T1 Mapping and Extracellular Volume in Cardiomyopathy Showing Left Ventricular Hypertrophy: Differentiation Between Hypertrophic Cardiomyopathy and Hypertensive Heart Disease

Critical Appraisal

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ORIGINAL RESEARCH

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- Original article
- Title clearly described the study

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- The authors are well written.
- The unit and institution involved are clearly written.
- Authors from relevant department (Collaboration of Department of Radiology and Heart Research Center)
- Single center study.

Abstract

Background: The aim of this study was to evaluate the capability of different magnetic resonance imaging (MRI) parameters for distinguishing between hypertrophic cardiomyopathy (HCM) and hypertensive heart disease (HHD).

Methods: Thirty-eight patients with HCM, 35 patients with HHD, and 29 healthy controls subjects were enrolled in this study. All subjects underwent cardiac MRI to measure T1 values and extracellular volume (ECV), as well as the extent and patterns of late gadolinium enhancement (LGE). Myocardial segments were categorized as non-hypertrophic, mild-hypertrophic, moderate-hypertrophic, and severe-hypertrophic based on end-diastolic wall thickness (EDWT). The differences in native T1 values between all four groups were evaluated.

- Objective of this study is straightforward.
- Sample size and study design are clearly stated.
- Study duration is not stated.

Results: Native T1 values were significantly higher in patients with HCM than in patients with HHD and in healthy controls (both $P < 0.001$). Moreover, significantly increased ECV was shown in patients with HCM than in patients with HHD and in healthy controls (both $P = 0.001$). Native T1 values in the basal slice and apex slice were significantly higher in patients with HCM than in patients with HHD ($P < 0.01$). In patients with HCM, the non-hypertrophic myocardial segments demonstrated significantly elevated T1 values compared with patients with HHD (both $P < 0.001$). Using a cut-off value of 28.8% for ECV, it could differentiate between HCM and HHD with 85% sensitivity, 62.07% specificity, and an area under the curve of 0.772.

Conclusion: In patients with HCM, T1 tissue remodeling occurs in the normal-appearing myocardial segments, but not in patients with HHD. Both native T1 values and ECV can support clinically relevant discrimination between HCM and HHD, although ECV had better diagnostic efficacy.

Keywords: extracellular volume, hypertrophic cardiomyopathy, magnetic resonance imaging, T1 mapping

- The conclusion clearly answers the question of interest.
- Keywords are clearly written.

Introduction

Address the problem encountered by radiologists and the rationale of the study

Introduction

Left ventricular hypertrophy (LVH) is a common clinical manifestation with many causes. It can be difficult to identify the etiology of diffuse LVH, and particularly to distinguish between hypertrophic cardiomyopathy (HCM) and hypertensive heart disease (HHD).

HCM is a relatively common genetic disorder that is most frequently characterized by asymmetric hypertrophy of the left ventricle (LV), the pathological basis of which is genetically driven hypertrophy of the cardiomyocytes.[1] HCM frequently has specific features, such as asymmetrical hypertrophy or other functional and morphological abnormalities (eg, dynamic LV outflow tract obstruction, elongated mitral valve leaflets, aberrant papillary muscle configuration, apical aneurysms, and myocardial crypts). Outflow tract obstruction is common in patients with HCM. Currently, the diagnosis of HCM is based on the finding of maximal LV wall thickness (LVWT) $\geq$ 15 mm in the absence of increased LV wall stress. Myocardial fibrosis in HCM is mainly manifested as collagen hyperplasia, disarray of fibers and fascicles, and myocardial cell disorder and necrosis.

LVH in HHD involves many mechanisms by which the heart may become abnormal due to hypertension; additionally, the LVH may be involved in the development of hypertension in the first place, as well as being a consequence of raised systemic pressure.[2,3] LVH caused by hypertension is an adaptive response of cardiomyocytes to long-term stress overload, which is manifested by cardiomyocyte hypertrophy and interstitial fibrosis.[4]

The background of 2 main pathologies (HCM and HHD) are clearly described.

The degree of myocardial fibrosis in HCM is significantly more serious than that associated with hypertension. The different histopathological mechanisms of LVH in HCM and HHD provide a theoretical basis for further distinction between the two causes of LVH. Late gadolinium enhancement (LGE) of cardiac magnetic resonance imaging (CMR) is currently recognized as the gold standard for noninvasive evaluation of localized myocardial fibrosis. However, LGE-CMR cannot quantitatively evaluate LVH and cannot effectively distinguish the diffuse type of LVH.

T1 mapping is a robust CMR technique capable of measuring T1 values in any region of the myocardium; then, the myocardial extracellular volume (ECV) fraction, which can quantitatively represent the degree of interstitial fibrosis, can be measured.[5,6]

Native T1 and ECV are complementary measures of different (but related) aspects of the myocardium, but it remains unclear which of these can effectively distinguish the etiology of the LVH.

Therefore, in this study, we evaluated the capability of magnetic resonance imaging (MRI) to differentiate between HCM and HHD as etiologies of LVH, based on detection of diffuse or regional fibrosis by T1 mapping and ECV.

- The concept of the role of T1 mapping and extracellular volume (ECV) in differentiating HCM and HHD is clearly described.
- Previous similar study on uses of T1 mapping and ECV is not stated.

