Clinical Radiology 74 (2019) 732.e9–732.e16

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Myocardial extracellular volume fraction measurements with MOLLI 5(3)3 by cardiovascular MRI for the discrimination of healthy volunteers from dilated and hypertrophic cardiomyopathy patients

Y. Cui [a,b,1], Y. Chen [a,b,1], Y. Cao [a,b], J. Liu [a,b], J. Song [a,b], S. Zhang [a,b], X. Kong [a,b], P. Han [a,b,**], H. Shi [a,b,*]

[a] *Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China*

[b] *Hubei Province Key Laboratory of Molecular Imaging, Wuhan 430022, China*

ARTICLE INFORMATION

Article history:
Received 10 July 2018
Accepted 18 April 2019

AIM: To investigate the diagnostic performance of myocardial native T1 time and the extracellular volume fraction (ECV) for differentiating dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) patients from healthy volunteers.

MATERIALS AND METHODS: Forty healthy volunteers, 57 DCM patients, and 30 HCM patients were enrolled, all of whom underwent cardiovascular magnetic resonance imaging (CMRI), including late gadolinium enhancement (LGE) and native and post-contrast T1 mapping acquired with the modified Look–Locker inversion recovery (MOLLI) sequence on a 1.5 T MRI system. ECV were calculated by native and post-contrast T1 times. Multivariate binary logistic regression analyses and receiver operating characteristic (ROC) curve analyses were used to assess the concordance with the clinical diagnosis of DCM and HCM.

RESULTS: DCM and HCM patients had significantly higher myocardial native T1 times and ECVs than healthy volunteers ($p<0.001$). Multivariate logistic regression analyses showed that ECV was an independent predictor of DCM and HCM diagnosis (OR=1.556, $p<0.001$ and OR=1.847, $p=0.001$, respectively). ROC curve analysis indicated that ECV provided greater distinction between DCM patients and healthy volunteers than native T1 time (AUC: 0.889 versus 0.780, $p=0.021$). At the optimal cut-off value, ECV identified DCM and HCM patients with 80.7% and 83.3% sensitivity, 87.5% and 70% specificity, 90.2% and 67.6% positive predictive value, and 76.1% and 84.8% negative predictive value, respectively.

* Guarantor and correspondent: H. Shi, Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 JieFang Avenue, Wuhan 430022, China. Tel.: +86 13871089008; fax: +86 02785727001.

** Guarantor and correspondent: P. Han, Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 JieFang Avenue, Wuhan 430022, China. Tel.: +86 13707170023; fax: +86 02785726020.

E-mail addresses: cjr.hanping@vip.163.com (P. Han), heshuishi@hust.edu.cn (H. Shi).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.crad.2019.04.019

CONCLUSION: The increased ECV in DCM and HCM patients reflects myocardial extracellular matrix expansion. Myocardial ECV provides good diagnostic performance for identifying DCM and HCM patients from healthy volunteers.

Introduction

Cardiomyopathies comprise a heterogeneous group of diseases with myocardial disorders that are linked to cardiac structural and functional abnormalities, often resulting in sudden cardiac death or progressive heart failure.[1–4] It has been reported that dilated cardiomyopathy (DCM) is the third most common cause of heart failure and hypertrophic cardiomyopathy (HCM) is the most common cause of sudden cardiac death among the young population.[1] Although the pathogenesis underlying DCM and HCM are highly complex and diverse, they share common features including compromised cell populations with consequent cell death and ultimately myocardial fibrosis.[3] Myocardial fibrosis may result in myocardial stiffness and dysfunction, ultimately leading to the progression of heart failure and adverse clinical outcomes.[5] Therefore, detecting and quantifying myocardial fibrosis may improve risk stratification and contribute to clinical therapies and prognostic stratification for cardiomyopathy patients.

Cardiovascular magnetic resonance imaging (CMRI) is becoming increasingly used to diagnose cardiomyopathy by assessing cardiac morphology and function and characterising cardiac tissue. Late gadolinium enhancement (LGE) CMRI is widely used to detect focal myocardial fibrosis; however, in DCM and HCM patients, the adverse tissue remodelling that occurs during diffuse myocardial fibrosis is difficult to accurately detect using LGE due to a lack of normal myocardium as a reference sample.

CMRI T1 mapping has emerged as a non-invasive alternative for quantifying diffuse myocardial fibrosis and has been validated by histology in a variety of heart diseases.[6–11] Although the CMRI native T1 time and ECV is increased in multiple cardiac pathologies, the optimal threshold for separating DCM and HCM patients from healthy volunteers has not been discussed systematically. The aim of this study was to assess the diagnostic performance of myocardial native T1 time and the ECV for discriminating healthy volunteers from individuals with diffuse myocardial diseases.

