

DOI: 10.1161/CIRCIMAGING.115.003285
underlying pathophysiology and may be able to discern the fundamentally different substrates based on the different pathophysiological pathways in these 2 conditions (Figure 1).8–12 Although T1 mapping supports detection of diffuse myocardial disease, late gadolinium enhancement (LGE) helps with visualizing regional changes, such as replacement fibrosis in phenotypically subexpressed HCM gene carriers (G+P− subjects) and overt HCM disease. In compensated LVH because of hypertension—that is before extensive structural and metabolic remodeling with cavity dilatation and functional impairment (eccentric remodeling)—findings reflect physiological adaptations with an increased cellular size because of addition of new, but functional myofibrilles in-parallel and in-series, enabling the ventricle to generate greater forces and to outweigh the increased wall stress.11,13–17 Interstitial fibrosis and the expansion of extracellular space in hypertension herald decompensation with eccentric remodeling and heart failure.12–15,18–22 In this study, we investigated the ability of CMR to discern hypertrophic phenotypes based on detection of diffuse myocardial disease and regional fibrosis by myocardial T1 mapping and LGE, respectively, first, in overt LVH, and second, in phenotypically subexpressed HCM gene carriers.

Methods

Consecutive subjects enrolled in the International T1 multicentre CMR study and meeting inclusion criteria below were included in this study. The multicenter-imaging consortium has been described previously (details in the Data Supplement).23 The study protocol was reviewed and approved by the respective institutional ethics committees and written informed consent was obtained from all participants. All procedures were carried out in accordance with the Declaration of Helsinki (2000). Inclusion criteria for respective patients groups were based on accepted diagnostic criteria1,24–26 using CMR measurements:

Group 1

Patients with HCM (n=95), by demonstration of an LVH (>15 mm) associated with a nondilated LV in the absence of increased LV wall stress or another cardiac or systemic disease that could result in a similar magnitude of hypertrophy.1,24 All patients with HCM had an expressed phenotype with typically asymmetrical septal hypertrophy of increased LVWT, permitting unequivocal clinical diagnoses. HCM patients with previous septal ablation or myectomy were not included.

Group 2

Patients With Hypertension and Compensated LVH

Evidence of treated essential hypertension (n=69; systolic blood pressure of >140 mmHg; diastolic blood pressure of >95 mmHg) and the presence of concentric LVH defined as >12 mm in the basal septal and inferolateral segments25 and without evidence of dilated LV cavity (end-diastolic diameter ≤5.4 cm for women and ≤5.9 cm for men)26,27 on transthoracic echocardiography.

Group 3

G+P− first-degree relatives of patients with HCM, identified carriers of the relevant sarcomere–gene mutations, but had no evidence of LVH (LVWT ≤13 mm; n=23).1,7–9

Group 4

Twenty-three normotensive age- and sex-matched healthy subjects, not taking any regular medications and normal CMR findings including normal LV mass indices, served as the control group to group 3. The datasets of control subjects were included in a previously published article.23

Exclusion criteria for all subjects were history of athletic activity, known diagnosis of amyloidosis or Anderson–Fabry disease, known history of coronary artery disease or previous coronary intervention, as well as the generally accepted contraindications to CMR (implantable devices, cerebral aneurysm clips, cochlear implants, and severe claustrophobia), or a history of renal disease with a current epidermal growth factor receptor of <30 mL/min per 1.73 m².

Cardiovascular Magnetic Resonance

All subjects underwent a routine clinical protocol for volumes and mass and tissue characterization using a 3-tesla MR scanner equipped with advanced cardiac package and multitransmit technology (Achieva, Philips Healthcare, Best, The Netherlands) after professional recommendation for standardized acquisition28 and as previously described.23,29 Details of imaging acquisition and post-processing are provided in the Data Supplement. Cine imaging was used for complete coverage of gapless short-axis slices as well as

Figure 1. Representatives images of hypertensive LVH (HTN) and hypertrophic cardiomyopathy (HCM). Top, End-diastolic cine images. Bottom, Late gadolinium enhancement (LGE) imaging. A, HTN. Arrows highlight an ischemic scar in the lateral wall. B, Concentric HCM with no areas of LGE. C, HCM with areas of LGE. Arrows highlight the areas of LGE in the superior and inferior right ventricular insertion points.
long-axis views. LGE imaging was performed in identical geome-
tries ≈20 minutes after administration of 0.2 mmol/kg body weight
gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany) T1
mapping was performed by using modified Look-Locker imaging
((3(3)3(3)5)) acquisition in a single midventricular short-axis slice,
before contrast administration and to scar imaging, respectively.

**Image Analysis**

Assessment of cardiac volumes and LV mass was performed af-
ter recommendations for standardized postprocessing30 using
commercially available software (CircleCVI 42, Calgary, Canada; for
details see Data Supplement). LGE images were visually examined
for the presence of regional fibrosis showing as bright areas within
the myocardium in corresponding longitudinal views and by exclu-
sion of potential artifacts.31 LGE was quantified using regions defined
as >50% of maximal signal intensity of the enhanced area (full width
at half maximum).30,31 Myocardial crypts were considered present as
visually as structural abnormalities consisting of narrow, deep blood–
filled invaginations considered on cine viewing to penetrate >50% of
the thickness of adjoining myocardium during diastole, perpendicular

