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Myocardial Native T₁ Time in Patients with Hypertrophic Cardiomyopathy

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Abstract

In hypertrophic cardiomyopathy (HC), there are significant variations in left ventricular (LV) wall thickness and fibrosis, which necessitates a volumetric coverage. Slice-interleaved T₁ (STONE) mapping sequence allows for the assessment of native T₁ time with complete coverage of LV myocardium. The aims of this study was to evaluate spatial heterogeneity of native T₁ time in HC patients. Twenty-nine HC patients (55±16 years) and 15 healthy adult control subjects (46±19 years) were studied. Native T₁ mapping was performed using STONE sequence which enables acquisition of 5 slices in the short-axis plane within a 90 sec free-breathing scan. We measured LV native T₁ time and maximum LV wall thickness in each 16 segments from 3 slices (basal, mid-ventricular and apical-slice). Late gadolinium enhanced (LGE) MRI was acquired to assess presence of myocardial enhancement. In HC patients, LV native T₁ time was significantly elevated compared to healthy controls, regardless of presence or absence of LGE (mean native T₁ time; LGE positive segments from HC, 1141±46 msec; LGE negative segments from HC, 1114±56 msec; segments from healthy controls, 1065±35 msec, p<0.001). Elevation of native T₁ time was defined as >1135 msec, which was +2SD of native T₁ time by STONE sequence in healthy controls. 120 of 405 (30%) LGE negative segments from HC patients showed elevated native T₁ time. Prevalence of segments with elevated native T₁ time for basal, mid-ventricular and apical slice was 29%, 25%, 38%, respectively. Significant correlation was found between LV wall thickness and LV native T₁ time (y=0.029x–22.6, p<0.001 by Spearman's correlation coefficient). In conclusion, substantial number of segments without LGE showed elevation of native T₁ time, and whole heart T₁ mapping revealed heterogeneity of myocardial native T₁ time in HC patients.

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Keywords

Native T1 mapping; Hypertrophic cardiomyopathy; Heterogeneity

Introduction

Hypertrophic cardiomyopathy (HC) is a genetic heart disease, characterized by unexplained left ventricular (LV) hypertrophy, myofibrillar disarray and myocardial fibrosis¹. HC is regarded as the most common non-traumatic cause of sudden death in young generation². Post-mortem studies revealed that fibrosis is either present as focal fibrosis, or diffuse fibrosis by intercellular deposition of collagen fibers³. In-vivo, focal fibrosis can be assessed non-invasively with late gadolinium enhanced (LGE) magnetic resonance imaging (MRI)⁴. Several studies showed that presence of myocardial enhancement on LGE MRI is associated with worse clinical outcome in HC^{5–8}. However, LGE MRI can delineate only focal myocardial fibrosis, not diffuse interstitial fibrosis. Therefore, noninvasive assessment of diffuse interstitial fibrosis is of interest in terms of better risk stratification in HC patients. Myocardial T₁ mapping emerged as a non-invasive method to quantify diffuse myocardial abnormality. Extra cellular volume calculated by pre- and post- T₁ mapping can detect diffuse myocardial abnormality in patients with diastolic heart failure⁹, diabetic cardiomyopathy¹⁰ and cardiac amyloidosis¹¹. Recent studies showed that native (non-contrast) T₁ mapping can differentiate myocardial abnormality of HC from healthy myocardium¹². However, in this study, myocardial T₁ time was calculated by one point sampling of mid septal wall. To date, no data are available regarding native T₁ time heterogeneity based on 16 segment model. The aims of this study were to compare native T₁ time between HC patients and healthy controls, and to evaluate spatial heterogeneity of native T₁ time in HC patients using slice-interleaved T₁ mapping.

Methods

Twenty-nine HC (56±16 years; 22 male) and 15 healthy adult control subjects (46±19 years; 9 male) free of any cardiovascular diseases were studied. Phenotypes of HC were septal hypertrophy (N=25) and apical hypertrophy (N=4). In our cohort, there were 6 HC patients with left ventricular outflow obstruction. Healthy controls had no history of hypertension, dyslipidemia, diabetes mellitus and smoking. All participants were in sinus rhythm at the time of scan. The study protocol was approved by our institutional review board. Written informed consent was obtained from all subjects. By using a 1.5 T MR scanner and 32 channel cardiac coil (Achieva, Philips Healthcare, Best, The Netherlands), cine MRI, LGE MRI and native T₁ mapping images of LV were acquired.