Materials and methods

Study participants

A total of 127 participants including 40 healthy volunteers, 57 DCM patients, and 30 HCM patients who underwent CMRI examination were enrolled in the present study. Forty healthy volunteers who responded to advertisements were recruited to serve as the control group. The participants had no systemic diseases, history of cardiovascular disease, hypertension, diabetes mellitus, or family history of cardiomyopathy, and they had a normal electrocardiogram and CMRI findings without LGE. DCM was diagnosed based on the presence of left ventricular (LV) dilatation and systolic dysfunction in the absence of coronary artery disease and abnormal loading conditions.[12] HCM was defined as LV hypertrophy without dilated ventricular chambers in the absence of systemic disease or cardiac disease accounting for a similar degree of hypertrophy.[1,13] HCM was diagnosed based on a LV wall thickness $\geq$15 or $\geq$13–14 mm with a family history of HCM according to echocardiography.[13] All patients with significant coronary artery disease were excluded by invasive or computed tomography (CT) coronary angiography. Additionally, patients who had a transmural or subendocardial LGE pattern indicating ischaemic cardiomyopathy were also excluded. The exclusion criteria for all participants were renal insufficiency with an enhanced glomerular filtration rate (eGFR) $<$30 ml/min/1.73 m^2 and contraindications to CMRI (severe claustrophobia, implantable device, and cochlear implants). This study was approved by the Ethics Committee. Written informed consent was obtained from all participants.

CMRI protocol

All participants underwent a standard CMRI examination using a 1.5 T machine (MAGNETOM Aera, Siemens Healthcare, Erlangen, Germany) with a phased-array 18-channel receiver coil. Cine images were acquired using a balanced steady state free precession (bSSFP) sequence to obtain a stack of short-axis sections covering the whole LV and three long-axis sections including two, three, and four chambers. The cine image parameters were 6 mm slice thickness, 2.9 ms repetition time (TR), 1.2 ms echo time (TE), 360$\times$270 mm^2 field of view, 256$\times$205 matrix, 80° flip angle. Native T1 mapping was performed in a single mid-ventricular short-axis section using a modified Look–Locker inversion recovery (MOLLI) sequence with a 5(3)3 sampling scheme. A motion-correction algorithm was used to correct cardiac and breathing motion artefacts. The T1 mapping parameters were as follows: 8 mm slice thickness, 3.8 ms TR, 1.1 ms TE, 360$\times$360 mm^2 field of view, 1.3$\times$1.3$\times$8 mm^3 voxel size, 144$\times$256 matrix, and 35° fiip angle. LGE imaging was performed 10 minutes after intravenous injection of a bolus of 0.2 mmol/kg gadopentetate dimeglumine (Magnevist, Bayer Healthcare, Germany) using a phase-sensitive inversion recovery (PSIR) sequence covering the entire LV short-axis sections. The LGE imaging parameters were as follows:

8 mm slice thickness, 12.4 ms TR, 1.2 ms TE, 360×270 mm2 field of view, 256×192 matrix, and 40° flip angle. Post-contrast T1 mapping of the short-axis sections identical to the native T1 maps were obtained 15 minutes after administration of gadopentetate contrast agent. The imaging parameters were the same as those used in the native T1 time. The haematocrit was determined by a blood sample analysis before CMRI. The ECV maps were automatically calculated using a prototype inline processing function from Siemens with the following equation:[14]

$$ECV=(1-\text{haematocrit})\times(\triangle R1_{myocardium}/\triangle R1_{blood}).$$

CMRI image analysis

All images were transferred to a dedicated workstation for further analysis with commercial software (Argus, Siemens Healthcare, Erlangen, Germany). The cardiac functional and volumetric parameters were calculated by manual delineation of the epicardial and endocardial borders with a stack of continuous short-axis section cine images after excluding papillary muscles from the myocardium. All the volumetric parameters were normalised to body surface area (BSA). The parameters included the LV ejection fraction (EF), end-diastolic volume index (EDVI), end-systolic volume index (ESVI), systolic volume index (SVI), cardiac index, and myocardial mass index.

The LGE image was identified as the image with a signal intensity 4 standard deviations (SDs) above the mean signal intensity of the remote non-enhanced myocardium.[15] The LGE images were evaluated by two experienced readers blinded to the results of the T1 and ECV measurements.

The myocardial native T1 time and ECV were measured by drawing regions of interest (ROIs) conservatively within the septal myocardium of the mid-ventricular section after excluding areas with LGE.[16] ROIs for all participants were drawn in the mid-wall region of the myocardium to minimise partial volume effects at the epicardial and endocardial borders. Then, the T1 time and ECV were displayed automatically on the maps. Segments with any artefacts were eliminated, which were assessed by two experienced readers, and disagreements were resolved by consensus with a third reader. Fig 1 shows T1 and ECV maps for the controls and DCM and HCM patients.