**Table 1. Patient Characteristics, Global Morphological, and Functional Measures Based on Cardiovascular Magnetic Resonance Measurements**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=23)</th>
<th>G+P− subjects (n=23)</th>
<th>HCM (n=95)</th>
<th>HTN (n=69)</th>
<th>Significance (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>44±15</td>
<td>41±18</td>
<td>55±14</td>
<td>54±13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Sex, male n (%)</strong></td>
<td>14 (61)</td>
<td>16 (69)</td>
<td>64 (68)</td>
<td>45 (65)</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>BSA, m²</strong></td>
<td>1.6±0.1</td>
<td>1.8±0.1</td>
<td>1.96±0.2</td>
<td>2.01±0.2</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Systolic BP, mm Hg</strong></td>
<td>119±10</td>
<td>120±15</td>
<td>120±20*</td>
<td>147±20</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Diastolic BP, mm Hg</strong></td>
<td>79±7</td>
<td>77±9</td>
<td>78±12</td>
<td>83±10</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td>65±11</td>
<td>67±17</td>
<td>70±12</td>
<td>74±15</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>NYHA, stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I (n, %)</td>
<td>23(100)</td>
<td>19 (83)</td>
<td>62 (65)</td>
<td>39 (57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage II (n, %)</td>
<td>...</td>
<td>4 (17)</td>
<td>21 (22)</td>
<td>27 (39)</td>
<td></td>
</tr>
<tr>
<td>Stage III (n, %)</td>
<td>...</td>
<td>12 (13)</td>
<td>3 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic dysfunction, grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n, %)</td>
<td>23(100)</td>
<td>17 (74)†</td>
<td>19 (20)</td>
<td>15 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade I (inverted E/A ratio) (n, %)</td>
<td>...</td>
<td>6 (26)</td>
<td>58 (61)</td>
<td>50 (72)</td>
<td></td>
</tr>
<tr>
<td>Grade II (pseudonormalization) (n, %)</td>
<td>...</td>
<td>...</td>
<td>18 (19)*</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td><strong>E/E’ (septal)</strong></td>
<td>5±2</td>
<td>7±4</td>
<td>13±4</td>
<td>11±6</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Deceleration time (ms)</strong></td>
<td>153±13</td>
<td>161±12</td>
<td>212±16</td>
<td>199±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LV-EDV index, mL/m²</strong></td>
<td>77±12</td>
<td>80±17</td>
<td>75±17</td>
<td>74±22</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>LV ejection fraction %</strong></td>
<td>63±8</td>
<td>62±8</td>
<td>64±10</td>
<td>62±11</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>RV ejection fraction %</strong></td>
<td>61±10</td>
<td>60±9</td>
<td>66±9</td>
<td>63±9</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>LV mass index, mg/m²</strong></td>
<td>58±16</td>
<td>56±14</td>
<td>97±29*</td>
<td>70±19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximal LVWT, mm</td>
<td>8±1</td>
<td>9±2</td>
<td>19±4*</td>
<td>14±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>LGE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (n, %)</td>
<td>0</td>
<td>2 (9)</td>
<td>65 (68)*</td>
<td>16 (23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LGE extent (FWHM)</td>
<td>...</td>
<td>1.1±0.9</td>
<td>5.5±4.8*</td>
<td>2.6±2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>**RV insertion points (n, %)</td>
<td>0</td>
<td>0</td>
<td>30 (46)*</td>
<td>1 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic pattern (n, %)</td>
<td>0</td>
<td>0</td>
<td>3 (3)*</td>
<td>7 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>T1 mapping</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal native T1 (ms)</td>
<td>1044±18</td>
<td>1105±17†</td>
<td>1169±41*</td>
<td>1058±29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAX native T1 (ms)</td>
<td>1023±44</td>
<td>1055±55</td>
<td>1102±58*</td>
<td>1033±68</td>
<td>0.001</td>
</tr>
<tr>
<td>Septal postcontrast T1 (ms)</td>
<td>446±70</td>
<td>434±67</td>
<td>379±47*</td>
<td>429±60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAX postcontrast T1 (ms)</td>
<td>466±37</td>
<td>424±79</td>
<td>390±44</td>
<td>422±66</td>
<td>0.07</td>
</tr>
<tr>
<td>Septal λ</td>
<td>0.43±0.1</td>
<td>0.45±0.8</td>
<td>0.52±0.9*</td>
<td>0.44±0.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal ECV</td>
<td>0.24±0.06</td>
<td>0.25±0.04</td>
<td>0.31±0.06*</td>
<td>0.24±0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>SAX λ</strong></td>
<td>0.44±0.1</td>
<td>0.46±0.1</td>
<td>0.51±0.1</td>
<td>0.46±0.1</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>SAX ECV</strong></td>
<td>0.23±0.07</td>
<td>0.24±0.06</td>
<td>0.30±0.09</td>
<td>0.24±0.06</td>
<td>0.31</td>
</tr>
<tr>
<td>Abnormal native T1 (n, %)</td>
<td>0 (0)</td>
<td>15 (65)†</td>
<td>92 (98)*</td>
<td>3 (4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abnormal native T1 (n, %)</td>
<td>0 (0)</td>
<td>15 (65)†</td>
<td>92 (98)*</td>
<td>3 (4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

One-way ANOVA or χ² tests, as appropriate for the type of the data, P<0.05 is considered significant. BP indicates blood pressure; BSA, body surface area; ECV, extracellular volume; EDV, end-diastolic volume; FWHM, full width at half maximum; HCM, hypertrophic cardiomyopathy; HTN, hypertensive LVH; LV, left ventricular; NYHA, New York Heart Association; LGE, late gadolinium enhancement; LWLT, LV wall thickness; RV, right ventricular; and SAX, short-axis slice.

Post-hoc tests for significant differences between *HCM vs HTN and †for G+P− subjects vs controls, respectively.

long-axis views. LGE imaging was performed in identical geometries ≈20 minutes after administration of 0.2 mmol/kg body weight gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany) T1 mapping was performed by using modified Look-Locker imaging ((3(3)3(3)5)) acquisition in a single midventricular short-axis slice, before contrast administration and to scar imaging, respectively.

