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Cardiovascular magnetic resonance T2* mapping for structural alterations in hypertrophic cardiomyopathy

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ABSTRACT

Purpose: Hypertrophic cardiomyopathy (HCM) is characterized by a heterogeneous morphology and variable prognosis. A mismatch between left ventricular mass (LVM) and microvascular circulation with corresponding relative ischemia has been implicated to cause myocardial replacement fibrosis that deteriorates prognosis. Besides parametric T1 mapping, Cardiovascular Magnetic Resonance (CMR) T2* mapping is able to identify ischemia as well as fibrosis in cardiac and extracardiac diseases. Therefore, we aimed to investigate the value of T2* mapping to characterize structural alterations in patients with HCM.

Methods: CMR was performed on a 1.5 T MR imaging system (Achieva, Philips, Best, Netherlands) using a 5-channel coil in patients with HCM (n = 103, 50.6 ± 16.4 years) and in age- and gender-matched controls (n = 20, 44.8 ± 16.9 years). T2* mapping (1 midventricular short axis slice) was acquired in addition to late gadolinium enhancement (LGE). T2* values were compared between patients with HCM and controls as well as between HCM patients with- and without fibrosis.

Results: HCM patients showed significantly decreased T2* values compared to controls (26.2 ± 4.6 vs. 31.3 ± 4.3 ms, $p < 0.001$). Especially patients with myocardial fibrosis presented with decreased T2* values in comparison to those without fibrosis (25.2 ± 4.0 vs. 28.7 ± 5.3 ms, $p = 0.003$). A regression model including maximum wall thickness, LVM and T2* values provided good overall diagnostic accuracy of 80% to diagnose HCM with and without fibrosis.

Conclusion: In this study, parametric mapping identified lower T2* values in HCM patients compared to controls, especially in a sub-group of patients with myocardial fibrosis. As myocardial fibrosis has been suggested to influence prognosis of patients with HCM, T2* mapping may add information for identifying a higher risk sub-group of HCM patients.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by a heterogeneity in myocardial structure and function, clinical presentation as well as prognosis. Increasing left ventricular mass (LVM) and wall thickness are common endpoints to different genetic and adaptive influences and cannot solely be explained by abnormal loading conditions of the heart [1]. On a structural level, HCM can be characterized by a small vessel disease that may aggravate a mismatch between myocardial mass and coronary blood circulation leading to myocardial ischemic reactions including myocyte degeneration [2–5]. Over time, myocardial ischemia is thought to trigger myocardial replacement fibrosis that can be seen in up to 65% of all HCM patients [1,6,7].

While HCM may exhibit a benign course, structural changes may deteriorate prognosis and outcome. In particular, the cascade of myocardial ischemia causing myocardial replacement fibrosis may be

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responsible for symptoms and an influence on mortality, heart failure and future cardiac events [5,8–11]. This makes fibrosis assessment in HCM of additional value for the clarification of symptoms, risk stratification and prognosis [3].

In addition to echocardiography, Cardiovascular Magnetic Resonance (CMR) is proposed a class IB recommendation for the diagnosis of HCM [1]. Besides morphology, CMR is able to provide insights into structural alterations by characterizing areas of fibrosis and scarring using late gadolinium enhancement (LGE) or post-contrast quantitative T1-mapping. For HCM, CMR perfusion studies with contrast agents have already detected a group of patients with localized microvascular dysfunction that is associated with myocardial ischemia and fibrosis [8,12]. However, in terms of further structural characterization and because not all HCM patients are able to receive contrast agents due to contraindications such as renal failure, T2* magnetic relaxation parameters (parametric mapping) have been exploited to visualize mesoscopic (structure of the tissue) magnetic field inhomogeneities [13–15]. For instance, T2* was demonstrated to characterize fibrosis in extracardiac tissues such as the intestinal tract, but also in ischemic and fibrotic segments after myocardial infarction [15–18]. In addition, histopathologic substrates of T2* and a correlation of T2* to flow analyses have already been studied in affected tissues [16,17,19,20]. The diagnostic value of T2* mapping during the course of HCM has not been investigated yet, but according to recent literature and structural alterations including relative ischemia and fibrosis, decreased T2* vales can be suggested [8,12].