Materials and Methods

Materials and Methods

Study Population

This retrospective study was performed at the Cardiology Department of Beijing Chaoyang Hospital, Capital Medical University, from January 2017 to November 2018. All individuals undergoing transthoracic echocardiogram evaluation for LVH in the hospital were enrolled. Subjects with any contraindication to CMR were ineligible. The patients who were diagnosed with HCM by the CMR exam were included in this study. The inclusion criteria were a maximal LVWT of ≥15 mm in adults without family history of HCM or ≥13 mm in adults with family history of HCM, and no other cardiac or systemic diseases that could result in similar LVH. Patients with LVWT <15mm but clear lack of apical tapering and high suspicion of apical HCM with family history were included into this study. The patients with HHD were undergoing treatment for primary hypertension (systolic blood pressure of >140 mmHg; diastolic blood pressure of >95 mmHg) and demonstrated LVH in the basal septal and inferolateral segments, defined as a maximal LVWT > 12 mm, with no evidence of a dilated LV cavity on transthoracic echocardiography. There were four exclusion criteria: 1) patients who underwent CMR scans without an extracellular contrast agent or who did not have hematocrit measured within 7 days of the CMR study, 2) patients with segments in the T1 mapping with poor motion correction, and 3) patients with acute heart failure. 4) patient that fulfilled HCM criteria were excluded if they also had arterial hypertension. Patients were compared with 29 healthy volunteers, with a similar age and gender distribution, who served as a healthy control group; they had no evidence of heart disease on physical examination, 12-lead electrocardiography, and echocardiography, and they were taking no medications. All subjects gave informed consent to participate in the study.

- The study design, study duration, inclusion and exclusion criteria are clearly stated.
- No specific sampling methods. All eligible patients are included.
- Small sample size. Total 102 patients (38 HCM, 35 HHD, 29 healthy controls).
- Patients with different cardiac function are included in this study. Those with end-stage HCM and low LVEF obviously have more extensive fibrosis as compared to the common phenotype of HCM, HHD or healthy controls.
- Method of diagnosis is clearly stated. However, the final diagnosis of HCM and HHD are made based on clinical history and transthoracic echocardiography finding of LVH. No endomyocardial biopsy is available as gold standard.

