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ORIGINAL ARTICLE

High T2-weighted signal intensity is associated with elevated troponin T in hypertrophic cardiomyopathy

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ABSTRACT

Objective Areas of high signal intensity (HighT2) on T2-weighted cardiovascular magnetic resonance (CMR) imaging have been demonstrated in hypertrophic cardiomyopathy (HCM). It has been hypothesised that HighT2 may indicate active tissue injury in HCM. In this context, we studied HighT2 in relation to cardiac troponin.

Methods Outpatient HCM patients without a history of coronary artery disease underwent CMR imaging at 1.5 T using T2-weighted, cine and late gadolinium enhancement (LGE) imaging to assess HighT2, left ventricular (LV) function, LV mass and the presence and extent of LGE. Highly sensitive cardiac troponin T (hs-cTnT) was assessed as a marker of injury, with hs-cTnT ≥14 and >3 ng/L defined as an elevated and detectable troponin.

Results HighT2 was present in 28% of patients (28/101). An elevated hs-cTnT was present in 54% of patients with HighT2 (15/28) compared with 14% of patients without HighT2 (10/73) (p<0.001). Hs-cTnT was detectable in 96% of patients with HighT2 (27/28) compared with 66% of patients without HighT2 (48/73) (p=0.002). In case of an undetectable hs-cTnT, HighT2 was only seen in 4% (1/26). In addition, the extent of HighT2 was related with increasing hs-cTnT concentrations (Spearman's ρ: 0.42, p<0.001).

Conclusions In this CMR study of patients with HCM, we observed HighT2 in a quarter of patients, and demonstrated that HighT2 was associated with an elevated hs-cTnT. This observation, combined with the very high negative predictive value of an undetectable hs-cTnT for HighT2, provides supportive evidence for the hypothesis that HighT2 is indicative of recently sustained myocyte injury.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common inheritable cardiomyopathy, characterised by unexplained left ventricular (LV) hypertrophy.[1 2] Myocardial ischaemia is considered to play a pivotal role in the pathophysiology of this disease, based on previous observations of perfusion abnormalities and fibrosis using various imaging techniques.[3 4]

Several reports have described elevated concentrations of highly sensitive cardiac troponin T (hs-cTnT) in about 25%–50% of patients with HCM.[5–7] In analogy to other conditions, the first study has been reported to suggest that hs-cTnT is associated with adverse long-term clinical outcome in HCM as well.[6]

With growing interest in cardiovascular magnetic resonance (CMR) imaging in HCM, hs-cTnT as a biomarker of myocardial injury has been associated with late gadolinium enhancement (LGE) as an imaging marker of fibrosis.[7 8] Previously, a few small-sized studies of selected patients with HCM have demonstrated areas of high signal intensity (SI) with the use of T2-weighted CMR imaging (HighT2).[9–15] Interestingly, these areas of HighT2 were almost exclusively present in patients with LGE, occurring within the boundaries of LGE. It has been postulated that areas with HighT2 might be indicative of myocardial oedema as a result of ischaemic injury, representative of a more active disease state in patients with HCM.[9 12] Although ischaemic injury is considered the final common pathway, the pathophysiology of ischaemia in HCM distinctly differs from, for example, acute myocardial infarction and myocarditis. This requires additional research on CMR imaging and the interpretation of HighT2 in HCM.

In the above-mentioned context, we aimed to explore the association between HighT2 and hs-cTnT in a well-defined cohort of patients with a clinical HCM.