Therefore, we aimed to investigate the value of parametric T2* mapping to describe structural alterations, especially fibrosis, in a group of patients displaying HCM.

2. Materials and methods

The study was conducted in accordance to the Declaration of Helsinki and its later amendments. All data used for this study were acquired for clinical purposes and handled anonymously. This retrospective study had ethics committee approval. Written informed consent requirement was waived.

2.1. Study population

In total, 103 patients with HCM were retrospectively analyzed with a CMR performed between June 2012 and May 2018. The patients were referred for clinical evaluation in our HCM outpatient clinic, in which patients are followed according to a specified care track with CMR every 3–5 years. Diagnosis with disease was made according to the 2014 ESC Guidelines with otherwise unexplained LVH and a maximal wall thickness ≥ 15 mm [1]. Most of the patients with implantable cardioverter defibrillators had to be excluded from the study due to safety guidelines. Patients with CAD using prior cardiac catheterization or non-invasive imaging were excluded due to a reduction of T2* values in ischemic segments [15,20]. Assuming decreased T2* values in the group of HCM, we sought to identify an effect in comparison to normal controls with a statistical power of 90% and type I error of less than 2.5%, resulting in an estimated sample size of 19 for the control group. Therefore, 20 age- and gender matched controls without myocardial hypertrophy of any cause or familiar predisposition of HCM were additionally evaluated through our outpatient clinic. To account for an influence of comorbidities, those parameters were matched as well.

2.2. Cardiovascular magnetic resonance

CMR was performed on a 1.5 T MRI System (Achieva, Philips, Best Netherlands) using a 5-channel phased array coil. After scout and reference scans, functional and geometric assessment was performed using cine steady state free precession (SSFP) images in standard long axis geometries (two-, three- and four-chamber view) as well as in short axis orientation with full ventricular coverage from base to apex (Repetition time (TR)/echo time (TE) = 3.3/1.6 ms, flip angle (FA) = 60°, spatial resolution = 1.5 × 1.5 × 8 mm^3, 50 phases, 2 slices per breath-hold) [15].

T2*-mapping was performed using a single-breath-hold multi-echo fast field-echo sequence in one short axis midventricular slice at end-diastole (6 echoes with shortest interecho spacing of 1.7 ms, TE: 3 ms, TR: 13 ms, flip angle 35°, acquired spatial resolution 1.6 × 2.8 × 8 mm^3, reconstructed spatial resolution: 1.2 × 1.2 × 8 mm^3, bandwidth 781 Hz/pixel) [15]. All HCM patients were eligible (glomerular filtration rate (GFR) > 35 ml/min) to receive gadolinium-based contrast agent (Gadovist, Bayer Healthcare, Berlin, Germany 0.2 mmol/kg) for late gadolinium enhanced imaging (LGE) in order to detect myocardial scarring or fibrosis. After 15 min, a 3-dimensional gradient spoiled turbo fast-field-echo sequence with a non-selective 180° inversion prepulse was acquired at end-diastole with anatomical reference taken from SSFP images [21].

2.3. Post processing

Post-processing was performed using commercial software (Cardiac MR Viewer, IntelliSpace Portal Version 8.0, Philips, Best, The Netherlands). Short and long axis slices were analyzed covering maximum end-diastolic interventricular septum thickness (IVS) at maximum extension, left and right ventricular end-diastolic volume indexed to body surface area (LVEDVi/RVEDVi), left and right ventricular ejection fraction (LVEF/RVEF), and LVM indexed to body surface area (LVMi).

T2* sequences were post-processed by one experienced observer (> 3 years in cardiac imaging) and according to recent guidelines: a region of interest (ROI) was manually drawn within the IVS of the midventricular slice using a standardized ROI size (≈50 mm^2) and avoiding partial volume effects at epicardial boarders (Fig. 1) [22]. This has been shown feasible in previous studies in addition to avoid susceptibility artifacts [23,19]. For every ROI, the time constant of the signal intensity decay over all echoes was derived by fitting a monoexponential decay curve. Afterwards, average T2* values and standard deviations (SD) for the ROI were calculated and color-coded using a spectral look-up table. T2* measurements were repeated in 20 subjects by a second experienced observer (> 3 years in cardiac imaging) to test interobserver agreement.