**Image Analysis**

Assessment of cardiac volumes and LV mass was performed after recommendations for standardized postprocessing30 using commercially available software (CircleCVI 42, Calgary, Canada; for details see Data Supplement). LGE images were visually examined for the presence of regional fibrosis showing as bright areas within the myocardium in corresponding longitudinal views and by exclusion of potential artifacts.31 LGE was quantified using regions defined as >50% of maximal signal intensity of the enhanced area (full width at half maximum).30,31 Myocardial crypts were considered present as visually as structural abnormalities consisting of narrow, deep blood–filled invaginations considered on cine viewing to penetrate >50% of the thickness of adjoining myocardium during diastole, perpendicular
(45–135°) to the endocardial border of otherwise normal compacted myocardium and evidence of subtotal or total obliteration during systole by surrounding tissue, as previously described.32

T1-mapping analysis was performed blinded to the underlying diagnosis (including the cine and LGE imaging) by measuring myocardial T1 relaxation in a midventricular short-axis slice using conservative septal sampling, as previously described and validated (details in the Data Supplement).23,29,33 T1 values were also reported for the complete midventricular short-axis slice. A total of 4 HCM subjects, where LGE overlapped with the septal region of interest for T1 mapping, were excluded. In addition to native T1, the hematocrit-corrected extracellular volume fraction (ECV), a marker of extracellular contrast agent accumulation, was also calculated.23,34

Statistical Analysis
Descriptive analysis, comparisons of the groups and assessment of associations have been performed using standard approaches (details in the Data Supplement). Categorical data are expressed as percentages, and continuous variables as mean±SD or median (interquartile range). All tests were 2-tailed and a P value of <0.05 was considered significant. Univariate and multivariate logistic regression was used to test the ability of CMR measures to discriminate between the HCM and hypertensive groups, as well as controls versus G+P− subjects. Sensitivity, specificity and discriminatory accuracy, cut-off values and area under the curve, were derived using receiver-operating characteristics curve analysis. Results of further subgroup analyses are presented in the Data Supplement.

Results
Subject characteristics are presented in Table 1. Compared with patients with hypertension, those with HCM had higher LV mass and LVWT (P<0.0001). Both LVH groups had diastolic impairment; more patients with HCM had grade II. G+P− subjects were similar to controls in functional and morphological measures. LGE was present in 68% of patients with HCM, 46% of which showed areas of LGE at one or both right ventricular insertion points. In the hypertensive group, 16 patients demonstrated LGE of which 10 were demonstrating an ischemic pattern. Two G+P− subjects of patients with HCM showed a nonischemic patch of LGE (Figure 2).

Comparisons of the Groups for T1 Mapping Indices
Native T1 and ECV were significantly higher in HCM compared with hypertensive patients (Table 1; Figure 3; P<0.0001), including in subanalysis of subjects without visible LGE (HCM_LGE− versus hypertension_LGE−, native T1 [ms]: 1165±36 versus 1059±29; ECV: 0.31±0.06 versus 0.26±0.04; P<0.0001 for all; Figures in the Data Supplement). There was no difference in T1-mapping indices in HCM patients with or without LGE (HCMLGE+ versus HCM_LGE−, native T1 [ms]: 1170±44 versus 1165±36; ECV: (%) 0.32±0.06 versus 0.31±0.06; P>0.05 for all). Various morphological types of HCM (concentric, septal, apical, or mid-LVH) were similar in T1 values (P>0.05 for all). Ninety-three patients with HCM (98%) had abnormal T1 values.23 Controlling for the magnitude of LVWT (≥15 mm),124 Patients with HCM had significantly higher T1-mapping indices compared with hypertension15mm subgroup (HCM versus hypertension15mm [n=19]; native T1 [ms]: 1169±41 versus 1059±38; ECV: 0.32±0.04 versus 0.26±0.04; P<0.001 for all).

Comparisons Between G+P− Subjects versus Controls
Compared with controls, native T1 was significantly higher in G+P− subjects (P<0.0001), whereas ECV values were similar (P=0.49). A total of 15 G+P− subjects (65%) had an abnormal native T1 value.23

Compared with hypertension13mm subgroup (n=24, age, years: 49±9), G+P− subjects had significantly raised native T1 (native T1 [ms], G+P− subjects versus hypertension13mm−:...
and 3; Figures 5). Results of further subgroup analyses are included in the Data Supplement.

**Discussion**

In selected patient populations with hypertrophic phenotypes, we provide a proof-of-concept that myocardial T1 mapping can be instrumental in discrimination between HCM and hypertension: first, T1-mapping indices are significantly different, and second, native T1 was identified as the strongest independent discriminator, also when controlling for LGE and similar magnitudes of LVWT. We further show that G+P− subjects have significantly raised native T1 compared with controls, as well as patients with mild hypertension. This important finding may support detection of subexpressed disease as well as separation of these subjects from borderline cases with mild hypertension. Our findings propose a novel systematic approach toward discrimination of common conditions presenting with overt or borderline hypertrophic phenotypes and potentially supporting differential management pathways, in terms of screening and treatment, respectively.

Difficulties in discrimination of overt hypertrophic phenotypes preclude the appropriate diagnosis, risk assessment, and clinical management. Currently, the diagnosis of HCM is based on the finding of LVH with LVWT≥15 mm in the absence of increase in LV wall stress. This approach commonly fails to support unequivocal confirmation of disease, or alternatively, its exclusion.1,2 The complex underlying histopathology3,4 and the consequent functional changes in HCM provide a conundrum of myocardial abnormalities, including replacement fibrosis, reduced ventricular deformation, and increased diastolic stiffness.7–12 Detecting these abnormalities have all been shown to help with disease confirmation in overt LVH.1,24 Visualization of replacement fibrosis by LGE, most commonly located in right ventricular insertion points, is particularly helpful in differential diagnosis,1,11 as well as risk stratification.35–37 However, ≈40% of patients with HCM show no evidence of LGE. Although the LGE relates to the regionally separated myocardial abnormality, T1-mapping techniques support noninvasively detection of diffuse myocardial involvement.7–9,12,18,19 We and others have previously shown that patients with HCM have abnormal T1 indices concordant with diffuse myocardial disease, even in the absence of LGE, as well as in the areas outside overt LGE.7–9,12 We now provide a further evidence that T1 mapping can support clinically relevant discrimination between HCM and hypertension, also in the subset of subjects without overt LGE and when controlling for similar magnitudes of LVWT. Of note, HCM patients group exhibited increased native T1 between 2 and 5 SD above the mean of the reference range, whereas in patients with hypertension native T1 were concentrated within the 2 SD.23 Our findings further resonate with a recent study in patients with hypertension, which demonstrated native T1 values were higher compared with their respective normotensive reference group, however, within 2 SD of the respective reference range.38 In summary, these findings accord with existing knowledge on the respective underlying pathophysiology.4,6–13