METHODS

Study population

Enrolment of our cohort of consecutive adult patients with HCM took place between April 2008 and January 2014 at two outpatient clinics (Radboud University Medical Centre, Nijmegen, The Netherlands and Albert Schweitzer Hospital, Dordrecht, The Netherlands) that perform mutation screening, repeated echocardiography, CMR imaging and clinical follow-up. Patients had an echocardiographically confirmed HCM,[1 2] including a careful case-by-case chart review, especially in those with a history of hypertension. In case of a discrepancy between the treating physician and the investigators, a third opinion of an independent reviewer was decisive. Patients with known coronary disease, stroke, aortic stenosis, previous septal reduction therapy, contraindication for CMR imaging or renal impairment (defined as modification of diet in renal disease (MDRD) <30 mL/min) were excluded.[5] The study complies with the Declaration of Helsinki and the protocol was approved by the local ethical committees and

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conducted accordingly. All participants provided written informed consent.

Study protocol

Eligible patients were invited to the hospital to plan and undergo CMR imaging. At baseline, symptoms and medical therapy were recorded and risk factors for cardiovascular disease[16] and sudden cardiac death[1] were scored. A blood sample was drawn for determination of renal function and assessment of cTnT concentration.

CMR imaging protocol

Image acquisition

CMR imaging was performed on a 1.5 T cardiac CMR system Philips Achieva (Philips Healthcare, Best, The Netherlands) or Siemens Avanto (Siemens Healthcare, Erlangen, Germany) according to local protocol. All images were acquired with ECG-gating and during repeated breath-holds of 10–15 s. Breath-hold triple inversion-recovery T2-weighted images with fat-saturation were acquired (short-axis stack covering the LV from base to apex) to assess the presence of HighT2 (typical imaging parameters: repetition time (TR): 2 RR-intervals; echo time (ET): 100 ms; slice thickness: 10 mm; field of view (FOV) 320×320 mm). A long-axis image was obtained to exclude artefacts.[17] For the assessment of LV function, cine imaging was performed using a steady-state free precession sequence (short-axis stack covering the LV from base to apex, typical imaging parameters: TR: 3.4 ms; TE: 1.7 ms; slice thickness: 10 mm; phases per cardiac cycle: 35; FOV: 320×320 mm). T1-weighted inversion-recovery imaging was performed to assess LGE 10 min after the administration of 0.2 mmol/kg contrast medium (Dotarem; Guerbet, Gorinchem, The Netherlands) (typical imaging parameters: TR: 4.0 ms; TE: 1.3 ms; slice thickness: 5 mm; FOV: 330×330 mm; TI was based on TI scout).

Assessment of LV function and mass

Images were analysed with commercially available software (QMass V.7.5, Medis, Leiden, The Netherlands) by two observers (DHFG and JB) unaware of the subjects' clinical and biomarker information. The endocardial and epicardial borders of the LV myocardium were manually drawn in end-diastole and end-systole on the short-axis cine images. Volumes were derived by summation of discs, and ejection fraction was calculated accordingly. LV mass was calculated by subtraction of the endocardial from epicardial volume at end-diastole and multiplication by 1.05 g/cm^3 and indexed to body surface area. LV maximal wall thickness at end-diastole was automatically measured per segment of the AHA-17-segment-model, except for the apex.

Assessment of HighT2 and LGE

The presence of HighT2 and LGE was assessed after equally dividing the LV in basal, mid and apical slices. Then, all 17 segments of the AHA-model were analysed separately. HighT2 and LGE were scored visually per segment as either present or absent. In case of discrepancy between both observers on the presence of LGE or HighT2, a third observer (H-JD) reviewed the images for final adjudication. The extent of LGE was scored according to a semiquantitative score[18] and expressed as a percentage of LV mass filled with LGE. Areas visually identified as HighT2 were manually delineated for determination of the extent of HighT2 as a percentage of the LV volume filled with HighT2. To be incorporated in the extent of HighT2, the SI of visually identified areas of HighT2 had to be above the mean SI plus 2 standard deviations of remote non-thickened myocardium, as described previously.[10]

Assessment of troponin T

For the determination of cTnT the hs-cTnT assay was used and performed on the Elecsys 2010 system (Roche Diagnostics, Almere, The Netherlands).[5] This test has a limit of blank of 3 ng/L, a 99th percentile cut-off point of 14 ng/L and a coefficient of variation of <10% at 13 ng/L.