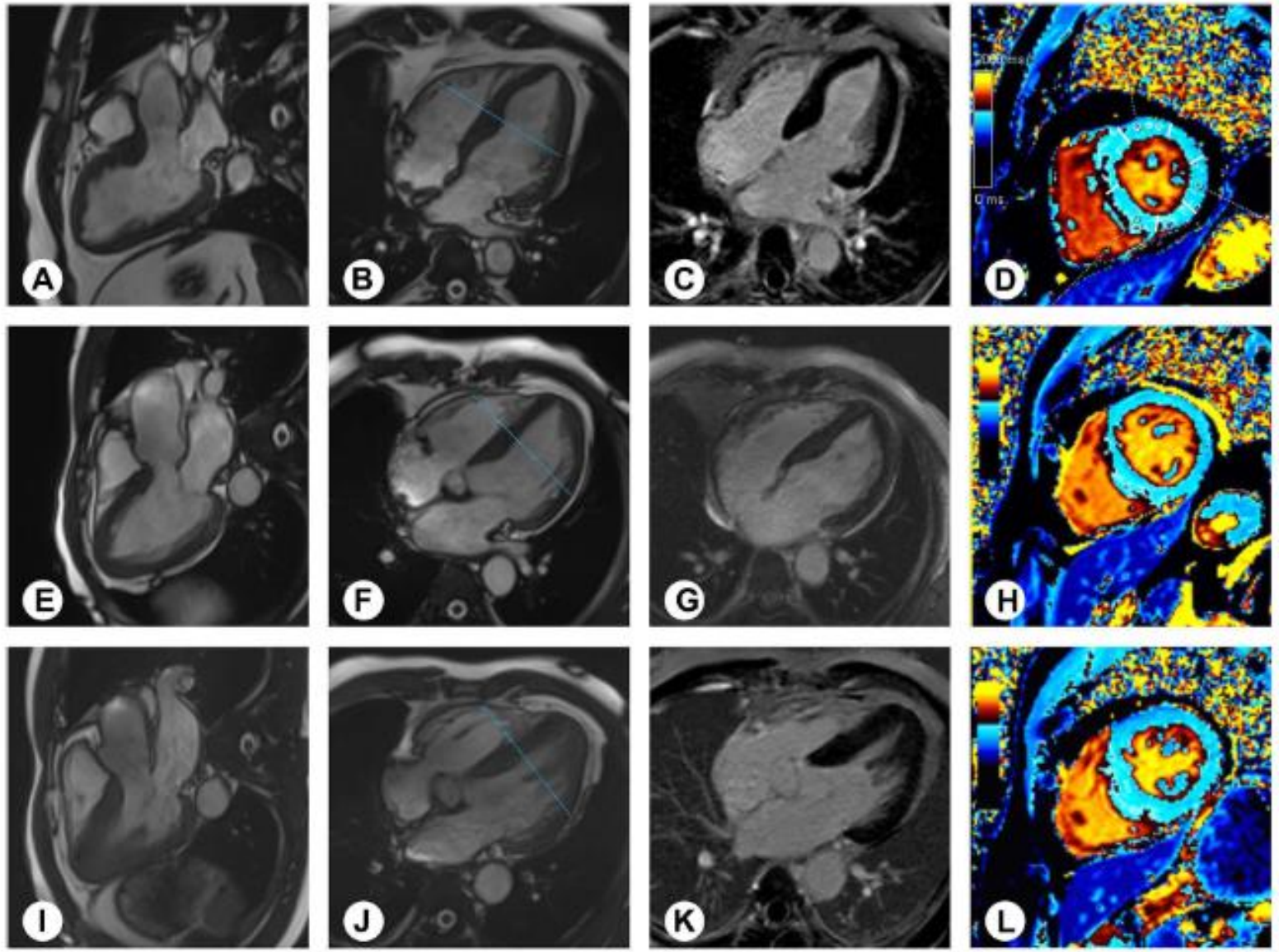


Figure 1 Images of a 47-year-old man with HHD (**A**–**D**). Images of a 59-year-old man with HCM (**E**–**H**), and follow-up after 3 year (**I**–**L**). Cine-magnetic resonance imaging in the three-chamber (**A** and **E**) and four-chamber (**B** and **F**) view showing similar looking hypertrophy of the interventricular septum in HHD and HCM, and the maximum septal wall thickness was 16 mm. And late gadolinium enhancement (**C** and **G**) was not found at the myocardium. At follow-up, theHCM myocardium became more hypertrophy, and clear lack of apical tapering. Native T1 maps in the LV center-chamber short-axis (**D, H, L**) showed with different average value: HHD=1195ms; HCM=1218ms; follow-up HCM=1285ms. Gray scale range: 0–2000 ms. The blue line in (**B, F, J**) represented the level at which the short axis mapping image is positioned on the long axis image.

Ethics Approval and Consent to Participate

The present study was performed in compliance with the principles outlined in the Declaration of Helsinki and was approved by both the Ethics Committee and the Prescription and Therapeutic Committee of Beijing Chaoyang Hospital, Capital Medical University (Beijing, China). All the patients provided written informed consent prior to enrollment.

- This study receives ethics approval from local ethics committee.

Cardiac MRI Acquisition

Cardiac MRI was performed at 3T scanner (Prisma, Siemens Healthcare, Erlangen, Germany) by using an anterior phased-array body coil (18-element) and a posterior phased-array spine coil (24-element) within 1 week of the patient undergoing transthoracic echocardiogram. A four-lead vectorcardiogram was used for cardiac gating. The breath-holding process was carefully explained to the subjects, and the abdominal belt was wrapped tightly.

Cardiac MRI Protocol

After acquisition of scout images, retrospective electrocardiographic gating cine imaging was performed using a segmented balanced steady-state free precession sequence in continuous short-axis views, spanning the entire LV from base to apex. The imaging parameters for cine images were as follows: repetition time (45.64 ms), echo time (1.43 ms), flip angle (80°), section thickness (8 mm), field-of-view (340 mm), matrix size (256 × 169), SENSE factor 2, and 25 cardiac phases/R–R interval on the electrocardiogram. After the acquisition of cine images, native T1 data were obtained from three short-axis images (basal, center, apical) of the LV using a modified look-locker inversion recovery (MOLLI) sequence. Imaging parameters were as follows: repetition time (315.96 ms), echo time (1.12 ms), flip angle (35°), section thickness (8 mm), field-of-view (360 mm), and matrix size (256 × 169). After native T1 mapping was obtained, gadolinium-based contrast medium (gadopentetate dimeglumine, Beilu Pharmaceutical, Beijing, China) was administered intravenously at 0.1 mmol/kg body weight. LGE images were obtained in short-axis locations from the base to the apex of the LV, by using a three-dimensional inversion recovery T1 turbo field-echo sequence, 10 minutes after contrast administration. The imaging parameters were as follows: repetition time (700 ms), echo time (1.96 ms), inversion time (300–500 ms) (adjusted to the null signal of the normal myocardium using the Look-Locker sequence), flip angle (20°), section thickness (8 mm), field-of-view (350 mm), matrix size (256 × 192), and SENSE factor 2. Fifteen minutes after contrast administration, post-contrast T1 data were obtained by using the same imaging sequence as for obtaining the native T1 data.

The cardiac MR image acquisition and protocol, including MRI machine, sequences, views and contrast agent are clearly stated.

Image Analysis

Image analysis was carried out by using dedicated cardiac MRI software (syngo.via, Siemens Healthcare) by one author of this paper (L.L, a radiologist with 4 years of MRI experience) and the findings were reviewed by another author (J.T., a radiologist with 30 years of MRI experience). LV borders were manually traced, and papillary muscles were excluded from determination of LV mass. Maximal end-diastolic wall thickness (EDWT) of the septum was manually measured by agreement between two radiologists with experience in the reading of CMR images. T1 maps were obtained using syngo.via. T1 values were quantified in 16 segments in each of the three LV slices (basal, center, and apical). Three regions of interest (ROI) were placed within each segment to avoid the signals from the blood pool and artifacts; these regions were placed independent of the results from LGE imaging.[7,8] The size of each ROI was completely consistent at approximately 0.1~0.2 cm^2, and at same 5 pixels were included Figure 1D. T1 values of the segment were calculated as the average of the three ROIs. T1 values of segments and slices and reproducibility were examined in all healthy controls.