Electrocardiogram monitoring leads were positioned with the subject in the supine position. Vertical and horizontal LV long-axis cine images were acquired using a steady-state free precession sequence. LV volumes and mass were calculated from an LV short-axis stack of cine images extending from the apex to the base (repetition time, 3.3 ms; echo time, 1.6 ms; flip angle, 60°; field-of-view, 320×320 mm; acquisition matrix, 128×128; slice thickness, 8 mm; gap, 2 mm)¹³. Native T₁ mapping was acquired using a slice-interleaved T₁ (STONE)

sequence which enables acquisition of 5 slices in the short-axis plane within a 90 sec free-breathing scan¹⁴ (repetition time, 2.8 ms; echo time, 1.4 ms; flip angle=70°, field-of-view, 360×351 mm, voxel size, 2.1×2.1 mm, slice thickness, 8 mm, TFE factor, 86, SENSE factor, 2). Fifteen minutes after the injection of 0.2 mmol/kg gadobenate dimeglumine, LGE images were acquired using a 3 dimensional sequence¹⁵ with following parameters: repetition time, 5.3 ms; echo time, 2.1 ms; flip angle, 70° field-of-view, 320×320×125 mm³; acquisition matrix, 224×224×23; spatial resolution, 1.4×1.4×1.5mm; reconstruction resolution, 0.6×0.6×0.8mm. Cine MRI were analyzed using a commercial workstation (Extend MR Workspace, version 2.3.6.3, Philips Healthcare). To determine LV mass, epi- and endocardial LV borders were manually traced on the short axis images. LV mass was calculated as the sum of the myocardial volume multiplied by the specific gravity (1.05g/mL) of myocardial tissue¹⁶. Visual assessment was performed to assess presence or absence of myocardial enhancement on LGE images using the 16 segment model. Myocardial segments from HC patients were allocated into 2 group base on the presence or absence of hyperenhancement on LGE MRI. Short-axis slices of native T₁ mapping images were analyzed using a custom software (MedIACare, Boston, Massachusetts). For calculating LV native T₁ time, the three short axis LV slices were divided into 6 segments for basal and mid-ventricular slices, 4 segments for apical slice using the anterior right ventricular-LV insertion point as reference. Motion correction was performed using the adaptive registration of varying contrast-weighted images for improved tissue characterization approach¹⁷. The 16 segment model was used to assess native T₁ time in each segments. To evaluate inter-observer reproducibility, measurements of LV native T₁ time from 10 HC patients were independently taken by two observers. One of the two observers measured LV native T₁ time twice to assess intra-observer reproducibility. Data were analyzed using SPSS software (version 17.0, SPSS, Inc., Chicago, IL, USA) and MedCalc for Windows (version 14.8.1, MedCalc Software, Ostend, Belgium). Continuous values are presented as mean ± standard deviation (SD). Categorical values are expressed as number (%). For continuous variables, normality was evaluated by Shapiro–Wilk test. Significance of difference was evaluated using unpaired-t test for normal distributed variables, Mann-Whitney U test for skewed variables. Chi-square test was used to assess the difference for categorical variables. Significance of difference of native T₁ time between 4 groups (Figure 2) were evaluated by one-way ANOVA with Tukey’s post-hoc test. Relationship between LV native T₁ time and LV wall thickness was calculated by Spearman’s correlation coefficient. To evaluate reproducibility of native T₁ time measurement, intraclass correlation coefficient (ICC) and repeatability coefficient were evaluated. Repeatability coefficients were calculated as 1.96 times the SD of the differences on the Bland-Altman plots¹⁸. A two-sided P value less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the characteristics of study subjects. HC patients were heavier than healthy controls. Table 2 summarizes cardiac MR findings. LV mass index was significantly higher in HC patients compared to control subjects. LGE hyperenhancement of LV myocardium was observed in 13 of 29 (45%) HC patients. Figure 1 showed representative