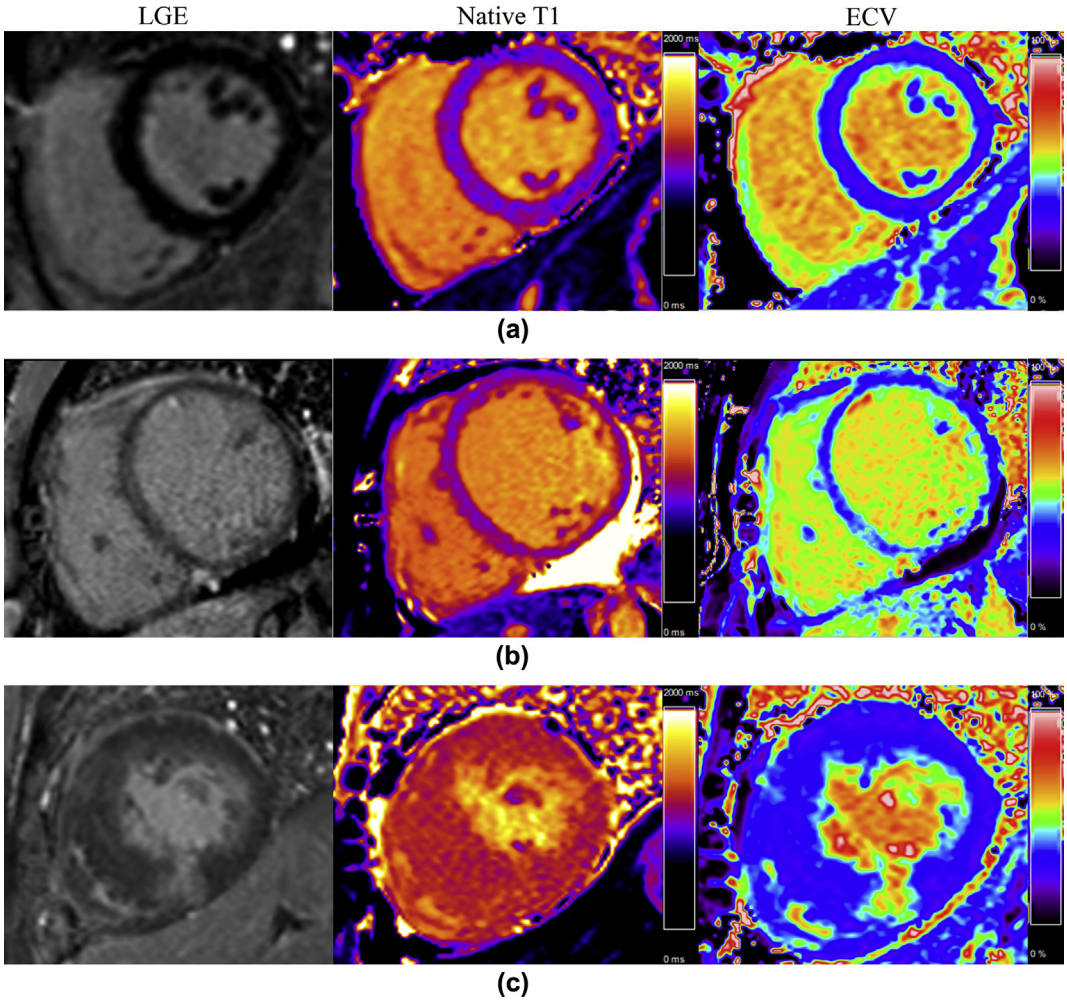

Figure 1 Examples of showing the native T1 time and ECV in a healthy volunteer (a), a DCM patient (b), and a HCM patient (c). Focal areas of LGE were observed in the inferior septum of the DCM patient and in the lateral septum of the HCM patient. The native T1 time and ECV were increased in the DCM and HCM patients.

Statistical analysis

All data were tested for normality using the Kolmogorov–Smirnov test. Continuous variables are expressed as the mean±SD, and categorical variables as percentages or frequencies. Comparisons between multiple groups were performed using one-way ANOVA or the Kruskal–Wallis test with Bonferroni correction as a post hoc test, as appropriate. Multivariate binary logistic regression analysis with a forward stepwise algorithm was applied to evaluate independent predictors of HCM or DCM patients. ROC curve analysis was used to assess the diagnostic performance of native T1 time and ECV for detection of DCM and HCM. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed and described with the corresponding 95% confidence intervals (CI). Intra- and interobserver variability of native T1 times and ECV were assessed using the intraclass correlation coefficient (ICC) and the Bland–Altman test. Statistical analyses were performed with IBM SPSS Statistics 19 (IBM, Armonk, NY, USA), MedCalc 16.2.0 (MedCalc Software, Mariakerke, Belgium), and GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA). A two-sided *p*-value of <0.05 was considered statistically significant for all tests.

Results

Patient characteristics

The clinical characteristics of the study population are provided in Table 1. No significant differences in age, sex, height, weight, body mass index (BMI), BSA, and haematocrit were observed between the healthy volunteers and the HCM or DCM patients. The heart rate of the DCM patients was significantly greater than the heart rates of the healthy volunteers and the HCM patients ($p<0.001$ and $p=0.007$, respectively). The percentages of diabetes mellitus, hypertension, family history of cardiomyopathy, and New York Heart Association (NYHA) functional class of the DCM and HCM patients are shown in Table 1. The average symptom duration was 3.6 years for the DCM patients and 4.4 years for the HCM patients. N-terminal pro-brain natriuretic peptide (NT-proBNP) was increased in both the DCM and HCM patients.

Comparisons of cardiac function and T1 mapping between controls and patients with cardiomyopathy

The CMRI parameters of the study population are listed in Table 2. As expected, the DCM group had a significantly lower LVEF and SVI and a greater EDVI, ESVI and myocardial mass index ($p<0.05$ for all) than the healthy control group; however, the HCM patients had a significantly higher myocardial mass index, maximum LV wall thickness, and a lower ESVI than the healthy controls ($p<0.05$ for all). The LV cardiac index was similar among the three groups. No significant differences in the EF, EDVI, and SVI were observed between the HCM patients and controls.