The 16 American Heart Association (AHA) segments in the patients with HCM were classified into non-hypertrophic (EDWT < 15 mm) and hypertrophic (EDWT ≥ 15 mm) based on the maximal LV EDWT. The hypertrophic segments were further stratified as mild (15 mm ≤ EDWT < 20 mm), moderate (20 mm ≤ EDWT < 25 mm), and severe (EDWT ≥ 25 mm) according to the criteria used in previous studies.[9,10]

The average T1 values of the three LV slices (basal, center, apical) were used to compare the HCM, HHD, and healthy controls (Figure 2). The mean T1 of the combined 16 LV segments was used to determine global T1. The average T1 values of non-hypertrophic, mild and moderate hypertrophic myocardial segments were used to compare the HCM and HHD groups.

In addition to the native T1, the hematocrit-corrected ECV fraction—a marker of extracellular contrast agent accumulation—was also calculated.[11,12] Estimation of the ECV (interstitium and extracellular matrix) requires measurement of myocardial and blood T1 before and after administration of contrast agents as well as the patient's hematocrit value according to the formula:

$$ECV = (1 - haematocrt)\frac{1/T1_{myocardial\,post} - 1/T1_{myocardial\,pre}}{1/T1_{blood\,post} - 1/T1_{blood\,pre}}$$

LGE imaging was evaluated by agreement between two radiologists experienced in the reading of CMR. A segment with LGE was defined as the presence of visually identified LGE. Evaluation of LGE was performed independent of the evaluation of T1 values.

The steps involved in image analysis are clearly stated, including the measurement of T1 value and calculation of ECV using formula.

Images are interpretated by 2 experienced radiologists.

Statistical Analysis

The mean and standard deviation were recorded for continuous variables, and frequency and percentage were recorded for categorical variables. For each variable, a normality test was performed. Continuous variables were compared using the *t*-test or the nonparametric Mann–Whitney *U*-test, as appropriate. For analysis of values, receiver operating characteristic (ROC) curves were generated and the areas under the curves (AUCs) were calculated and compared using the method of Hanley and McNeil for comparison at a single time-point. The ROC characteristics of native T1 and ECV were compared for basal, center, apex and mean native T1 and ECV, and then diagnostic values of the parameters were confirmed. Two-tailed P values <0.05 were considered statistically significant. All statistical analyses were performed in SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

- The statistical analysis is clearly explained.

Results

Table 1 Baseline Characteristics of Healthy Controls, HHD, and HCM Patients

	Normal (n=29)	HHD (n=35)	HCM (n=38)	P
Age, y	42.9±19.5	48.5±16.3	52.1±13.9	0.085
Male, %(n)	41.4(12)	88.6(31)	65.8(25)	<0.001
Heart rate, bpm	69.7±24.1	90.5±16.6#	71.7±13.4*	<0.001
Systolic BP, mmHg	129.7±14.2	149.2±24.3#	131.2±16.4*	<0.01
Diastolic BP, mmHg	72.4±18.3	88.9±20.7#	76.6±12.0*	<0.01
Smokers, %(n)	23.8(5)	50(15)	34.8(8)	0.155
Diabetes, %(n)	6.9(2)	11.4(4)	21.1(8)	0.221
Hematocrit, L/L	40.1±3.1	42.9±4.5#	40.9±4.5	0.037
LVEF, %	67.9±9.7	57.7±17.8	68.3±9.8	0.003
LVEDV mL	46.2±6.6	52.9±10.3#	45.5±4.5*	<0.01
LVESV, mL	26.6 ± 6.4	36.6±12.2#	26.6±6.4*	<0.001
NT-proBNP, mmol/L	45.7±63.1	1787.5±2364.9#	995.3±1209.0§	<0.001
Outflow tract obstruction, %(n)	0(0)	0(0)	50(18)	<0.001

Notes: Values are the mean ± SD. *P < 0.05 HHD vs HCM; #P < 0.05 HHD vs control; §P < 0.05 HCM vs control.

Abbreviations: HHD, hypertensive heart disease; HCM, hypertrophic cardiomyopathy; BP, blood pressure; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

- The statistical results of the study for each group (healthy control, HHD and HCM) are well tabulated.
- The p-value for each variable is included to demonstrate the statistical significance.

Table 2 Functional Measures Based on Cardiovascular Magnetic Resonance Imaging Measurements

	Control (N = 29)	HHD (N = 35)	HCM (N = 38)	*P*
LGE				
Present, % (n)	0 (0)	34.6 (9)	84.8 (28)	0.001
RV insertion points, % (n)	0 (0)	7.7 (2)	21.2 (7)	0.02
T1 mapping				
Basal native T1 (ms)	1229.3 ± 47.1	1257.1 ± 85.0	1291.5 ± 53.6*§	0.001
Central native T1 (ms)	1228.4 ± 42.7	1277.8 ± 70.5#	1290.0 ± 64.3§	<0.001
Apex native T1 (ms)	1250.6 ± 61.2	1258.2 ± 66.8	1299.5 ± 65.7*§	0.005
Native T1 (ms)	1236.1 ± 42.6	1264.3 ± 67.7	1293.6 ± 53.8*§	<0.001
ECV (%)	26.8 ± 5.8	27.1 ± 6.7	34.9 ± 9.8*§	0.001
Outflow tract obstruction, % (n)	0 (0)	0 (0)	50 (18)	

Notes: Values are mean ± SD. *P < 0.05 HHD vs HCM; # P < 0.05 HHD vs control; §P < 0.05 HCM vs control.