Previous studies revealed that the genetically driven diffuse myocardial process is fundamental in development of HCM and an early consequence of sarcomere mutations rather
than a downstream response to the LVH, outflow obstruction, or sequel to microvascular disease.7–9 Our findings corroborate the observations of previous reports by showing the relationship between native T1 and LVWT and LV mass, indicating association between diffuse myocardial involvement and phenotypic expression of disease.12,20,39 In this study, diffuse myocardial abnormalities, evidenced by abnormally high native T1,23 were found in nearly all patients with HCM (98%), indicating that overt HCM with native T1 within the normal range is exceedingly rare. Two thirds of G+P− subjects in our study exhibited abnormal native T1, suggesting that diffuse disease is present and detectable in the absence of an overt phenotype.7–9 As more families undergo genetic testing and phenotypic assessment for HCM, a new preclinical population is growing.1,24 Genetic diagnosis aids to identify the relevant sarcomere mutations in subexpressed relatives, potentially at risk for development of future disease. Native T1 may serve to identify those with subclinical myocardial abnormalities, complementary to genetic testing in identifying the subclinical expression of disease. Given that diffuse myocardial remodeling may be a dynamic process, monitoring native T1 as oppose to LVWT might provide a more reliable means of monitoring disease progression.

Previous observations revealed higher prevalence of myocardial crypts in patients with HCM and G+P− subjects, suggesting that they represent markers of HCM disease.32,40,41 Although

**Figure 4.** Bivariate correlation between native T1 and left ventricle (LV) mass and LV wall thickness. Hypertrophic cardiomyopathy (HCM) subjects showed a positive correlation between native T1 and indexed LV mass ($r=0.47$, $P<0.01$) and maximal left ventricular wall thickness (LVWT; $r=0.44$, $P<0.01$). Patients with hypertensive LVH (HTN) showed no significant associations between native T1 and indexed LV mass and LVWT.

**Table 2.** Results of ROC and Binary Logistic Regression Analysis of CMR Parameters for Discrimination in HCM vs HTN Subjects

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>AUC (95% CI)</th>
<th>Cut-Off Values</th>
<th>Specificity (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Diagnostic Accuracy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM vs HTN</td>
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<td>Univariate analysis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Septal native T1, ms</td>
<td>0.97 (0.94–1.00)**</td>
<td>1110</td>
<td>98 (94–99)</td>
<td>96 (90–98)</td>
<td>97 (93–98)</td>
<td>98 (91–99)</td>
<td>97 (92–99)</td>
</tr>
<tr>
<td>SAX native, ms</td>
<td>0.79 (0.70–0.89)**</td>
<td>1067</td>
<td>77 (67–89)</td>
<td>71 (58–82)</td>
<td>71 (58–82)</td>
<td>73 (63–81)</td>
<td>71 (61–81)</td>
</tr>
<tr>
<td>Septal ECV</td>
<td>0.76 (0.67–0.84)**</td>
<td>0.29</td>
<td>71 (63–81)</td>
<td>76 (67–84)</td>
<td>74 (65–81)</td>
<td>71 (61–81)</td>
<td>73 (63–82)</td>
</tr>
<tr>
<td>SAX ECV</td>
<td>0.66 (0.54–0.75)</td>
<td>0.30</td>
<td>63 (49–70)</td>
<td>70 (58–78)</td>
<td>72 (59–73)</td>
<td>61 (54–67)</td>
<td>63 (51–73)</td>
</tr>
<tr>
<td>LGE (present)</td>
<td>0.76 (0.64–0.82)**</td>
<td>…</td>
<td>68 (61–74)</td>
<td>76 (67–84)</td>
<td>80 (72–87)</td>
<td>63 (56–70)</td>
<td>71 (64–78)</td>
</tr>
<tr>
<td>Maximal LVWT, mm</td>
<td>0.93 (0.92–0.99)**</td>
<td>16</td>
<td>84 (78–88)</td>
<td>91 (81–95)</td>
<td>92 (85–96)</td>
<td>81 (73–85)</td>
<td>87 (79–90)</td>
</tr>
<tr>
<td>LV mass (index), g/m²</td>
<td>0.82 (0.73–0.87)**</td>
<td>0.84</td>
<td>64 (54–71)</td>
<td>80 (73–86)</td>
<td>75 (68–80)</td>
<td>71 (60–78)</td>
<td>73 (65–79)</td>
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<tr>
<td>Multivariate analysis</td>
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<tr>
<td>Native T1, ms</td>
<td>26.1</td>
<td>1.121 (1.057–1.217)**</td>
<td>98 (94–99)</td>
<td>96 (90–99)</td>
<td>96 (90–99)</td>
<td>98 (94–99)</td>
<td>97 (93–99)</td>
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</table>

For further subgroup analyses see Data Supplement. Variables not included (significance [P value]): ECV (0.173); LGE (present; 0.01); Maximal LVWT (0.003); LV mass (index; 0.60). For the model: $\chi^2$: 127; $P<0.001$; $-2\log Lh$: 47.9; Cox and Snell $R^2$: 0.63; Nagelkerke $R^2$: 0.85. AUC indicates area under the curve; CI, confidence interval; CMR, cardiovascular magnetic resonance; ECV, extracellular volume fraction; HCM, hypertrophic cardiomyopathy; HTN, hypertensive LVH; LGE, late gadolinium enhancement; LH, likelihood; LV, left ventricle; LVWT, LV wall thickness; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver-operating characteristics; and SAX, short-axis slice.