The native T1 time and ECV of the study participants are summarised in Table 2. The native T1 times and ECV were significantly greater in the HCM and DCM groups than those in the control group ($p<0.001$; Fig 2).

Table 1
Demographics of the study cohort.

Clinical parameters	Healthy volunteers ($n=40$)	DCM ($n=57$)	HCM ($n=30$)	*p*-Value
Age (years)	46.1±13.1	45.2±12.9	52.0±12.2	0.055
Male, *n* (%)	26 (65)	46 (80.7)	21 (70)	0.205
Height (cm)	166.6±8.1	168.0±6.6	168.2±6.7	0.553
Weight (kg)	65.4±9.9	69.3±15.4	72.7±13	0.074
BMI (kg/m^2)	23.5±2.8	24.5±4.9	25.6±3.6	0.308
BSA (m^2)	1.8±0.2	1.8±0.2	1.9±0.2	0.084
Heart rate (beats/min)	64.5±9.9	77.5±14.3[a]	67.9±12.7[b]	<0.001
Haematocrit (%)	42.4±3.7	41.8±5	42.4±5.1	0.813
Hypertension, *n* (%)	0 (0)	14 (24.6)	15 (50)	–
Diabetes mellitus, *n* (%)	0 (0)	7 (12.3)	3 (10)	–
Family history of cardiomyopathy, *n* (%)	0 (0)	7 (12.3)	2 (6.7)	–
NYHA functional class, *n* (%)				
I	–	2 (3.5)	14 (46.7)	–
II	–	6 (10.5)	11 (36.7)	–
III	–	19 (33.3)	3 (10)	–
IV	–	30 (52.6)	2 (6.7)	–
Duration (years)	–	3.6±3.4	4.4±5.4	–
NT-proBNP (pg/ml; $n=18$)	–	1,425.2±3,213.5	183.4±338.6	–
BUN (mmol/l)	–	7.2±3.4	6.5±2.5	–
Creatinine (μmol/l)	–	91.3±54.2	81.6±31.5	–

Values are expressed as the mean±standard deviation.
[a] $p<0.05$ DCM versus control.
[b] $p<0.05$ HCM versus DCM.
DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; BUN, blood urea nitrogen.

Table 2
CMRI parameters of the study population.

CMRI parameters	Healthy volunteers (n=40)	DCM (n=57)	HCM (n=30)	p-Value
LVEF (%)	57.9±4.6	16.5±8.2[a]	65.3±16.5[b]	<0.001
LVEDVI (mL/m^2)	66.3±11.5	195.5±80.1[a]	55.4±23.8[b]	<0.001
LVESVI (mL/m^2)	28.5±6.8	166.5±75.2[a]	20.3±20.5[bc]	<0.001
LV stroke volume (mL)	37.9±6.2	28.9±13.2[a]	35.1±11.3[b]	<0.001
LV cardiac index (L/min/m^2)	2.4±0.5	2.3±1.1	2.3±0.8	0.244
LV mass index (g/m^2)	63.4±9.2	122.3±38[a]	103.7±51.9[bc]	<0.001
Maximum LV wall thickness (mm)	8.5±1.4	–	21.1±5.2	<0.001
Presence of LGE, n (%)	0 (0)	38 (66.7)[a]	18 (60)[c]	<0.001
Native T1 time (ms)	1025.7±34.8	1063.1±42.1[a]	1060.6± 47[c]	<0.001
ECV (%)	24.9±3	32.0±5.6[a]	28.7±3.7[bc]	<0.001

Values are expressed as the mean±standard deviation.
[a]p<0.05 DCM versus control.
[b]p<0.05 HCM versus DCM.
[c]p<0.05 HCM versus control.
CMRI, cardiac magnetic resonance; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVEF, left ventricle ejection fraction; LVEDVI, left ventricle end-diastolic volume index; LVESVI, left ventricle end-systolic volume index; ECV, extracellular volume fraction.

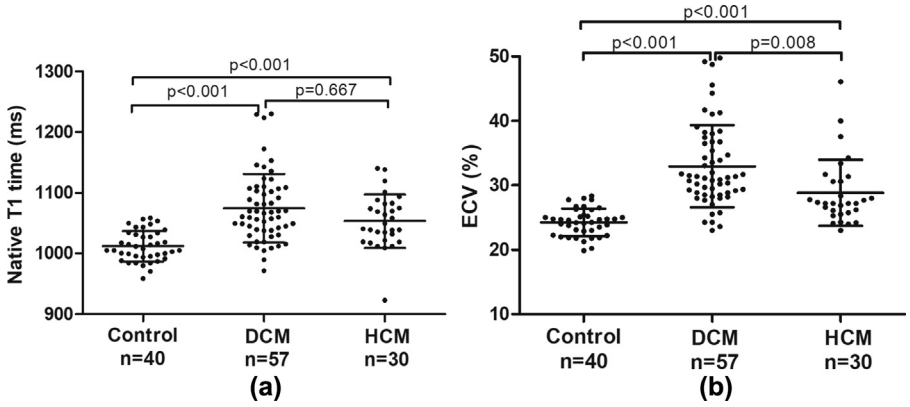

Figure 2 Comparisons among controls, DCM patients, and HCM patients. Comparisons of myocardial native T1 time (a) and ECV (b) among the DCM patients, HCM patients, and controls.