Abbreviations: HHD, hypertensive heart disease; HCM, hypertrophic cardiomyopathy; ECV, extracellular volume; LGE, late gadolinium enhancement; RV, right ventricular.

- The late gadolinium enhancement (LGE), T1 values and extracellular volume (ECV) between each group is compared and clearly stated.
- Answers the objectives of this study.

Table 3 Native T1 Values in Different Degrees Hypertrophic Myocardial Segments of HCM and HHD Patients

Parameters		No-Hypertrophic Segment	Mild Hypertrophic Segment	Moderate Hypertrophic Segment	Severe Hypertrophic Segment
HCM	N	474	96	21	17
	Native T1 (ms)	1287.32±85.41	1310.80±67.38	1339.44±101.39	1394.55±66.99
HHD	N	518	37	6	0
	Native T1 (ms)	1269.04±86.88	1291.62±92.04	1345.18±66.99	–
P value		0.000	0.644	0.900	–

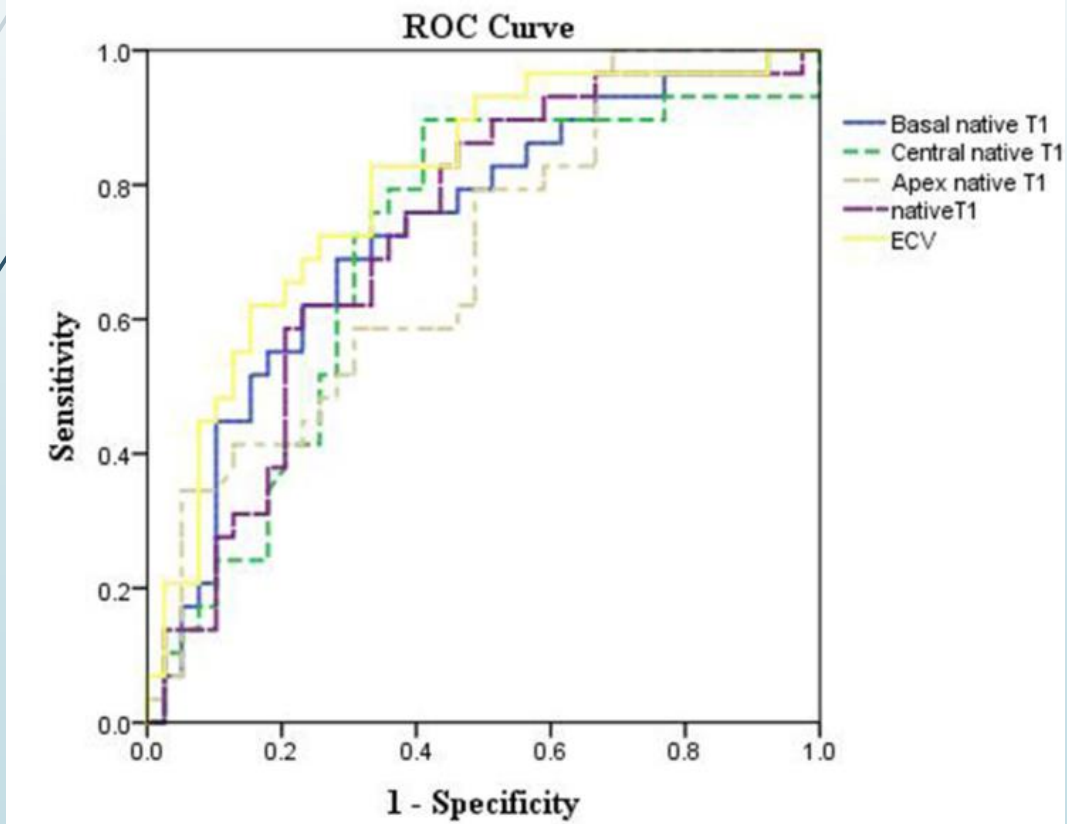
Notes: Continuous variables are expressed as mean ± standard deviation; P value: statistical significance between HCM and HHD segments using Mann–Whitney *U*-test.
Abbreviation: N, number.

- Native T1 values in different degree of hypertrophic myocardial segments are compared.

Table 4 Cut-off Values from Receiver-Operating Characteristic Curve Analysis

Parameter	Cut-Off Value	AUC (95% CI)	P value	Specificity (%) (95% CI)	Sensitivity (%) (95% CI)
Basal native T1	1282	0.733 (0.612–0.854)	0.001	63.16 (46.0–78.2)	89.66 (72.6–97.8)
Central native T1	1236	0.704 (0.575–0.834)	0.004	86.84 (71.9–95.6)	72.41 (52.8–87.3)
Apex native T1	1267	0.693 (0.568–0.818)	0.007	65.79 (48.6–80.4)	75.86 (56.5–89.7)
Mean native T1	1282	0.726 (0.604–0.848)	P <0.001	63.16 (46.0–78.2)	89.66 (72.6–97.8)
ECV	28.8	0.772 (0.689–0.904)	0.000	85.00 (59.0–91.7)	62.07 (43.4–87.4)

Abbreviations: AUC, area under the curve; CI, confidence interval; ECV, extracellular volume.