$P$ value of $<0.05$ was considered significant. *$P<0.05$, **$P<0.01$. 

P value of $<0.05$ was considered significant. *$P<0.05$, **$P<0.01$.
not reproduced in larger and broader cohorts,\textsuperscript{32,40} none of G+P− subjects in the present cohort showed crypts, and the proportion of these were similar between hypertensive and HCM groups, indicating that crypts are more visible with increased LVWT as well as preserved global systolic function.\textsuperscript{32,40}

A few limitations apply to this study. Prospective studies in large and broad populations are required to validate our findings for widespread use. We strived to exclude patients with overt LVH phenocopies including subjects with history of substantial athletic activity,\textsuperscript{42} as well as known cardiac amyloidosis or known Anderson–Fabry disease.\textsuperscript{1,24} A small number of patients excluded because of overlap of LGE with septal region of interest is unlikely to have caused a significant bias; on the contrary, this approach permitted a blinded read to the underlying diagnosis and the proof-of-concept, that the found effects are not because of the LGE type of scar. The chosen LVWT cut-offs, although based on the diagnostic criteria, may seem arbitrary against the increasingly apparent recognition that HCM represents a continuum of disease across the spectrum of LVWT.\textsuperscript{8–10}

Superior discrimination based on native T1 compared with ECV may relate to the T1-mapping methodology based on modified Look-Locker imaging and its greater precision of native myocardial measurements, concordant with the previous results in discrimination between normal and diffusely diseased myocardium of us and others.\textsuperscript{12,20,29,33,38,39} We recognize that native T1 and ECV are complementary measures of different, but related

### Table 3. Results of ROC and Binary Logistic Regression Analysis of CMR Parameters for Discrimination in Controls vs G+P− Subjects

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>AUC (95% CI)</th>
<th>Cut-Off Values</th>
<th>Specificity (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Diagnostic Accuracy (95% CI)</th>
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<tbody>
<tr>
<td>Controls vs G+P− subjects</td>
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<tr>
<td>Septal native T1, ms 0.97 (0.94–1.00)** 1089</td>
<td>96 (91–99)</td>
<td>87 (79–91)</td>
<td>92 (79–97)</td>
<td>97 (92–99)</td>
<td>92 (81–98)</td>
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<tr>
<td>SAX native T1, ms 0.78 (0.69–0.87)** 1056</td>
<td>76 (64–88)</td>
<td>69 (56–77)</td>
<td>67 (54–75)</td>
<td>70 (61–78)</td>
<td>68 (56–78)</td>
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<tr>
<td>Septal ECV 0.65 (0.48–0.82)…</td>
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<tr>
<td>SAX ECV 0.97 (0.94–1.00)** 1089</td>
<td>96 (91–99)</td>
<td>87 (79–91)</td>
<td>92 (79–97)</td>
<td>97 (92–99)</td>
<td>92 (81–98)</td>
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<tr>
<td>ECV 0.65 (0.48–0.82), NS</td>
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<td>LGE (present) 0.54 (0.38–0.71), NS</td>
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<tr>
<td>Native T1, ms 0.75 (0.61–0.89)NS</td>
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<tr>
<td>LV mass (index), g/m² 0.49 (0.31–0.65), NS</td>
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### Multivariate analysis

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<th>Wald</th>
<th>Exp(B) (95% CI)</th>
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<td>Native T1, ms</td>
<td>11.2</td>
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</table>

For further subgroup analyses see Data Supplement. Variables not included (significance \( P \) value): ECV (0.51); LGE (present; 0.87); Maximal LVWT (0.004); LV mass (index; 0.32). For the model: \( \chi^2: 45.5, P<0.001; -2\log LH: 18.3, Cox and Snell \( R^2: 0.63, \) Nagelkerke \( R^2: 0.84. \) AUC indicates area under the curve; CI, confidence interval; CMR, cardiovascular magnetic resonance; ECV, extracellular volume fraction; LGE, late gadolinium enhancement; LH, likelihood; LV, left ventricle; LVWT, LV wall thickness; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver-operating characteristics; and SAX, short-axis slice.

\( P \) value of <0.05 was considered significant. \( *P<0.05, **P<0.01. \)

Figure 5. Receiver-operating characteristics (ROC) curves in discrimination between hypertrophic cardiomyopathy (HCM) vs hypertensive LVH (HTN; A) and controls vs G+P− subjects (B). ECV, extracellular volume fraction; LGE, late gadolinium enhancement; and LVWT, left ventricular wall thickness.
aspects of the myocardium. Our demonstration that native T1 can detect the earliest changes in HCM myocardium endorses the importance of considering both parameters in defining the natural history of myocardial changes in genopositive individuals. Such an integrated approach is essential to develop timely interventions targeting underlying molecular and structural events to halt or reverse disease progression and improve outcomes.

In conclusion, our study demonstrates that T1-mapping indices may discriminate between overt LVH because of HCM or hypertension with high accuracy. We further show that native T1 value may serve as a novel, noninvasive, and clinically robust biomarker to detect early expression of diffuse myocardial involvement in subexpressed G+P− subjects.

Sources of Funding

This study was supported by Department of Health via the National Institute for Health Research comprehensive Biomedical Research Centre award to Guy’s & St. Thomas’ NHS Foundation Trust in partnership with King’s College London and King’s College Hospital National Health Service Foundation Trust. This study was also supported by the King’s BHF Centre of Research Excellence. Dr Hinojor was supported by the Spanish Cardiology Society, Dr Yu is supported by Victor Chang Cardiac Research Institute. Dr Child is supported by Saint Jude Medical. Dr Nagel is supported by the German Centre for Cardiovascular Research (DZHK) and the German Federal Ministry for Education and Research (BMBF).