native T₁ mapping images from a HC patient with asymmetric septal hypertrophy and a healthy control. Mean native T₁ time over the 16 segments was elevated to 1175 msec in this HC patient (Figure 1, B). However, no myocardial enhancement was observed on LGE images (Figure 1, C). Figure 2 demonstrated segment based comparison of native T₁ time between HC and healthy controls. We excluded 6 segments due to severe artifacts on T₁ mapping images from analysis. Comparing to segments from healthy controls (n=240), mean native T₁ time was significantly elevated in HC patients (1117±55 msec vs 1065±35 msec, p<0.001). Furthermore, mean native T₁ time of LGE negative segments from HC was significantly higher than healthy controls (1114±56 msec vs 1065±35 msec, p<0.001). LGE positive segments from HC showed highest native T₁ time (1141±46 msec). Figure 3 demonstrated the location of segments with elevated native T₁ time in HC patients. Elevation of native T₁ time was defined as >1135 msec, which was +2SD of native T₁ time by STONE sequence in healthy controls. 120 of 405 (30%) LGE negative segments showed elevated native T₁ time. Prevalence of segments with elevated native T₁ time for basal, mid-ventricular and apical slice was 29%, 25%, 38%, respectively. Figure 4 illustrated myocardial native T₁ time across all myocardial segments in both HC and healthy controls. Substantial regional heterogeneity was found in myocardial native T₁ time in HC patients. Comparing to healthy controls, native T₁ time was significantly elevated in HC patients in 15 of 16 myocardial segments except for basal inferolateral wall. Figure 5 showed relationship between native T₁ time and LV wall thickness in end-diastole. Significant positive correlation was found between native T₁ time and LV wall thickness ($y=0.029x-22.6$, p<0.001). Reproducibility of native T₁ time measurement was high, with ICC of 0.91 (95%CI: 0.88–0.93) and repeatability coefficient of 46 msec (4.1% of mean native T₁ time) for intra-observer reproducibility, ICC of 0.86 (95%CI: 0.86–0.92) and repeatability coefficient of 51 msec (4.5% of mean native T₁ time) for inter-observer reproducibility.

Discussion

This is the first study demonstrating substantial heterogeneity of native T₁ time in HC patients. We also showed that myocardial T₁ time is elevated in LGE negative segments from HC, and native T₁ time is positively correlated with LV wall thickness.

Myocardial enhancement on LGE MRI is an established prognostic marker for HC patients^{5–7}. Presence of LGE is associated with increased risk of non-sustained ventricular tachyarrhythmia¹⁹. A recent international multicenter study demonstrated that extensive LGE, 15% of LV mass, can identify HC patients at increased risk for sudden cardiac death and progressive heart failure⁸. Therefore, quantitative assessment of myocardial enhancement using LGE MRI is crucial for the risk stratification for HC patients. However, a histological report demonstrated that standard LGE sequence can delineate only focal myocardial fibrosis, not diffuse interstitial myocardial fibrosis²⁰. On LGE MRI, it may be impossible to define an area of completely normal myocardium as “nulled” myocardium in diffuse myocardial disease, because the signal intensity of LGE MRI depends on regional differences in gadolinium accumulation between normal and diseased myocardium. Therefore, non-invasive imaging to be able to detect interstitial fibrosis can potentially provide incremental prognostic information over LGE MRI. Recent studies demonstrated that the measurement of T₁ relaxation time could be useful for the quantitative assessment of

diffuse myocardial fibrosis^{21–26}. In a study done by Puntmann et al., native T₁ mapping can differentiate diffuse diseased myocardium of cardiomyopathy from normal myocardium with sensitivity of 100%, specificity of 96%, accuracy of 98%¹². In the current study, native T₁ time was significantly increased in HC patients in comparison to healthy controls, and substantial number of LGE negative segments showed elevated native T₁ time. These results indicate that native T₁ mapping is potentially useful for detecting diffuse myocardial abnormality, which is undetectable by LGE MRI. Furthermore, LV wall thickness is correlated with LV native T₁ time. Our observations were similar with the results of previous studies showing association of abnormal native T₁ time and LV mass index in HC patients¹². Further histological validation is required to investigate whether abnormal native T₁ time corresponds to diffuse interstitial myocardial fibrosis in HC patients.

In the previous reports showing elevated native T₁ time of HC patients^{12, 27}, myocardial T₁ time was calculated by one point sampling of mid septal wall. In HC, there are significant variations in LV wall thickness and distribution of myocardial fibrosis, which necessitates a full coverage of the heart. Therefore, we used slice-interleaved T₁ mapping sequence, STONE, for the assessment of heterogeneity of native T₁ time in HC patients. STONE sequence uses a free-breathing acquisition scheme, which enables sampling of the undisturbed inversion recovery curve. Therefore, it could provide similar precision and improved accuracy for native T₁ time measurement compared to the conventional breath-hold modified look locker inversion recovery (MOLLI) sequence¹⁴. Our segmental analysis covering entire LV myocardium showed that native T₁ time was significantly elevated in HC patients compared to healthy controls in 15 of 16 myocardial segments (except for base inferolateral wall, Figure 4). In addition, 120 of 405 (30%) LGE negative segments showed elevated native T₁ time. These results indicated that single-slice approach in the previous studies might miss substantial number of segments with elevated native T₁ time in HC patients. Whole-heart T₁ mapping would be advantageous for the accurate assessment of myocardial T₁ abnormality in HC patients.