- The cut-off values for each parameter are derived from ROC curve analysis, which is important for application in daily MRI reporting or future research study.

Discussion

Discussion

LVH has long been recognized as an important clinical prognostic entity, as it is associated with increased morbidity and mortality related to myocardial infarction, heart failure, and stroke. There is a continuous graded relationship between LV mass (reflecting LVH) and the development of cardiovascular disease, with no distinct threshold separating the postulated "compensatory" LVH from "pathological" LVH.[13] Difficulties in discrimination of hypertrophic etiologies interfere with appropriate diagnosis, risk assessment, and clinical management. The differential diagnosis of LVH related to HCM and HHD, in particular, remains challenging in clinical practice. The complex underlying histopathology[14] and the consequent functional changes in HCM result in various myocardial abnormalities, including replacement fibrosis, reduced ventricular deformation, and increased diastolic stiffness.[15,16] Diffuse myocardial disease is a characteristic feature of both HCM and HHD, exacerbating the diagnostic dilemma. Thus, we evaluated whether T1 mapping and ECV on cardiac MRI could distinguish between LVH related to HCM and HHD. We found that both T1 mapping and ECV were able to distinguish between these etiologies, with ECV providing the greatest diagnostic accuracy.

- The challenges faced by radiologists and the role of the result in this study to overcome the challenges are well explained.

According to our study, basal native T1, center native T1, apex native T1, and mean ECV had certain diagnostic efficacy for distinguishing LVH etiology, among which ECV demonstrated the best diagnostic efficacy. One of the reasons for this result was that the pathology is different in HHD and HCM. Cardiac myocytes of the LV are enlarged in HHD,[25] and fibrosis is another feature of the adverse structural remodeling found in the myocardium in HHD.[26] On the other hand, HCM is fundamentally a cardiomyocyte disease (sarcomere protein mutations), and myocardial fibrosis characterized by disproportionate collagen accumulation is a key pathogenic process.[27] Nevertheless, This was a significant share of HHD and HCM patients demonstrated average T1/ECV results that would be within 2SD of the mean of healthy volunteers (considered normal range). As such, one who had the relevant clinical history, myocardial thickness and LGE extent would need to diagnose abnormality although the range is considered normal.

Native T1 is decreased in some diseases (fat infiltration and iron overload) and is increased in others (fibrosis, edema, and amyloidosis). In myocardial fibrosis, the native T1 elevation likely arises from the interstitial compartment, rather than from the cardiomyocyte compartment, but this is not clear. In contrast to native T1, ECV exploits the extracellular nature of gadolinium contrast agents. The concentration of contrast in the myocardium relative to the concentration in plasma (not in whole blood) provides a direct measure of the interstitial space after equilibration, as long as contrast agents are not protein-bound. Because the ECV and the partition coefficient are ratios, some systematic T1 biases may be canceled out. For these reasons, ECV had the best diagnostic efficacy for diagnosing LVH.

- The pathogenesis lead to increased T1 value and ECV in HHD and HCM patients are well explained.
- Other factors or condition which can affect T1 value and ECV are also described.

- There are several previous research done on the similar topics and objectives, which were never mentioned in the discussion.
- The limitation of the previous study and how the current study can overcome these limitations were not addressed.

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RESEARCH Open Access

Cardiac MRI T1 mapping and extracellular volume application in hypertrophic cardiomyopathy

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Abstract

Background: Hypertrophic cardiomyopathy (HCM) is one of the commonest inheritable cardiac disorders. Being a global disease with diffuse myocardial fibrosis, it has a wide range of adverse outcomes ending with sudden cardiac death. Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) has become a reference standard for visualization of focal myocardial fibrosis. In the setting of less severe or more diffuse fibrosis, LGE is unlikely to reveal the presence of abnormal tissue given the lack of normal myocardium as a reference. Direct measurement of myocardial T1 time (T1 mapping) may improve these methodologic problems of LGE CMR in the setting of diffuse retention of gadolinium-based contrast material. So, we aim at this study to evaluate the clinical application of CMRI native and post-contrast T1 relaxation in assessing diffuse myocardial fibrosis non-invasively in hypertrophic cardiomyopathy.

Results: There was a significant difference between the percent of fibrosis detected by measuring the extracellular volume percent compared to that detected by LGE, with the former detecting fibrosis in 45.1% of the examined cardiac segments while the latter showed fibrosis in 20.9% of the cardiac segments. Also, measuring the native T1 values showed evidence of fibrosis in about 32.2% of the cardiac segments superseding the percent of fibrosis detected using the LGE alone. The ejection fraction percent showed a negative correlation with the left ventricular mass with a correlation coefficient value of – 0.139 where both interstitial and replacement fibrosis play an important role in the pathophysiology of diastolic dysfunction as well as impairing the myocardial contractility. Also, in cases of obstruction, the extracellular volume (ECV) is more likely to increase in the basal anterior and antero-septal segments as well as the basal inferior segment with *P* values 0.015, 0.013, and 0.045, respectively.