For LGE imaging, the amount of fibrosis was calculated semi-automatically by manually applying epi- and endocardial contours to the short axis LGE images in every slice. Additional ROIs were placed within the hyperenhanced and normal appearing myocardium using the software and reviewed by the reader. Afterwards, the amount of fibrosis was calculated by using a full-width at half-maximum (FWHM)

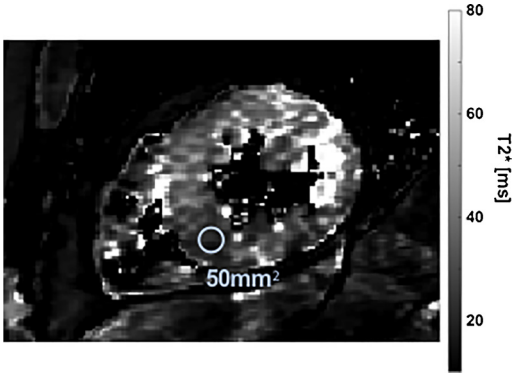

Fig. 1. T2* measurement within the IVS of a midventricular slice of a patient with HCM by placing a standardized ROI.
HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; ROI, region of interest.

algorithm in which a multi-pass region-growing algorithm enabled to identify the boundaries of the fibrotic segments [24,25]. The percentage of fibrotic tissue as % to total LVM was calculated.

2.4. Statistical analysis

Statistical analysis was performed using SPSS (version 24.0, IBM, Armonk, NY, US). Unless otherwise stated, continuous variables are presented as mean ± SD. Normal distribution was tested using the Kolmogorov-Smirnov test. Categorical variables are reported as percentages. Data between two different groups were analyzed by 2-sided unpaired Student's t-tests for normally distributed data and Mann-Whitney *U*-tests for not normally distributed data. Fisher's exact *t*-test was used to examine significant differences between nominal classifications. Coefficient of variance (CoV) for interobserver agreement was calculated by taking the SD of the differences divided by the mean values.

Pearsons correlation was performed to analyze correlations between different CMR parameters including T2* values. Variables with a univariate statistical significance were entered into a stepwise binomial logistic regression model to differentiate HCM with and without fibrosis (+/- LGE). In the end, receiver operating characteristics (ROC) were used to generate cut-off values to optimize sensitivity and specificity for the differentiation between the different groups (HCM and controls as well as HCM + versus – LGE). P-values below 0.05 were considered as statistically significant.

3. Results

3.1. Patient population

The enrolled 103 HCM patients (mean age 50.6 ± 16.4 years) were age- and sex-matched with the 20 control subjects (CMR between August 2017 and January 2019). According to the ESC Guidelines on HCM, 49 out of the 103 patients had a diagnosis of HOCM as defined by an instantaneous Doppler LV outflow tract gradient > 30 mmHg at rest and/or during provocation [1]. Clinical baseline characteristics are summarized in Table 1.

3.2. CMR parameters in HCM compared to controls

Baseline CMR characteristics of all patients compared to controls are displayed in Table 2. HCM patients showed significantly elevated IVS and LVMi. Although being different, LVEF was preserved in both groups according to recent heart failure guidelines [26]. T2* values were significantly decreased for patients with HCM in comparison to the control group (26.2 ± 4.6 vs. 31.3 ± 4.3 ms, $p < 0.001$) (Figs. 2 and 3). A further division of HCM patients in HOCM and HNCM is displayed in Table 2. Despite exhibiting a significant difference in IVS and LVMi (all increased in HOCM), there was no significant difference in T2* values between HOCM and HNCM. T2* measurement showed a good interobserver variability with a CoV of 6.0%.

There was no significant correlation between T2* values and body surface area. Although being significant, the correlations between T2* values and age ($R = -0.22$, $p = 0.016$), IVS ($R = -0.36$, $p < 0.001$) and LVMi ($R = -0.24$, $p = 0.008$) were weak. Men and women exhibited no significant difference in T2* values (27.1 ± 4.8 ms for men and 26.8 ± 5.4 ms for women).

The significant CMR parameters between HCM and controls were further entered into receiver operating characteristics. ROC analysis identified IVS (are under the curve (AUC): 1.0) and LVMI (AUC: 0.93) as the best parameters to differentiate between those groups. T2* values showed a slightly higher area under the curve (AUC: 0.80) in comparison to LVEF (AUC: 0.74), but not to RVEDVi (AUC: 0.84) and RVEF (AUC: 0.87). A cut-off below 27.8 ms discriminated between HCM and controls with a sensitivity of 80% and a specificity of 62%.