Aim of the study

We sought to assess the association between HighT2 and an elevated hs-cTnT (≥14 ng/L). In addition, we studied the association with a detectable hs-cTnT (>3 ng/L) and we explored the association between the extent of HighT2 and hs-cTnT as a continuous variable.

Statistical analysis

Continuous variables are presented as means±standard deviations or medians (IQR). Comparisons between groups were made with use of the Student's t-test or Mann-Whitney U test, in case of two groups, or one-way analysis of variance or Kruskal-Wallis, in case of three. Dichotomous variables were compared using a χ^2 or Fisher's exact test, whichever appropriate. In case of missing values we did not use data imputation (99% of baseline data was complete).

In our primary analysis, we compared the proportions of patients with an elevated hs-cTnT between patients with and without HighT2. As a secondary analysis, we compared the proportions of patients with a detectable hs-cTnT. Finally, Spearman's ρ was calculated to study the relation between the extent of HighT2 and the hs-cTnT concentration.

To study the association between HighT2 and hs-cTnT, we followed the general approach to adjust for (confounding) variables by multivariate logistic regression. First, we identified variables that differed ($p<0.10$) between patients with and without HighT2. The second step was to check for relevant confounding of each of these variables by separately adding these to HighT2 as independent variable. We defined relevant confounding as a ≥10% change of the regression coefficient of the association between HighT2 and elevated hs-cTnT. Based upon previous reports in HCM on the association between LV mass and hs-cTnT, we planned to study the association between HighT2 and an elevated hs-cTnT, with specific focus on the relation with LV mass, and also in relation to LGE status.[5 7 8] A p value of <0.05 was considered significant (two-sided). Statistical analysis was performed with IBM SPSS Statistics V.20.0 (IBM, Armonk, New York, USA).

RESULTS

Study population

Baseline clinical and imaging characteristics of the 101 included patients with HCM are displayed in table 1, of whom 28 patients (28%) had HighT2. LGE was significantly more often present, and its extent was higher in patients with HighT2. A characteristic example of a patient with HighT2 is displayed in figure 1.

In 26 patients HighT2 was observed midwall within an area of LGE, in the other two patients with HighT2 there were no segments with LGE. In four of these 26 patients with colocalised HighT2 and LGE, HighT2 was also observed in a segment without LGE. Of all the 96 segments with HighT2 87 (91%) also demonstrated LGE. Furthermore, segments with HighT2