Discrimination of DCM and HCM patients from healthy volunteers

Multivariate binary logistic regression analysis including age, sex, BMI, heart rate, native T1 time, and ECV revealed that the ECV was an independent predictor for discriminating DCM patients from healthy volunteers (OR=1.556, 95% confidence interval [CI]=1.268–1.908, p<0.001; Table 3). Multivariate binary logistic regression analysis including age, sex, BMI, LV mass index, maximum LV wall thickness, LVEF, native T1 time, and ECV revealed that the ECV was an independent predictor for discriminating HCM patients from healthy volunteers (OR=1.847, 95% CI=1.294–2.638, p=0.001; Table 3). In the ROC curve analysis, the areas under the curves (AUCs) for the ECV and native T1 time for differentiating between DCM patients and controls were 0.889 and 0.780, respectively (Fig 3a). Furthermore, compared to native T1 time, ECV provided better distinction between DCM patients and healthy volunteers (z=2.32, p=0.021). Similarly, the AUCs for the ECV and native T1 time were 0.816 and 0.780, respectively, for HCM patients (Fig 3b). The ROC curve analysis indicated that an ECV of 27.6% is the optimal cut-off for discriminating between DCM patients and healthy volunteers with a sensitivity of 80.7% and a specificity of 87.5% and that an ECV of 25.9% is the optimal cut-off for discriminating between HCM patients and healthy volunteers with a sensitivity of 83.3% and a specificity of 70% (Table 4).

Repeatability analysis

Intra-observer and interobserver variability were analysed in 15 randomly selected healthy volunteers. The ICCs and 95% CIs for intra-observer and interobserver agreement were 0.988 (95% CI=0.964–0.996) and 0.977 (95% CI=0.933–0.992) for ECV measurements and 0.978 (95% CI=0.935–0.992) and 0.978 (95% CI=0.936–0.993) for native T1 times measurements, respectively. The mean interobserver and intra-observer differences for native T1 times were 5.8 and −6.3 ms, respectively. The average interobserver and intra-observer differences in ECV measurements were 0.23% and −0.25%, respectively.

Discussion

This study demonstrated that the myocardial ECV increased in the DCM and HCM patients compared to that in the healthy volunteers, which was indicative of myocardial

Table 3
Univariate and multivariate binary logistic regression analyses for DCM and HCM patients.

Variable	B	SE	χ^2	*p*-Value	OR (95% CI)
DCM					
Univariate analysis					
Heart rate	0.090	0.022	16.688	<0.001	1.094 (1.048–1.143)
Native T1 times	0.026	0.007	15.147	<0.001	1.027 (1.013–1.040)
ECV	0.484	0.101	23.152	<0.001	1.622 (1.332–1.976)
Multivariate analysis					
Heart rate	0.066	0.027	6.193	0.013	1.068 (1.014–1.125)
ECV	0.442	0.104	17.971	<0.001	1.556 (1.268–1.908)
HCM					
Univariate analysis					
BMI	0.217	0.089	5.917	0.015	1.243 (1.043–1.481)
Native T1 times	0.023	0.007	9.312	0.002	1.023 (1.008–1.038)
ECV	0.410	0.116	12.571	<0.001	1.507 (1.201–1.890)
LVEF	0.059	0.024	6.242	0.012	1.061 (1.013–1.112)
LV mass index	0.081	0.021	14.385	<0.001	1.084 (1.040–1.130)
Multivariate analysis					
ECV	0.614	0.182	11.404	0.001	1.847 (1.294–2.638)
LVEF	0.197	0.080	6.150	0.013	1.218 (1.042–1.423)
LV mass index	0.106	0.037	8.356	0.004	1.112 (1.035–1.195)

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ECV, extracellular volume fraction; OR, odds ratio; BMI, body mass index; LVEF, left ventricle ejection fraction.

extracellular matrix expansion. Even in the segments without LGE, the ECV was elevated in the DCM and HCM patients, suggesting that the ECV has the potential to discern diffuse myocardial pathological changes. The present findings showed that ECV derived from CMRI was an independent predictor for the diagnoses of DCM and HCM. Furthermore, the myocardial ECV provided excellent diagnostic specificity and PPV for DCM and good diagnostic sensitivity and NPV for HCM to differentiate patients with diffuse myocardial diseases from healthy volunteers.