Table 1
Demographic and clinical baseline characteristics.

	All patients (n = 103)	Controls (n = 20)	*P*-value
Demographics			
Age (years)	50.6 ± 16.4	44.8 ± 16.9	0.155
Male (%)	79 (77)	13 (65)	0.270
BSA (m^2)	1.9 ± 0.2	2.0 ± 0.2	0.596
HOCM (%)	49 (48)	–	–
Family history HCM n(%)	33 (32)	–	–
Positive biopsy n(%)	12 (12)	–	–
Comorbidities			
Diabetes, n(%)	6 (6)	2 (7)	0.865
Hypertension, n(%)	32 (31)	1 (5)	0.016
Hypercholesterolemia, n(%)	23 (22)	3 (15)	0.170
Renal failure (GFR < 60 ml/min), n(%)	9 (9)	0 (0)	0.576
CAD, n(%)	0 (0)	0 (0)	1.00
Previous Stroke, n(%)	10 (10)	1 (5)	0.499
Class NYHA III-IV n(%)	10 (10)	0 (0)	0.146

BSA, body surface area; CAD, coronary artery diseases; GFR, glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; NYHA, New York Heart Association.

3.3. CMR parameters in HCM with and without fibrosis

Overall, 75 out of 103 HCM patients (73%) displayed left ventricular fibrosis in LGE imaging. Within the HNCM group, 39 out of 54 (72%) patients exhibited fibrosis with a range of 1–38% of the LVMi. Within the HOCM group, 35 out of 49 patients (71%) displayed LGE with a range of 1–28%.

Separately comparing the groups of HCM patients with and without fibrosis, there was a difference in left-ventricular mass with an elevated LVMi and a significantly thickened IVS (Table 3) for the fibrosis-group. In addition, the fibrosis-group displayed significantly decreased T2* values (25.2 ± 4.0 vs. 28.7 ± 5.3 ms, $p = 0.003$) (Figs. 3 and 4). Separately comparing patients without fibrosis to controls, the statistical significance for the group of HCM showed a tendency ($p = 0.074$). No correlation between T2* values and the amount of fibrosis, IVS and LVMi could be detected. Vice versa, patients with T2* values below the first quartile did not show significant differences in the amount of fibrosis, IVS or LVMi.

T2* values ($p = 0.002$), IVS ($p = 0.010$) and LVMi ($p = 0.040$) showed a significant association to fibrosis in univariate regression model. Including those parameters into the multivariate regression model, the model was statistically significant, $\chi^2(3) = 19.2$, $p < 0.001$, for the likelihood of having a HCM with fibrosis. Decreasing T2* values ($p = 0.006$) and increasing IVS ($p = 0.070$) were associated with an increased likelihood of having a HCM with fibrosis. The model classified 80% of cases correctly with a sensitivity for fibrosis of 96% and a specificity of 36%. Accounting for age as another covariate, the association between fibrosis and T2* ($p = 0.006$) and IVS ($p = 0.072$) remained.

Comparing the fibrosis and non-fibrosis group in the different, significant CMR parameters, ROC analysis exhibited good results for T2* values (AUC: 0.68) compared to IVS and LVMi (IVS-AUC: 0.67, LVMi-AUC: 0.62) (Fig. 5). Choosing a cut-off below 25.3 ms, a sensitivity of 71% and specificity of 44% was calculated to differentiate between fibrosis and non-fibrosis.

4. Discussion

In the present study, T2* mapping identified reduced T2* values in patients with HCM in comparison to a healthy control group. Within the HCM cohort, a sub-group of patients with left-ventricular fibrosis exhibited most pronounced T2* value reduction. We identified optimal cut-off values for additional diagnostic accuracy to differentiate those

Table 2
Baseline CMR characteristics in all patients compared to controls and divided into HOCM and HNCM.