Table 1 Baseline characteristics of patients with HCM with and without HighT2

	Total (n=101)	HighT2+ (n=28)	HighT2− (n=73)	p Value
Age (years)	54±15	52±15	55±15	0.38
Men	54 (54%)	19 (68%)	35 (48%)	0.07
Age at diagnosis (years)	47±16	44±15	49±16	0.23
Pathogenic mutation present	55 (58%)	14 (56%)	41 (59%)	0.82
Atrial fibrillation	16 (16%)	5 (18%)	11 (15%)	0.77
Cardiovascular risk				
Hypertension	36 (36%)	9 (32%)	27 (37%)	0.65
Current smoker	17 (17%)	7 (25%)	10 (14%)	0.23
Dyslipidaemia	25 (25%)	6 (21%)	19 (26%)	0.63
Diabetes	5 (5%)	1 (4%)	4 (6%)	1.0
Recent creatinine (μmol/L)	84±16	87±17	82±15	0.21
Systolic blood pressure (mm Hg)	131±22	131±19	132±23	0.86
Heart rate (bpm)	74±13	79±15	72±12	0.01
Framingham 10-year heart risk (%)	12 (5–25)	15 (8–28)	12 (5–25)	0.68
Risk factors for SCD				
Aborted cardiac arrest/sustained VT	–	–	–	–
Family history of SCD	11 (11%)	3 (11%)	8 (11%)	1.0
Syncope	5 (5%)	2 (7%)	3 (4%)	0.62
Non-sustained VT (Holter)	17 (18%)	6 (24%)	11 (16%)	0.38
Abnormal BP response	12 (12%)	7 (25%)	5 (7%)	0.04
Maximal wall thickness ≥30 mm	3 (3%)	1 (4%)	2 (3%)	1.0
Symptoms				
Chest pain	21 (21%)	3 (11%)	18 (25%)	0.12
Dyspnoea (NYHA class ≥II)	47 (47%)	17 (61%)	30 (41%)	0.08
Therapy				
β-blocker	45 (45%)	13 (46%)	32 (44%)	0.81
Calciumantagonist	16 (16%)	3 (11%)	13 (18%)	0.55
Echocardiography				
LV outflow tract gradient at rest ≥30 mm Hg	19 (19%)	5 (18%)	14 (19%)	0.88
Systolic anterior motion mitral valve	36 (36%)	11 (39%)	25 (35%)	0.67
Left atrial diameter (mm)	43 (39–49)	43 (40–54)	43 (39–48)	0.33
CMR imaging				
Maximal LV wall thickness (mm)	18 (14–21)	21 (19–24)	16 (13–19)	<0.001
LVMI (g/m^2)	61 (52–83)	85 (63–116)	57 (50–73)	<0.001
LVMI≥median	50 (50%)	22 (79%)	28 (39%)	<0.001
LV ejection fraction (%)	59±7	55±7	61±6	<0.001
LGE present (n)	66 (65%)	26 (93%)	40 (55%)	<0.001
LGE extent (% of LV mass)	3 (0–10)	10 (4–19)	1 (0–7)	<0.001

Data are presented as means±standard deviations, medians (IQR) or numbers (percentages).
BP, blood pressure; CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; HighT2, high signal intensity on T2-weighted cardiovascular MRI; LGE, late gadolinium enhancement; LV, left ventricle; LVMI, LV mass indexed to body surface area; NYHA, New York Heart Association; SCD, sudden cardiac death; VT, ventricular tachycardia.

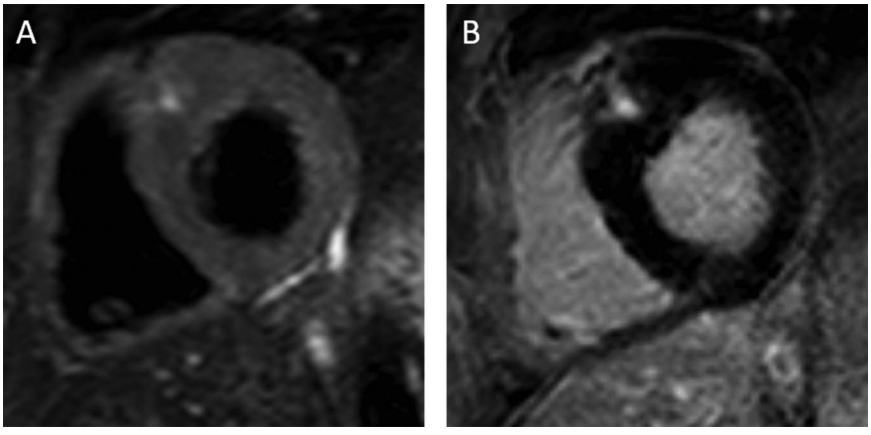

Figure 1 An example of a patient with high signal intensity on T2-weighted cardiovascular MRI (HighT2), increased wall thickness and late gadolinium enhancement (LGE). A characteristic example of a patient with HighT2. HighT2 was focally present in the left ventricle, at the insertion point of the right ventricle, with increased wall thickness and a larger area of LGE on (A) T2-weighted and (B) LGE imaging.

had a higher wall thickness than segments without HighT2 (17 vs 12 mm, p<0.001).