T1 mapping by CMRI reflected the image-based signal intensities of the myocardium based on different longitudinal relaxation times of the myocardial tissue. Variations in myocardial tissue composition manifested as differences in signal intensity. Therefore, CMRI T1 mapping has emerged as a valuable technology for assessing the amount of diffuse myocardial fibrosis and has been validated by histology. Previous studies have suggested that native T1 times, post-contrast T1 times, and ECVs are correlated with histological fibrosis in patients with aortic stenosis, heart failure, and cardiomyopathies.[6–11,17–21] According to a meta-analysis discussed comprehensively by Diao *et al.*, the ECV corresponds to the highest correlation among these three parameters based on analyses of multiple histological studies[11]; however, recent studies by Nakamori *et al.* and Lurzd *et al.* have provided new insights into ECV measurements and demonstrated that the ECV represents the extracellular space, including myocardial fibrosis, oedema, intracapillary plasma volume, and interstitial infiltration rather than only myocardial fibrosis, especially in the presence of myocardial infiammation and other coexisting pathologies.[22,23] In addition, Puntmann *et al.* reported that non-invasive quantification of diffuse myocardial disease by T1 mapping yields a stronger predictor of all-cause mortality and heart failure events in DCM than classic parameters.[24] Therefore, the present findings revealed that the increased native T1 time and ECV in DCM and HCM patients may reflect myocardial extracellular matrix expansion. A previous prospective study investigated several cardiac diseases and showed that the ECV was larger in patients with various myocardial pathologies relative to that in controls.[25] The results of the present study are consistent with these findings. In addition, the ECV was demonstrated to be an independent predictor for discriminating DCM and HCM patients from healthy volunteers.

A previous study by Dass *et al.* reported that the myocardial native T1 time was significantly higher in DCM and HCM patients than that in controls and that native T1 time was associated with impaired myocardial energetics and circumferential strain[26]; however, a limitation of this study was the lack of post-contrast T1 mapping, and the ECV could not be calculated for further analyses. Another study by Puntmann *et al.* including 27 DCM and 25 HCM patients indicated that the native T1 value was elevated and showed the highest diagnostic accuracy among post-contrast T1 time and ECV for differentiating healthy participants from DCM and HCM patients.[27] Similarly, the native T1 times and ECVs of DCM and HCM patients were also compared with those of the controls and it was found

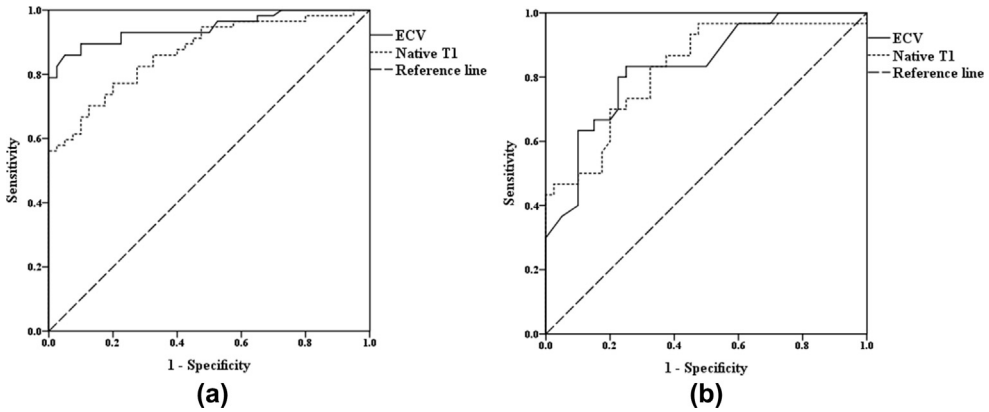

Figure 3 ROC curve for discrimination between controls and DCM or HCM patients. ROC curve analyses for the diagnosis of DCM (a) and HCM (b) based on ECV and native T1 time.

Table 4
Diagnostic performance of ECV and native T1 times for DCM and HCM patients.

Variable	Cutoff value	AUC (95% CI)	*p*-Value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
DCM							
Native T1 times (ms)	1025.8	0.780 (0.684–0.857)	<0.001	84.2 (72.1–92.5)	65.0 (48.3–79.4)	77.4 (65.0–87.1)	74.3 (56.7–87.5)
ECV (%)	27.6	0.889 (0.809–0.944)	<0.001	80.7 (68.1–90)	87.5 (73.2–95.8)	90.2 (78.6–96.7)	76.1 (61.2–87.4)
HCM							
Native T1 times (ms)	1030.0	0.780 (0.665–0.870)	<0.001	83.3 (65.3–94.4)	67.5 (50.9–81.4)	65.8 (48.6–80.4)	84.4 (67.2–94.7)
ECV (%)	25.9	0.816 (0.706–0.899)	<0.001	83.3 (65.3–94.4)	70.0 (53.5–83.4)	67.6 (50.2–82)	84.8 (68.1–94.9)

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ECV, extracellular volume fraction; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