	All patients	Controls	*P*-value	HNCM (n = 54)	HOCM (n = 49)	*P*-value
LVEF (%)	64.8 ± 8.4	60.1 ± 4.4	< 0.001	63.4 ± 9.5	66.4 ± 6.6	0.152
IVS (mm)	19.7 ± 4.4	8.5 ± 1.5	< 0.001	18.6 ± 4.2	20.9 ± 4.2	< 0.01
LVMi(g/m^2)	85.6 ± 28.8	47.6 ± 10.7	< 0.001	81.2 ± 28.3	90.4 ± 28.9	0.065
LVEDVi (ml)	74.6 ± 16.3	78.0 ± 13.6	0.380	74.4 ± 18.1	74.7 ± 14.3	0.925
RV-EF (%)	70.0 ± 8.3	58.4 ± 7.0	< 0.001	69.4 ± 8.1	70.7 ± 8.4	0.436
RVEDVi (ml)	59.3 ± 14.6	78.5 ± 16.9	< 0.001	58.6 ± 15.6	60.0 ± 14.6	0.592
T2* (ms)	26.2 ± 4.6	31.3 ± 4.3	< 0.001	26.9 ± 5.1	25.4 ± 4.0	0.095

HNCM, hypertrophic non-obstructive cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; IVS, interventricular septum; LVEDVi/RVEDVi, left/right ventricular end-diastolic volume indexed by body surface area; LVEF/RVEF, left/right ventricular ejection fraction; LVMi, left ventricular mass indexed by body surface area.

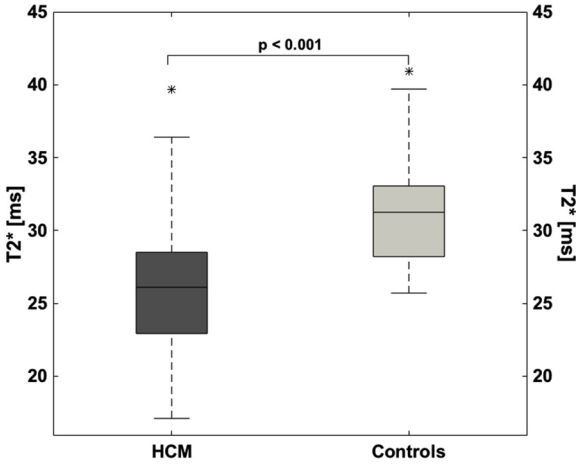

Fig. 2. Comparison of T2* values between patients with HCM and a healthy control group.
HCM, hypertrophic cardiomyopathy.

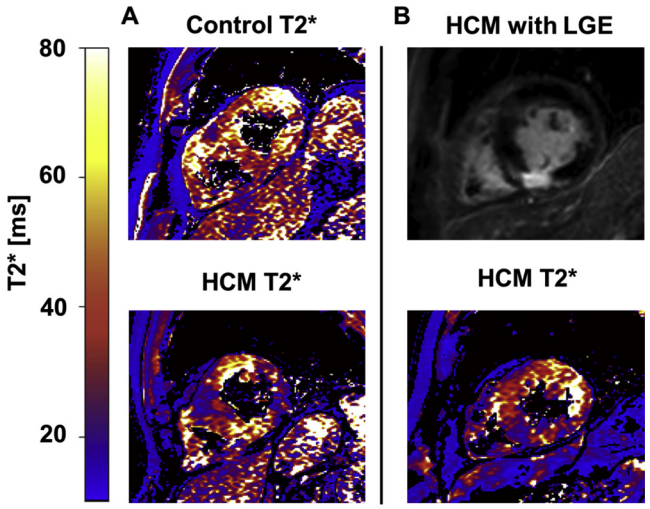

Fig. 3. (A) T2* map of a normal control (upper panel) compared to a patient with HCM (lower panel) and (B) LGE image (upper panel) and corresponding T2* map (lower panel) to visualize the reduction of T2* values in the areas of myocardial fibrosis.
HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement.

groups.

An increase in LVMi and IVS are commonly used for the diagnosis of HCM in current guidelines [1]. Results of the current IVS and LVMi analyses are in line with those guidelines, showing good diagnostic accuracy for the differentiation of HCM and healthy controls. However,

Table 3
Baseline CMR characteristics in patients with HCM plus fibrosis (+LGE) and without fibrosis (-LGE).