Disclosures

Dr Puntmann and Nagel hold a patent of invention for a method for differentiation of normal myocardium from diffuse disease using T1 mapping in nonischemic cardiomyopathies and others (based on PR-MS 33.297, PR-MS 33.837, PR-MS 33.654; with no financial interest). The other authors report no conflicts.

References


9 Hinojar et al. Native T1 in Discrimination Between Hypertension and HCM


CLINICAL PERSPECTIVE

Using selected population patients with hypertrophic phenotypes, we provide a proof-of-concept that myocardial T1 mapping may be instrumental in discrimination between HCM and hypertension. T1-mapping indices are significantly higher in HCM in comparison with hypertension also when controlling for LGE and similar magnitudes of LVWT. Native T1 was the strongest independent discriminator between these 2 conditions. We further show that a majority of gene positive subjects have raised native T1 in the absence of phenotypically expressed disease (G+P−). Our findings propose a novel systematic approach toward discrimination of common conditions presenting with overt or borderline hypertrophic phenotypes, potentially supporting differential treatment pathways, as well as a screening tool for subclinical cardiomyopathy in G+P− subjects.
T1 Mapping in Discrimination of Hypertrophic Phenotypes: Hypertensive Heart Disease and Hypertrophic Cardiomyopathy: Findings From the International T1 Multicenter Cardiovascular Magnetic Resonance Study

Rocio Hinojar, Niharika Varma, Nick Child, Benjamin Goodman, Andrew Jabbour, Chung-Yao Yu, Rolf Gebker, Adelina Doltra, Sebastian Kelle, Sitara Khan, Toby Rogers, Eduardo Arroyo Ucar, Ciara Cummins, Gerald Carr-White, Eike Nagel and Valentina O. Puntmann

_Circ Cardiovasc Imaging_. 2015;8:
doi: 10.1161/CIRCIMAGING.115.003285

_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

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SUPPLEMENTARY MATERIAL

T1 Mapping in Discrimination of Hypertrophic Phenotypes - Hypertensive Heart Disease and Hypertrophic Cardiomyopathy: Findings from the International T1 Multicenter CMR Study

Hinojar et al: Native T1 in Discrimination between HTN and HCM

Rocio Hinojar 1,2, MD; Mres; Niharika Varma1, MBBS; Bsc; Nick Child1, BM MRCP;
Benjamin Goodman1, MSc; Andrew Jabbour3, MD, PhD; Chung-Yao Yu3; MBBS, MD;
Rolf Gebker,4 MD, PhD; Adelina Doltra4, MD, PhD; Sebastian Kelle4, MD, PhD;
Sitara Khan5, MD, PhD; Toby Rogers1, MD; Eduardo Arroyo Ucar1, MD;
Ciara Cummins1, MSc; Gerald Carr-White1, MBBS, PhD; Eike Nagel1,7, MD, PhD;
Valentina O. Puntmann1,6*, MD, PhD
**Supplemental Methods**

Patient characteristics were recorded for all subjects, including age, gender, body mass index, and presence of traditional cardiovascular risk factors. NYHA stage, systolic/diastolic blood pressure and parameters of diastolic function by transthoracic echocardiography were also recorded.

Genotyped relatives (G+P-) were identified as a part of routine clinical work-up in selected subject with considerable pretest likelihood as carriers of hereditary cardiac condition as a cascade genetic screening of the relatives of patients with overt disease [1]. Sequencing methodologies were performed for the most commonly implicated sarcomere protein genes, as per guidelines [1].

Multicenter-imaging consortium has been described previously [2]. A standardized T1-mapping sequence and imaging protocol, developed and validated at King’s College London (KCL) [2-5], were distributed to CMR centers identified via the worldwide Philips Healthcare clinical science network that hold individual partnership research agreements allowing for adequate clinical science support and provision of compatible sequences and scanner software packages. Imaging parameters were unified across participating sites. Inter-centre comparisons of measured T1 values at each location for each field strength, as well as reproducibility and transferability of postprocessing have been reported previously [2-5].

**Imaging parameters**

All cine CMR were performed using a balanced steady-state free precession sequence in combination with parallel imaging (SENSitivity Encoding, factor 2) and retrospective gating during a gentle expiratory breath- hold (TE/TR/flip-angle: 1.7ms/3.4ms/60°, spatial resolution 1.8x1.8x8 mm) [4,6].

Late gadolinium enhancement (LGE) was performed using gapless whole heart coverage of short axis (SAX) slices 20 minutes after administration of 0.2 mmol/kg body weight gadobutrol (Gadovist®, Bayer, Leverkusen, Germany) using a mid-diastolic inversion prepared 2-dimensional gradient echo sequence (TE/TR/flip-angle 2.0 msec/3.4 msec/25°,
acquired voxel size 1.4x1.4x8mm) with an individually adapted prepulse delay to achieve optimally nulled myocardium [4,6].

Balanced steady state free precession single breath-hold modified Look-Locker Imaging (MOLLI, (3(3)3(3)5)) was used for T1 mapping and performed in a single midventricular short axis slice at mid-diastole, prior to contrast administration and to LGE imaging, respectively (TE/TR/flip-angle: 1.64msec/3.3msec/50°, acquired voxel size 1.8 x 1.8 x 8 mm, phase encoding steps n=166, 11 images corresponding to different inversion times ((3(3)3(3)5) MOLLI scheme), adiabatic prepulse to achieve complete inversion) [2-5]. The acquisitions were checked for motion and artifacts as well as for goodness of fit immediately after acquisition. Poor quality acquisitions were repeated.

Image analysis

Assessment of cardiac volumes and LV mass was performed following recommendations for standardized postprocessing [7]. Endocardial LV borders were manually traced at end-diastole and end-systole. The papillary muscles were included as part of the LV cavity volume. LV end-diastolic (EDV) and end-systolic (ESV) volumes were determined using rule of discs. Ejection fraction (EF) was computed as EDV-ESV/EDV. All volumetric indices were normalized to body surface area (BSA).