that the native T1 time and ECV increased in cardiomyopathies; however, the multivariate logistic regression analysis revealed that ECV was an independent predictor and showed the highest diagnostic performance for differentiating DCM and HCM patients from healthy volunteers in contrast to the above studies. Native T1 time represents the signal intensity of the interstitium and myocytes, which is affected by the intracellular water content. Therefore, the relationships of native T1 time and physiological variations with diffuse myocardial fibrosis in DCM and HCM patients are less understood. In addition, the variability in the native T1 times reported among previous studies is relatively high. Some studies have indicated that native T1 time is favourably related to myocardial fibrosis based on histopathology[17]; however, another study reported that native T1 time was not associated with histological myocardial fibrosis.[10] The native T1 times reported in these studies may have been affected by different field strengths, scanning techniques, and individual conditions, which may also contribute to the lower diagnostic performance of native T1 time observed in the present study; however, the ECV was defined as the extracellular space, and the increased ECV in the present study reflected myocardial extracellular interstitial expansion in DCM and HCM myocardial pathologies. Siepen *et al.* reported that ECV measurements were associated with expansion of the myocardial extracellular space in a model of DCM confirmed by histology.[8] The study indicated that the ECV increased at earlier stages of DCM, and that the ECV of DCM patients, but not native T1 time, differed from those of normal controls, which is consistent with the present study. Additionally, a previous study indicated that fibrotic changes are triggered early in HCM pathogenesis. The ECV is increased before left ventricular hypertrophy manifests in HCM with recognised genetic mutations.[28] Ellims *et al.* reported that genotyped HCM patients have significantly more myocardial fibrosis than those without the HCM genotype.[29] Measurement of the myocardial ECV may help characterise the development of myocardial fibrosis in HCM. Additionally, a previous study indicated that the ECV may serve as a novel marker for monitoring early therapeutic responses and clinical risk stratification.[8] The ROC curve analysis performed in the present study demonstrated that an ECV of 27.6% serves as the best cut-off value for discerning DCM patients from controls with a specificity of 87.5% and a sensitivity of 80.7%. The present findings suggest that an ECV of 25.9% is the optimal cut-off for discriminating between HCM patients and healthy volunteers with a higher a sensitivity of 83.3% and specificity of 70%. The different results may be explained by differences in MRI systems, imaging techniques, patient selection, and stages of disease among the study cohorts.

Several studies have validated the good correlation between post-contrast T1 time and histological fibrosis.[18–20] Unfortunately, the focus of the present study was not post-contrast T1 mapping because many factors affect post-contrast T1 time measurements, including the renal clearance rate, contrast agent dose and type, time points of T1 mapping scanning after gadolinium administration, and individual pharmacokinetics[30]; however, the ECV was corrected for the haematocrit, thus minimising the impact of the above factors, and may be a relatively accurate marker for detecting myocardial interstitial expansion in heart diseases.

Currently, T1 mapping can not only help determine a differential diagnosis among HCM and healthy people in phenotypically expressed patients, but also differentiate between other sources of LV hypertrophy. A study by Hinojar *et al.* showed that native T1 time can distinguish HCM from hypertensive heart disease.[31] Additionally, the ECV could discriminate between HCM and athlete's heart disease with high diagnostic accuracy.[32] Although LV hypertrophy was increased in both diseases, the ECV was reduced in athletes, but increased in HCM patients, because in athletes myocardial hypertrophy is mediated by cellular hypertrophy rather than extracellular matrix expansion.

The present study includes a few limitations. First, this was a single-centre study with a relatively small sample size, and a larger multicentre study is needed to validate the results. Second, histological correlations were not performed in this study; however, previous studies have validated the high correlation between ECV and myocardial extracellular matrix expansion.[6–10] Furthermore, the invasive nature and sampling error associated with endomyocardial biopsies limit the clinical applications of the results. Third, confounding factors, such as age, sex, hypertension, and diabetes mellitus, may have affected ECV and native T1 time measurements. Nevertheless, potentially confounding effects were excluded by performing a multivariate analysis, and correlations between the above factors and the ECV and native T1 time were not observed. Finally, the study mainly focused on T1 mapping to characterise cardiomyopathies, and the effects of T2 mapping remain to be determined. Infiammatory and oedematous states may occur in some

end-stage patients, and their infiuences on T1 values also require further investigation.

In conclusion, the ECV is a useful non-invasive tool for detecting expansion of myocardial extracellular matrix in DCM and HCM patients. The present study suggests that the ECV is an independent predictor and exhibits good diagnostic performance for DCM and HCM discrimination. Further studies are required to extend these results to other cardiomyopathies.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This study was funded by the National Natural Science Foundation of China (grant nos. 81271570 and 81371661).