	+ LGE (n = 75)	- LGE (n = 28)	*P*-value
LVEF (%)	64.8 ± 9.2	65.0 ± 5.6	0.870
IVS (mm)	20.4 ± 4.7	17.8 ± 2.7	0.010
LVMi(g/m^2)	89.2 ± 30.7	75.8 ± 20.4	0.055
LVEDVi (ml)	74.7 ± 17.1	74.3 ± 14.4	0.922
RV-EF (%)	70.6 ± 8.8	68.6 ± 6.5	0.287
RVEDVi (ml)	58.4 ± 13.5	61.5 ± 17.2	0.544
T2* (ms)	25.2 ± 4.0	28.7 ± 5.3	0.003

HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LGE, late gadolinium enhancement; LVEDV/RVEDV, left/right ventricular end-diastolic volume; LVEF/RVEF, left/right ventricular ejection fraction; LVMi, left ventricular mass indexed by body surface area; SV, stroke volume.

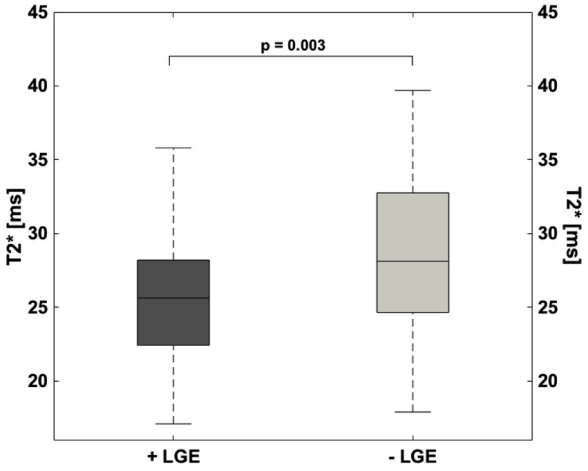

Fig. 4. Comparison of T2* values between patients with (+) and without (-) LGE.
LGE, late gadolinium enhancement

HCM can be characterized by additional structural and functional changes during the course of the disease that can influence the prognosis of the disease [1,8,9]. One of those alterations is microvascular dysfunction with its pathophysiologic cascade resulting in myocardial fibrosis and scarring [8]. These structural alterations can commonly be seen in HCM patients. Imaging modalities, such as CMR, have already been able to correlate reduced myocardial blood flow to areas of LGE in HCM [8,27]. As the presence of fibrosis in HCM patients has shown an influence on symptoms, prognosis or cardiovascular events, there has been a fundamental interest to identify this sub-group of patients. This can help to eventually adapt clinical assessment strategies for a wider range of patients that cannot be classified with common risk

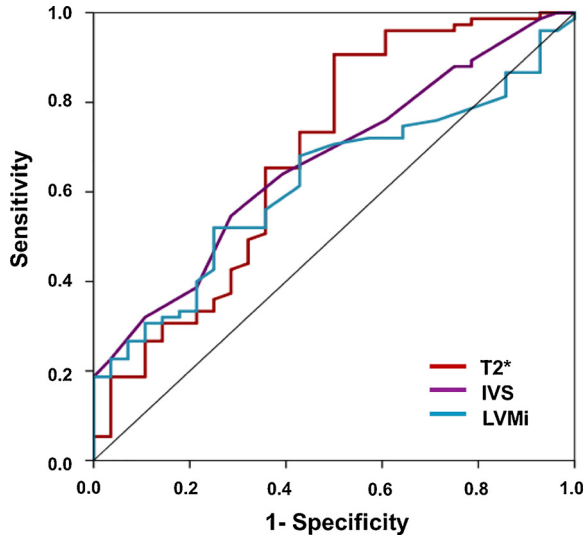

Fig. 5. ROC analysis to differentiate HCM with- and without fibrosis adding LVMi, IVS and T2* to the model.
ROC, receiver operating characteristics; LVMi, left ventricular mass indexed by body surface area; IVS, interventricular septum.

stratification models [28].