HighT2 and hs-cTnT

Hs-cTnT was elevated in 54% (15/28) of patients with HighT2 and in 14% (10/73) of patients without HighT2 (p<0.001). Also, a detectable hs-cTnT was more often present in patients with HighT2 compared with those without (96% (27/28) vs 66% (48/73), p=0.002). In the 26 patients without a detectable hs-cTnT, HighT2 was present in only one (4%) (table 2). The median extent of HighT2 comprised 1.2% (0.6%–2.9%) of the LV myocardial volume. The median hs-cTnT concentration increased according to the extent of HighT2; from 7 ng/L (3–12) in patients with no HighT2 to 23 ng/L (9–33) in patients with a HighT2 extent above the median (p<0.001) (figure 2). Lastly, the extent of HighT2 significantly correlated with the concentration of hs-cTnT (Spearman's ρ: 0.42, p<0.001).

HighT2 and hs-cTnT: relation to LV mass and the presence of LGE

HighT2 was univariately associated with an elevated hs-cTnT (odds ratio (OR): 7.3; 95% CI 2.7 to 19.7) (table 3). Also left ventricular mass indexed to body surface area (LVMI), the presence and the extent of LGE were associated with an elevated hs-cTnT.

LV mass

Of the 28 patients with HighT2 there were 22 (79%) with an LVMI greater than or equal to the median. In patients with an LVMI greater than or equal to the median (n=50), an elevated hs-cTnT was seen in 64% of patients with HighT2 (14/22) and 21% in patients without HighT2 (6/28) (p=0.002). In patients with an LVMI less than the median (n=50), an elevated hs-cTnT was seen in one out of six patients with HighT2 (17%) and in four out of 44 patients (9%) without HighT2 (p=0.49). After correction for LVMI, HighT2 remained associated with an elevated hs-cTnT (adjusted OR: 3.6; 95% CI 1.2 to 11.1).

Late gadolinium enhancement

Of the 28 patients with HighT2, only two did not have LGE (7%) (hs-cTnT was 7 ng/L in both). Therefore, further analysis of the association between HighT2 and hs-cTnT among patients without LGE was not performed. Although in the total cohort (n=101) the extent of LGE was associated with an elevated hs-cTnT, this association was no longer observed in case only patients with LGE (n=66) were considered. Among the 66 patients with LGE, those with HighT2 had an elevated hs-cTnT in 58% (15/26) compared with 18% of those without HighT2 (7/40) (p=0.001). In addition, the patients with both LGE and HighT2 (n=26) also had the highest median hs-cTnT concentration (table 4).

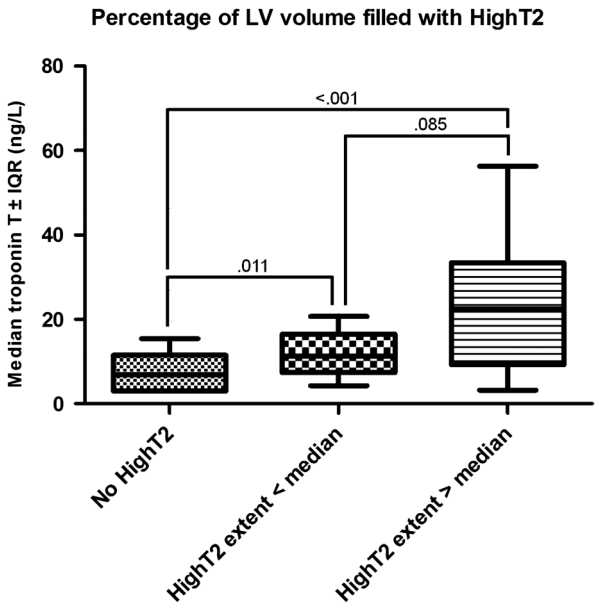

Figure 2 Troponin T concentrations according to extent of HighT2. The median hs-cTnT concentrations increased according to the extent of HighT2 (Spearman's ρ 0.42, p<0.001). Box and whiskers display median, IQR 10th and 90th percentile. HighT2, high signal intensity on T2-weighted cardiovascular MRI; hs-cTnT, highly sensitive cardiac troponin T; LV, left ventricular.