T1 mapping analysis

We have previously shown that T1 mapping acquisition in a single midventricular SAX slice and conservative septal measurements are feasible in clinical routine [2-5]. Standardization of T1 measurements using conservative septal myocardial sampling within the midventricular SAX slice, is in part based on the findings that this geometry is acquired with good reproducibly, as well as sufficient LVWT to avoid blood contamination of the T1 signal and does not suffer from partial volume effects found in the basal or apical slices [5]. This approach intends to capture diffuse disease, not seen by LGE, and to be representative of diffuse myocardial involvement of the whole myocardium [4], allowing us to capture the
global effects of genetically induced diffuse myocardial disease in HCM as well as abnormalities driven by increased afterload in HTN [1]. The advantage of whole-heart T1 mapping and its feasibility for the use of clinical practice is presently unknown and subject to further technical development [8].

T1 mapping analysis was performed blinded to the underlying diagnosis (including the cine and LGE imaging (RH and NV) by measuring myocardial T1 relaxation in a mid-ventricular SAX slice using conservative septal sampling as previously described and validated [2-5]. Blinded read was made possible by a prospective review of all studies, ensuring that there was no overlap of LGE within the septal ROI of T1 mapping acquisition (Figures 1S and 2S).

Upon review a total of 4 HCM patients were excluded from the analysis. Care was also taken to avoid unintentional partial volume inclusion by contamination with the signal from the blood pool. Following offline image co-registration and motion correction, T1 values were determined by fitting an exponential model to the measured data applying Look-Locker, noise and heart rate correction. Assessment of interstudy, inter- and intra-observer reproducibility has been previously reported [2-5]. In addition to T1-values of native and post-contrast myocardium the partition coefficient $\lambda$ and the hematocrit-corrected extracellular volume fraction (ECV) as markers of extracellular contrast agent accumulation were calculated [9].

**Statistical analysis**

Statistical analysis was performed using SPSS software (version 22.0; SPSS, Chicago, IL, USA). Normality of distributions was tested with the Kolmogorov-Smirnov statistic. Categorical data are expressed as percentages, and continuous variables as mean±SD or median (interquartile range), as appropriate. For comparison of 2 and more than 2 normally distributed variables, Student t test, one-way analysis of variance (with Bonferroni post-hoc test) for continuous variables and chi-square tests for categorical variables were used, as appropriate. Assessment of reproducibility was performed using Bland Altman approaches. Associations were explored by linear regression analyses. The ability of significant variables to discriminate between the groups and subgroups was tested using univariate and
multivariate binary logistic regression; cut-off values and area-under-the-curve (AUC) was derived using the receiver operating characteristics (ROC) curve.

Comparisons were made for the two main clinical dilemmas: firstly, HCM vs. HTN; and secondly, G+P- subjects vs. controls. Further subgroup analyses were made for:

- HCM vs. HTN subjects with no evidence of LGE (HCM_{LGE-} vs. HTN_{LGE-});
- HCM vs. HTN_{15mm} (HTN subjects matching the LVWT-based diagnostic criteria for equivocal disease (LVWT ≥ 15 mm));
- G+P- subjects vs. HTN_{13mm} (matching diagnostic criteria of LVWT≤ 13 mm for G+P- subjects) [1,10-12].

All tests were two-tailed and a P value of less than 0.05 was considered significant.

Supplemental results

General characteristics

HTN patients had higher systolic blood pressure (p<0.05). Five HTN subjects had diet-controlled type II diabetes mellitus.

Gene analysis in G+P- subjects revealed presence of MYBPC3 (n=11, 49%), MYH7 (n=9, 39%) and TNNT2 (n=3, 13%).

Myocardial crypts were present in 5% of HCM subjects, in 6% of HTN.

No subjects in the control group or G+/P- showed eGFR less than 60 ml/min. However, 3 patients in HTN group (4%) and 4 in the HCM group (4%) showed moderately impaired renal function.

Native T1 and ECV comparisons in HTN and HCM subgroups with no LGE were significantly increased in HCM LGE- compared to HTN LGE- population (HCM_{LGE-} vs. HTN_{LGE-}, native T1 (msec): 1165±36 vs. 1059±29; ECV 0.31±0.06 vs. 0.26±0.04; p<0.0001 for all) (Figure 3S).

There was an association between hematocrit and ECV, which was somewhat stronger for men than women (men: r=-0.42, p<0.001, women: r=-0.37, p<0.01). There was no significant
correlation between hematocrit and native T1 (men: r=-0.11, p=0.12, females: r=-0.09, p=0.17).

**Reproducibility and variability of measurements**

Assessment of interstudy, inter- and intraobserver reproducibility and its relation to pathological changes in LV geometry and LVWT have been reported previously [5].

In assessment of the present observers (R.H, N.V), T1 mapping showed excellent intra-observer (r=0.98, p < 0.01) and inter-observer (r=0.96, p < 0.01) agreement for all subject groups (6 patients of each groups, 24 patients in total). In comparison to native myocardial T1 values, $\lambda$ showed consistently higher intra-observer coefficient of variation (CoV, native T1: 1.0%; $\lambda$: 6.6%) and inter-observer coefficient of variation (native T1: 1.8%; $\lambda$: 7.7%) for all subject groups.