Our study has several limitations. The sample size was small and prevalence of LGE positive HC patients was relatively low in our study. Therefore, results may be biased by small sample size. Further large scale study is necessary to generalize our observation. We do not have pathological data comparing myocardial native T₁ time and myocardium fibrosis in HC patients. Therefore, we do not know the true cause of the elevated LV native T₁ time in HC patients. Furthermore, native T₁ time increases by aging²⁸. In our study, HC patients were 10 years older than controls, therefore, difference in age potentially may contribute to the difference in native T₁ time between HC and controls.

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Figure 1. Native T_1 mapping images from a hypertrophic cardiomyopathy patient and a healthy control

(A) Native T_1 mapping images from a healthy control. Bull's eye maps to the right in each panel demonstrate native T_1 time in myocardial segments based on a 16-segment model.

(B) Native T_1 mapping images from a hypertrophic cardiomyopathy patient. In this patient, native T_1 time is diffusely elevated and elevation was prominent in hypertrophied septal wall.

(C) Short-axis late gadolinium enhanced magnetic resonance images from the same hypertrophic cardiomyopathy patient shown in (B). No myocardial enhancement was found.

Figure 2. Comparison of native T₁ time between hypertrophic cardiomyopathy and controls
 The error bars represent standard deviation. Significance of difference between groups were calculated by one-way ANOVA with Tukey's correction.

Segments without enhancement N=405 segments

Figure 3. Location of segments with elevated T_1 time in hypertrophic cardiomyopathy patients
Elevated native T_1 time was defined as >1135 msec, which was $+2SD$ of native T_1 time by slice-interleaved T_1 sequence in healthy volunteer (mean T_1 time in healthy volunteers: 1065 ± 35 msec).

Figure 4. Regional heterogeneity of myocardial native T₁ time in hypertrophic cardiomyopathy patients

Variability in segmental native T₁ time across all 16 myocardial segments in hypertrophic cardiomyopathy patients (orange) and healthy controls (blue). Segmental comparison between segments without enhancement (n=405) and segments from healthy controls (n=240). The error bars represent standard deviation.

Figure 5. Correlation between left ventricular wall thickness and native T₁ time

Significant positive correlation was found between left ventricular wall thickness and native T₁ time.

P value was calculated by Spearman's correlation coefficient.

Table 1

Subjects' characteristics

	Hypertrophic cardiomyopathy (N=29)	Healthy controls (N=15)	* P-value
Demographics			
Male	22 (76%)	9 (60%)	0.27
Age (years)	56 ± 16	46 ± 19	0.091
Height (cm)	173 ± 9	173 ± 9	0.98
Body weight (kg)	88 ± 14	78 ± 14	0.028
Body mass index (kg/m ²)	29.3 ± 5	26 ± 4	0.012
Body surface area, (m ²)	2.05 ± 0.19	1.92 ± 0.21	0.045
Systolic blood pressure (mmHg)	122 ± 17	122 ± 11	0.93
Diastolic blood pressure (mmHg)	71 ± 16	71 ± 10	0.90
Heart rate (beats per minute)	65 ± 10	70 ± 10	0.15
New York Heart Association functional classification			
Class I	20 (69%)	–	–
Class II	9 (31%)	–	–
Class III or IV	0 (0%)	–	–

Values are represented as mean ± standard deviation or number (%)

* P-value represents significance of difference between hypertrophic cardiomyopathy patients and healthy controls.

Table 2

Cardiac magnetic resonance imaging parameters

	Hypertrophic cardiomyopathy (N=29)	Healthy controls (N=15)	* P-value
End diastolic volume index (mL/m ²)	75 ± 16	80 ± 12	0.33
End systolic volume index (mL/m ²)	27 ± 10	31 ± 7	0.11
Stroke volume index (mL/m ²)	48 ± 9	48 ± 7	0.89
Left ventricular ejection fraction (%)	65 ± 8	61 ± 5	0.051
Left ventricular mass index (g/m ²)	74 ± 22	47 ± 12	<0.001
Heart rate (beats per minute)	65 ± 10	70 ± 10	0.15
Late gadolinium enhancement positive subjects	13 (45%)	0 (0%)	0.003

Values are represented as mean ± standard deviation or number (%)

* P-value represents significance of difference between hypertrophic cardiomyopathy patients and healthy controls.