DISCUSSION

To our knowledge, this manuscript reports on the largest cohort of patients with HCM, in which the association between HighT2 and an elevated hs-cTnT has been addressed so far. In this outpatient cohort of patients with HCM, we have demonstrated that HighT2 was present in about one-quarter of patients. In the presence of HighT2 the chances of an elevated hs-cTnT were threefold higher, and the concentration of hs-cTnT was significantly related with a higher extent of HighT2. Notably, in case of an undetectable hs-cTnT we observed a very high negative predictive value for HighT2 (>95%). These observations corroborate with the hypothesis that HighT2 in HCM may be indicative of recently sustained myocardial injury.

Table 2 Troponin T in patients with HCM with and without HighT2

	Total (n=101)	HighT2+ (n=28)	HighT2− (n=73)	p Value
Primary outcome				
Hs-cTnT ≥14 ng/L	25 (25%)	15 (54%)	10 (14%)	<0.001
Secondary outcomes				
Hs-cTnT >3 ng/L	75 (74%)	27 (96%)	48 (66%)	0.002
Hs-cTnT (ng/L)	8 (3–14)	15 (8–26)	7 (3–12)	<0.001

Data are presented as medians (IQR) or numbers (percentages).
HCM, hypertrophic cardiomyopathy; HighT2, high signal intensity on T2-weighted cardiovascular MRI; Hs-cTnT, highly sensitive cardiac troponin T.

Table 3 Logistic regression analysis for the association of HighT2 with an elevated hs-cTnT

	OR (95% CI)	p Value
Univariate		
HighT2	7.3 (2.7 to 19.7)	<0.001
	aOR (95% CI)	**p Value**
Adjusted for LVMI		
HighT2	3.6 (1.2 to 11.1)	0.025

Multivariable analyses revealed that other variables (sex, heart rate, dyspnoea, LV ejection fraction) had no relevant impact on the association between HighT2 and an elevated hs-cTnT.
aOR, adjusted odds ratio; HighT2, high signal intensity on T2-weighted cardiovascular MRI; hs-cTnT, highly sensitive cardiac troponin T; LV, left ventricular; LVMI, left ventricular mass indexed to body surface area; OR, odds ratio.

Table 4 Characteristics of patients with HCM with and without LGE and/or HighT2

	LGE− and HighT2− (n=33)	LGE+ and HighT2− (n=40)	LGE+ and HighT2+ (n=26)	p Value
Age (years)	56±16	54±15	51±15	0.54
Men	12 (36%)	23 (58%)	18 (69%)	0.03
CMR imaging				
Maximal LV wall thickness (mm)	14 (13–16)	18 (15–21)	21 (19–24)	<0.001
LV mass indexed to BSA (g/m^2)	52 (46–61)	62 (51–75)	85 (62–115)	<0.001
LV ejection fraction (%)	62±6	60±7	55±7	<0.001
LGE extent (% of LV mass)	–	7 (3–10)	10 (6–21)	<0.001
Highly sensitive cardiac troponin T				
Cardiac troponin T (ng/L)	6 (3–11)	8 (3–12)	15 (9–28)	<0.001
Cardiac troponin T >3 ng/L	20 (61%)	28 (70%)	25 (96%)	0.007
Cardiac troponin T ≥14 ng/L	3 (9%)	7 (18%)	15 (58%)	<0.001

Data are presented as means±standard deviations, medians with IQR or numbers and percentages.
BSA, body surface area; CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; HighT2, high signal intensity on T2-weighted cardiovascular MRI; LGE, late gadolinium enhancement; LV, left ventricle.