Conclusion: Diffuse fibrosis was found to be difficult to be distinguished using LGE. The unique ability of CMR to use proton relaxation times provides a quantitative measurement to detect increased interstitial volume in diffuse myocardial fibrosis. Moreover, it showed that in cases of obstruction, the segments exposed to the highest pressure are more vulnerable to the fibrotic process denoting a relationship between the pressure gradient and the adverse myocardial remodeling.

Keywords: T1 mapping, ECV (extracellular volume), HCM (hypertrophic cardiomyopathy), Myocardial fibrosis

Assessing Myocardial Extracellular Volume by T1 Mapping to Distinguish Hypertrophic Cardiomyopathy From Athlete's Heart

Athletes who train regularly can develop left ventricular (LV) hypertrophy, which can be difficult to differentiate from hypertrophic cardiomyopathy (HCM), the leading cause of sudden cardiac death in young athletes. Current guidelines advise that patients with HCM should avoid competitive sport, and it is therefore imperative that HCM and physiological remodeling are correctly identified. Cardiovascular magnetic resonance (CMR) T1 and extracellular volume (ECV) mapping provide quantitative assessment of myocardial composition. We hypothesized that ECV could differentiate athletic from pathological hypertrophy, particularly in subjects with indeterminate maximum wall thickness, defined as 12 to 15 mm (1).

Fifty HCM patients, 40 athletes and 35 sedentary volunteers, underwent 3.0-T CMR including 5 beats (3 seconds) 3 beats Modified Look-Locker Inversion (MOLLI) T1 maps before and 15 min after administration of 0.15 mmol/kg intravenous gadobutrol. HCM was diagnosed independently according to current guidelines (1). The 40 competitive athletes (11 runners, 13 triathletes, and 16 cyclists) trained >6 h per week, had mean maximal oxygen consumption (Vo_2 max) concentration of 58.3 ± 9.0 ml/min/kg and were <45 years of age. Sedentary volunteers exercised <3 h per week. The study was approved by the local ethics committee (14/YH/0126).

Analysis was carried out using cvi42 software (Circle CVI, Calgary, Canada). Maximum wall thickness was measured from diastolic short-axis cine images, and native T1 and ECV were measured in the thickest segment. ECV was calculated from hematocrit, native, and post-contrast T1 times of myocardium and blood pool (2). A Mann-Whitney *U* test was used to compare athletes and HCM subjects. Receiver operating characteristic analysis was used to determine the diagnostic accuracies (SPSS version 20.00 software; IBM Corp., Armonk, New York).

Both native T1 and ECV of the thickest segment were lower in athletes than HCM (1182.7 ± 42.4 ms vs. 1261.0 ± 66.0 ms and 22.7 ± 3.3% vs. 32.3 ± 7.9% of subjects, respectively; $p < 0.001$ for both). Two athletes (5%) had subepicardial lateral late gadolinium enhancement (LGE) in a myocarditis pattern, no controls had LGE, and 35 HCM subjects (70%) had LGE.

ECV of the thickest segment was significantly lower in athletes than in controls (22.7 ± 3.3% vs. 24.3 ± 2.6%, respectively; $p = 0.006$). Differences between native T1 in athletes and that in controls did not reach statistical significance ($p = 0.18$).

In athletes, there were significant negative correlations between ECV and maximum segment thickness ($R = -0.40$; $p = 0.01$) and LV mass ($R = -0.37$; $p = 0.02$) (Figure 1). In controls there were also significant negative correlations between ECV and maximum segment thickness ($R = -0.45$; $p < 0.01$), and LV mass ($R = -0.42$; $p = 0.01$). In HCM subjects there was a significant positive correlation between ECV and maximum segment thickness (Spearman's rank [R_s] = 0.43; $p = 0.002$) but not LV mass ($p = 0.33$). For athletes, controls, and HCM subjects there were no significant correlations among native T1 and maximum segment thickness or LV mass.

To detect the 50 cases of HCM from the 40 athletes, the diagnostic accuracy (area under the curve [AUC]) of maximal segment thickness, native T1, and ECV were 0.986 (95% confidence interval [CI]: 0.935 to 0.999), 0.847 (95% CI: 0.756 to 0.914), and 0.936 (95% CI: 0.864 to 0.977), respectively ($p < 0.001$ for all). There were no significant differences between AUCs. The AUC of LGE to diagnose HCM correctly was 0.825 (range: 0.731 to 0.897; $p < 0.001$; sensitivity: 70%; specificity: 83%). The AUC of ECV was superior to that of LGE ($p = 0.004$), although the differences between native T1 and LGE were nonsignificant ($p = 0.66$).

In 26 subjects (10 athlete and 16 HCM subjects), the maximum segment thickness fell in the intermediate range of 12 to 15 mm. In these subjects, native T1 in the thickest segment was 1170.6 ± 34.8 ms in athletes versus 1251.9 ± 47.2 ms in HCM subjects ($p < 0.001$)

ORIGINAL ARTICLE

Myocardial Extracellular Volume Fraction Adds Prognostic Information Beyond Myocardial Replacement Fibrosis

See Editorial by Cheng and Masri

BACKGROUND: Cardiac magnetic resonance techniques permit quantification of the myocardial extracellular volume fraction (ECV), representing a surrogate marker of reactive interstitial fibrosis, and late gadolinium enhancement (LGE), representing replacement fibrosis or scar. ECV and LGE have been independently linked with heart failure (HF) events. In deriving ECV, coronary artery disease type LGE, but not non-coronary artery disease type LGE, has been consistently excluded. We examined the associations between LGE, global ECV derived from myocardial tissue segments free of any detectable scar, and subsequent HF events.