The non-invasive imaging of myocardial structural alterations is one of the core strengths of CMR, e.g. using LGE or ECV to detect fibrosis with contrast agents [29]. In fact, LGE has been described in up to 65% of all HCM patients [7,22,30]. In the presence of contraindications to gadolinium chelates or for further validation of structural alterations, parametric mapping techniques without the use of contrast agents have gained additional value to describe structural alterations in various cardiovascular- and non-cardiovascular diseases [22]. In this context, T1 mapping of the longitudinal relaxation of the myocardium has already been used to correlate areas of fibrosis to elevated T1 values, elevated wall thickness, and the extent of LGE [31,32]. T2* mapping, as another parametric mapping technique, is able to characterize the relaxation of the transverse magnetization that is influenced by macroscopic and mesoscopic magnetic field inhomogeneities [14,22]. While macroscopic inhomogeneities are caused by inhomogeneities of the magnetic field, mesoscopic field inhomogeneities are influenced by the structure of the tissue. As a consequence, T2* value can be reduced due to structural tissue alterations. From extracardiac tissues it is known, that the T2* relaxation time in fibrotic intestinal segments of crohn's disease as detected by contrast enhancement or in collagen rich tissue becomes short and these observations have already been verified by histologic analyses [18]. From cardiac tissues it is known, that myocardial microstructure can be visualized using T2* imaging at high magnetic fields and that reduced T2* values correlated with the area of myocardial fibrosis or collagen fractional area as determined by histology, even when LGE was inconclusive [33–35]. Despite the influence on T2* of extracellular matrix differences in collagen composition, another explanation for the reduction of T2* values could be that in areas of reduced perfusion or fibrosis, oxyhemoglobin and –myoglobin as local oxygen suppliers are decreased while deoxyhemoglobin and -myoglobin are increased. In contrast to oxygenated proteins, deoxygenated proteins are paramagnetic and therefore reduce local T2* values. In the present study, patients with HCM, and especially patients with myocardial fibrosis, exhibited significantly reduced T2* values with a good diagnostic accuracy in logistic regression. As this may underline the diagnosis of myocardial replacement fibrosis, T2* has the ability to add diagnostic value in borderline cases or where contrast agents cannot be applied. In this context, T2* values potentially identify a sub-group of patients being at higher risk for future cardiac events, warranting further verification of the relation between T2* and fibrosis in histologic analyses.

In addition to those findings, the tendency towards decreased T2* values in the non-fibrosis group may suggest ischemic or structural alterations in the absence of LGE. Although the current study was performed under resting conditions, a previous study using blood-oxygenation level-dependent MR showed a reduced oxygenation in areas without fibrosis by using stress perfusion [36]. This reduced oxygenation has been suggested another influencing factor on T2* [15,20]. In addition, a higher SD of patients without fibrosis compared to patients with fibrosis or controls may suggest different stages in those patients.

We could not find a correlation between reduction of T2* values and the amount of replacement fibrosis. Explanations for this could be that abnormal myocardial perfusion has also been found in areas of normal wall thickness [8,36]. Further influencing factors for T2* may also be the dynamic histopathological states of HCM with a varying degree of edema, cell death, fiber disarray, and myocardial scarring [27].

The following limitations must be acknowledged to our study. Most of the patients with implantable cardioverter defibrillators had to be excluded from the study due to safety guidelines. This may have introduced a selection bias by limiting the study group to a lower risk population.

As the study was conducted retrospectively, we were not able to quantify perfusion by CMR or verify the relation between T2* and fibrosis in histopathologic analyses. However, studies from different tissues have already shown a correlation between T2* values and collagen or LGE [14,16–18]. In addition, microvascular dysfunction in HCM has already been described in literature and perfusion studies in CMR have shown good accuracy for the description of microvascular dysfunction [8,12]. In addition to LGE as widely accepted technique for the detection of fibrosis, T1 mapping would have been of additional value to detect interstitial fibrosis [37]. Nevertheless, LGE imaging is regarded the reference standard to detect myocardial fibrosis and replacement fibrosis due to ischemic alterations showed good correlation to LGE extend during histological analyses underlining feasibility of LGE to detect fibrosis [25,38,39].

The study was conducted as a single-center study and a multicenter study could strengthen the above results in the future. In addition, not all patients were followed over time, therefore hampering the report of major adverse cardiac events within this study.

5. Conclusions

In conclusion, parametric mapping with CMR identified a sub-group of HCM patients with decreased T2* values alongside myocardial replacement fibrosis. As myocardial fibrosis has been suggested to influence the prognosis of patients with HCM, this could be of importance in certain clinical settings as T2* has the ability to potentially identify a sub-group of patients being at higher risk for future cardiac events.

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