**Supplemental discussion**

T1 mapping acquisition in a single midventricular SAX slice is feasible in clinical routine [2-5]. It is employed on assumption that it is representative of diffuse involvement affecting myocardium uniformly [4]. The advantage of whole-heart T1 mapping and its feasibility for the use of clinical practice is presently unknown; a single study showed that whereas corresponding segments show little variation between the apical, midventricular and basal slices, regional variation of values persist within the slice [8], complicating the use of absolute segmental values. Standardization of T1 measurements using conservative septal myocardial sampling within the midventricular SAX slice, is additionally based on the findings that this geometry is acquired with good reproducibly, as well as sufficient LVWT to avoid blood contamination of the T1 signal and does not suffer from partial volume effects found in the basal or apical slices. While measuring native T1 requires standardization we have overcome this issue by a unified sequence shared between the participating sites. Native T1 is also independent of influences such as water exchange or the inaccuracies inherent in the determination of blood T1 required to control for the individual clearance and distribution
of contrast agents [9]. While native T1 may not solely reflect the changes within the extracellular space, the above mentioned issues related to indices may explain the better separation of groups based on native T1.

**Supplemental references**


Supplemental Tables

Table 1S. Results of ROC and binary logistic regression analysis of CMR parameters for discrimination between HCM vs. HTN15mm, G+P- subjects vs. HTN13mm, and HCM LGE- vs. HTN LGE-. For further subgroup analyses see Supplementary material (AUC - area-under-the curve, ROC - receiver operating characteristics, PPV positive predictive value, NPV – negative predictive value, LH- likelihood, LV – left ventricular, LVWT – LV wall thickness, LGE – late gadolinium enhancement, ECV – extracellular volume, *p<0.05, **p<0.01).

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>AUC (95%CI), p-value</th>
<th>Cut-off values</th>
<th>Specificity (95%CI)</th>
<th>Sensitivity (95%CI)</th>
<th>PPV (95%CI)</th>
<th>NPV (95%CI)</th>
<th>Diagnostic Accuracy (95%CI)</th>
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<tbody>
<tr>
<td><strong>HCM vs. HTN15mm</strong></td>
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<td>Univariate analysis</td>
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<tr>
<td>Native T1 (msec)</td>
<td>0.98 (0.94-1.00)**</td>
<td>1102</td>
<td>97 (91-99)</td>
<td>98 (93-99)</td>
<td>99 (92-99)</td>
<td>91 (86-97)</td>
<td>98 (91-99)</td>
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<tr>
<td>ECV</td>
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<td>0.26</td>
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<td>73 (59-76)</td>
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<td>58 (30-62)</td>
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<tr>
<td>LGE (present)</td>
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<td>68 (65-70)</td>
<td>95 (90-99)</td>
<td>19 (9-25)</td>
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<tr>
<td><strong>Native T1 (msec)</strong></td>
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<td>98 (92-99)</td>
<td></td>
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<td></td>
<td></td>
<td>99 (91-99)</td>
<td></td>
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<td></td>
<td></td>
<td>91 (85-98)</td>
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<tr>
<td></td>
<td></td>
<td>98 (91-99)</td>
<td></td>
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</tr>
</tbody>
</table>

Variables not included (Sig. (p-value)): ECV (0.175); LGE(present) (0.04)

For the model: Chi²: 31, p<0.001; -2Log LH: 25.2, Cox&Snell R²: 0.29, Nagelkerke R²: 0.61

### G+P- subjects vs. HTN_{13mm}

<table>
<thead>
<tr>
<th></th>
<th>Wald</th>
<th>Exp(B) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Native T1 (msec)</strong></td>
<td>0.86(0.78-0.95)**</td>
<td>1095</td>
</tr>
<tr>
<td><strong>ECV</strong></td>
<td>0.63(0.50-0.77)</td>
<td>/</td>
</tr>
<tr>
<td><strong>LGE (present)</strong></td>
<td>0.45(0.31-0.59)</td>
<td>/</td>
</tr>
<tr>
<td><strong>LV mass (index) (g/m²)</strong></td>
<td>0.41(0.26-0.55)</td>
<td>/</td>
</tr>
<tr>
<td><strong>Maximal LVWT (mm)</strong></td>
<td>0.47(0.31-0.59)</td>
<td>/</td>
</tr>
</tbody>
</table>

Multivariate analysis not performed, as native T1 is the only significant variable.

### HCM_{LGE} vs. HTN_{LGE-}

<table>
<thead>
<tr>
<th></th>
<th>Wald</th>
<th>Exp(B) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Native T1 (msec)</strong></td>
<td>0.98 (0.94-1.00)**</td>
<td>1106</td>
</tr>
<tr>
<td><strong>ECV</strong></td>
<td>0.78 (0.65-0.87)**</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>LV mass (index) (g/m²)</strong></td>
<td>0.85 (0.75-0.94)**</td>
<td>84</td>
</tr>
<tr>
<td><strong>Maximal LVWT (mm)</strong></td>
<td>0.91 (0.86-0.98)**</td>
<td>16</td>
</tr>
</tbody>
</table>
### Multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Wald</th>
<th>Exp(B) (95% CI)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Native T1 (msec)</strong></td>
<td>16.1</td>
<td>1.079 (1.040-1.120)**</td>
<td>96(84-99)</td>
<td>98(90-99)</td>
<td>98(90-99)</td>
<td>96(84-99)</td>
</tr>
</tbody>
</table>

Variables not included (Sig. (p-value)): ECV (0.62); maximal LVWT (0.009); LV mass(index); (0.31)

For the model: Chi²: 61, p<0.001; -2Log LH: 39, Cox&Snell R²: 0.61, Nagelkerke R²: 0.82
Supplemental Figures and Figure Legends

**Figure 1S.** An illustrative example where LGE overlaps with septal ROI within the imaging slice.

**Figure 2S.** Flowchart of patients’ inclusion.

**Figure 3S.** Native T1 and ECV comparisons in HTN and HCM subgroups with no LGE were significantly increased in HCM LGE- compared to HTN LGE- population (HCM\textsubscript{LGE-} vs. HTN LGE-, native T1 (msec): 1165±36 vs. 1059±29; ECV 0.31±0.06 vs. 0.26±0.04; p<0.0001 for all).
Figure 1S.

Figure 2S.
Figure 3S.