References

1. Maron BJ, Towbin JA, Thiene G, *et al*. Contemporary definitions and classification of the cardiomyopathies. *Circulation* 2006;**113**(14):1807–16.
2. Elliott P, Andersson B, Arbustini E, *et al*. Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases. *Eur Heart J* 2007;**29**(2):270–6.
3. Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. *N Engl J Med* 2011;**364**(17):1643–56.
4. Felker GM, Thompson RE, Hare JM, *et al*. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;**342**(15):1077–84.
5. Gulati A, Jabbour A, Ismail TF, *et al*. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA* 2013;**309**(9):896–908.
6. Miller CA, Naish J, Bishop P, *et al*. Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. *Circ Cardiovasc Imaging* 2013;**6**(3):373–83.
7. Kammerlander AA, Marzluf BA, Zotter-Tufaro C, *et al*. T1 mapping by CMRI imaging: from histological validation to clinical implication. *JACC Cardiovasc Imaging* 2016;**9**(1):14–23.
8. aus dem Siepen F, Buss SJ, Messroghli D, *et al*. T1 mapping in dilated cardiomyopathy with cardiac magnetic resonance: quantification of diffuse myocardial fibrosis and comparison with endomyocardial biopsy. *Eur Heart J Cardiovasc Imaging* 2014;**16**(2):210–6.
9. Flett AS, Hayward MP, Ashworth MT, *et al*. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis. *Circulation* 2010;**122**(2):138–44.
10. de Ravenstein CdM, Bouzin C, Lazam S, *et al*. Histological Validation of measurement of diffuse interstitial myocardial fibrosis by myocardial extravascular volume fraction from modified Look–Locker imaging (MOLLI) T1 mapping at 3 T. *J Cardiovasc Magn Reson* 2015;**17**(1):48.
11. Diao K-y, Yang Z-g, Xu H-y, *et al*. Histologic validation of myocardial fibrosis measured by T1 mapping: a systematic review and meta-analysis. *J Cardiovasc Magn Reson* 2016;**18**(1):92.
12. Elliott P. Diagnosis and management of dilated cardiomyopathy. *Heart* 2000;**84**(1). 106-106.
13. Gersh BJ, Maron BJ, Bonow RO, *et al*. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. *Circulation* 2011;**142**(6):1303–38.
14. Arheden Hk, Saeed M, Higgins CB, *et al*. Measurement of the distribution volume of gadopentetate dimeglumine at echo-planar MR imaging to quantify myocardial infarction: comparison with 99mTc-DTPA autoradiography in rats. *Radiology* 1999;**211**(3):698–708.
15. Beliveau P, Cheriet F, Anderson SA, *et al*. Quantitative assessment of myocardial fibrosis in an age-related rat model by *ex vivo* late gadolinium enhancement magnetic resonance imaging with histopathological correlation. *Comput Biol Med* 2015;**65**:103–13.
16. Rogers T, Dabir D, Mahmoud I, *et al*. Standardization of T1 measurements with MOLLI in differentiation between health and disease—the ConSept study. *J Cardiovasc Magn Reson* 2013;**15**:78.
17. Bull S, White SK, Piechnik SK, *et al*. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. *Heart* 2013;**99**(13):932–7.
18. Iles LM, Ellims AH, Llewellyn H, *et al*. Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. *Eur Heart J Cardiovasc Imaging* 2014;**16**(1):14–22.
19. Iles L, Pfluger H, Phrommintikul A, *et al*. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *JACC* 2008;**52**(19):1574–80.
20. Sibley CT, Noureldin RA, Gai N, *et al*. T1 Mapping in cardiomyopathy at cardiac MR: comparison with endomyocardial biopsy. *Radiology* 2012;**265**(3):724–32.
21. Cui Y, Cao Y, Song J, *et al*. Association between myocardial extracellular volume and strain analysis through cardiovascular magnetic resonance with histological myocardial fibrosis in patients awaiting heart transplantation. *J Cardiovasc Magn Reson* 2018;**20**(1):25.
22. Nakamori S, Dohi K, Ishida M, *et al*. Native T1 mapping and extracellular volume mapping for the assessment of diffuse myocardial fibrosis in dilated cardiomyopathy. *JACC Cardiovasc Imaging* 2018;**11**(1):48–59.
23. Lurz JA, Luecke C, Lang D, *et al*. CMRI-derived extracellular volume fraction as a marker for myocardial fibrosis: the importance of coexisting myocardial inflammation. *JACC Cardiovasc Imaging* 2018;**11**(1):38–45.
24. Puntmann VO, Carr-White G, Jabbour A, *et al*. T1-mapping and outcome in nonischemic cardiomyopathy: all-cause mortality and heart failure. *JACC Cardiovasc Imaging* 2016;**9**(1):40–50.
25. Sado DM, Flett AS, Banypersad SM, *et al*. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. *Heart* 2012;**98**(19):1436–41.
26. Dass S, Suttie JJ, Piechnik SK, *et al*. Myocardial tissue characterization using magnetic resonance non-contrast t1 mapping in hypertrophic and dilated cardiomyopathy. *Circ Cardiovasc Imaging* 2012;**5**(6):726–33.
27. Puntmann VO, Voigt T, Chen Z, *et al*. Native T1 mapping in differentiation of normal myocardium from diffuse disease in hypertrophic and dilated cardiomyopathy. *JACC Cardiovasc Imaging* 2013;**6**(4):475–84.
28. Ho CY, Abbasi SA, Neilan TG, *et al*. T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. *Circ Cardiovasc Imaging* 2013;**6**(3):415–22.
29. Ellims AH, Iles LM, Ling LH, *et al*. A comprehensive evaluation of myocardial fibrosis in hypertrophic cardiomyopathy with cardiac magnetic resonance imaging: linking genotype with fibrotic phenotype. *Eur Heart J Cardiovasc Imaging* 2014;**15**(10):1108–16.
30. Gai N, Turkbey EB, Nazarian S, *et al*. T1 mapping of the gadolinium-enhanced myocardium: adjustment for factors affecting interpatient comparison. *Magn Reson Med* 2011;**65**(5):1407–15.
31. Hinojar R, Varma N, Child N, *et al*. T1 Mapping in discrimination of hypertrophic phenotypes: hypertensive heart disease and hypertrophic cardiomyopathy: findings from the International T1 Multicenter Cardiovascular Magnetic Resonance Study. *Circ Cardiovasc Imaging* 2015;**8**(12):e003285. pii.
32. Swoboda PP, McDiarmid AK, Erhayiem B, *et al*. Assessing myocardial extracellular volume by T1 mapping to distinguish hypertrophic cardiomyopathy from athlete's heart. *J Am Coll Cardiol* 2016;**67**(18):2189–90.