METHODS: Mid short-axis T1 maps were divided into 6 cardiac segments, each classified as LGE absent or present. Global ECV was derived from only segments without LGE. ECV was considered elevated if >30%, the upper 95% bounds of a reference group without known cardiac disease (n=28). Patients were divided into 4 groups by presence of elevated ECV and of any LGE. Subsequent HF hospitalization and any death were ascertained. Their relationship with ECV was examined separately and as a composite with Cox proportional hazard models.

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RESULTS: Of 1604 serial patients with T1 maps, 1255 were eligible after exclusions and followed over a median 26.3 (interquartile range, 15.9–37.5) months. Patients with elevated ECV had increased risk for death (hazard ratio [HR] 2.45 [95% CI, 1.76–3.41]), HF hospitalization (HR, 2.45 [95% CI, 1.77–3.40]), and a combined end point of both outcomes (HR, 2.46 [95% CI, 1.94–3.14]). After adjustments for covariates including LGE, the relationship persisted for death (HR, 1.82 [95% CI, 1.28–2.59]), hospitalization (HR, 1.60 [95% CI, 1.12–2.27]), and combined end points (HR, 1.73 [95% CI, 1.34–2.24]).

CONCLUSIONS: ECV measures of diffuse myocardial fibrosis were associated with HF outcomes, despite exclusion of replacement fibrosis segments from their derivation and even among patients without any scar. ECV may have a synergistic role with LGE in HF risk assessment.

Key Words: epidemiology ■ extracellular matrix ■ extracellular space ■ fibrosis ■ gadolinium ■ magnetic resonance imaging ■ myocardium

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CLINICAL RESEARCH
Imaging

Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology

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Aims Conventional late gadolinium enhancement (LGE) cardiac magnetic resonance can detect myocardial infarction and some forms of non-ischaemic myocardial fibrosis. However, quantitative imaging of extracellular volume fraction (ECV) may be able to detect subtle abnormalities such as diffuse fibrosis or post-infarct remodelling of remote myocardium. The aims were (1) to measure ECV in myocardial infarction and non-ischaemic myocardial fibrosis, (2) to determine whether ECV varies with age, and (3) to detect sub-clinical abnormalities in 'normal appearing' myocardium remote from regions of infarction.

Methods and results Cardiac magnetic resonance ECV imaging was performed in 126 patients with T1 mapping before and after injection of gadolinium contrast. Conventional LGE images were acquired for the left ventricle. In patients with a prior myocardial infarction, the infarct region had an ECV of 51 $\pm$ 8% which did not overlap with the remote 'normal appearing' myocardium that had an ECV of 27 $\pm$ 3% ($P < 0.001$, $n = 36$). In patients with non-ischaemic cardiomyopathy, the ECV of atypical LGE was 37 $\pm$ 6%, whereas the 'normal appearing' myocardium had an ECV of 26 $\pm$ 3% ($P < 0.001$, $n = 30$). The ECV of 'normal appearing' myocardium increased with age ($r = 0.28$, $P = 0.01$, $n = 60$). The ECV of 'normal appearing' myocardium remote from myocardial infarctions increased as left ventricular ejection fraction decreased ($r = -0.50$, $P = 0.02$).

Conclusion Extracellular volume fraction imaging can quantitatively characterize myocardial infarction, atypical diffuse fibrosis, and subtle myocardial abnormalities not clinically apparent on LGE images. Taken within the context of prior literature, these subtle ECV abnormalities are consistent with diffuse fibrosis related to age and changes remote from infarction.

Keywords Magnetic resonance imaging • Myocardial infarction • Fibrosis • Aging • Gadolinium

Conclusion

- Overall, this is a good study.
- Strength:
  - Good healthy control study
  - Results and conclusion answer the research question.
  - The T1 values in different degree of myocardial hypertrophy are compared.
  - Provides cut-off value of T1 and ECV for use in clinical practice and future study.

- Limitations:
  - Unblinded study
  - Single center study with small sample size
  - Inclusion of patients with varying LVEF and degree of myocardial fibrosis, which can affect the result of the study
  - The possible association with other factors which can affect T1 value or ECV (fat infiltration, iron overload, ischemic fibrosis, amyloidosis) are not addressed and these patients are not excluded from the study
  - No endomyocardial biopsy is available as gold standard of diagnosis

Suggestions

- The interpretating radiologists should be blinded on the patient's clinical history and diagnosis.
- This is a retrospective study. The study duration should be extended to include a larger sample size.
- Future study should address other possible causes which may affect the result of the study.
- To include biopsy as gold standard.

Potentially can be practiced in our department, because:-

- No additional sequence or scanning time
- No additional cost to patients
- Availability of software (Philips IntelliSpace Portal) for T1 mapping and ECV calculation.
- The techniques are easily to be learnt and applied.

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Thank
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