Based upon the concept that myocardial injury is associated with adverse prognosis, the impact of troponin as well as of HighT2 have been addressed in clinical studies. Elevated hs-cTnT has been demonstrated in up to 50% of patients with HCM, and has been related to adverse remodelling and prognosis in HCM.[6 7] HighT2 has been shown to be associated with malignant ventricular arrhythmias.[10 11 14] The present report is the first to demonstrate an association between HighT2 and hs-cTnT, independent of LVMI. Moreover, in patients with an undetectable troponin concentration, chance of HighT2 is extremely low (<5%). As previously suggested by others,[12 19 20] our results support that HighT2 is indeed indicative of recently sustained myocardial tissue injury in HCM. For the interpretation of HighT2 contrasting theories have been postulated varying from myocardial injury due to ischaemia,[9 10 12] to regional myocardial differences in water content and the suggestion that HighT2 merely reflects specific characteristics of various collagen species.[12 21 22]

Currently, the possible mechanisms involved in the appearance of HighT2 at CMR imaging in patients with HCM have not been thoroughly studied. Given the distinct differences in pathophysiology between myocarditis, myocardial infarction and HCM, the interpretation of HighT2 in areas of LGE may not be interchangeable, as it may not reflect the similar histological process.[23 24]

Whereas in myocardial infarction information on the evolution of the extent and coexistence of HighT2 and LGE is available, follow-up information on HighT2 in HCM is lacking. Importantly, patterns in myocardial infarction can be explained by a front of (transmural) ischaemia that extends from areas near the endocardium with HighT2 coinciding with LGE (ie, necrotic tissue) to more epicardially located HighT2, outside the area of LGE as indicator of salvaged myocardium. In HCM, however, the areas of ischaemia are not defined by the territory of the supplying infarct-related artery, and thus do not result in circumscript segments of jeopardised myocardium. In fact, the observed pattern of injury in HCM is not endocardial to epicardial, but is characterised by focal midwall areas of LGE containing HighT2. This may be related to the distinct difference in the aetiology of ischaemia, with diffuse microvascular disease, myocyte disarray and sarcomere dysfunction. Interestingly, in areas of fibrosis there is histological proof of viable cardiomyocytes.[25] Although the interpretation of HighT2 in areas of LGE remains speculative, these cells could form the substrate responsible for HighT2 in areas of LGE. Our finding that an elevated troponin level is three times more likely in patients with HighT2 than in patients without HighT2 could be the first clue to support this hypothesis, but requires confirmative studies and CMR follow-up.

In HCM, HighT2 and hs-cTnT may be indicative of the same, that is, recently sustained myocardial injury, but it needs to be elucidated which mechanisms contribute to injury in HCM. One of the proposed causes of injury might be an increase in oxygen demand due to LV hypertrophy. This is supported by the fact that in both patients with HCM and the general population, LV mass has been associated with hs-cTnT.[5 26] Moreover, in previous studies on HighT2 in HCM it has consistently been reported that HighT2 was almost exclusively present in hypertrophic myocardium.[9–14]

Other causes of injury include small vessel disease, myocardial disarray and sarcomere dysfunction,[27 28] which may account for insufficient myocardial perfusion, which has been related to areas of HighT2.[10 13] Notably, in patients with an LVMI below the median, we still observed an elevated hs-cTnT in about 10% and HighT2 in 20%.

In short, various mechanisms may contribute to active tissue injury in HCM, evident at some point in time as HighT2. This may finally result in evidence of a more chronic form of injury, visualised by LGE, which is present in the majority of patients with HCM.[9–12] Due to the cross-sectional design of our study, this scenario remains hypothetical, and requires confirmation in larger studies with sequential CMR imaging.

In analogy to previous reports, we observed that the presence of LGE was associated with hs-cTnT.[7 8] This corroborates with the general concept that LGE is considered to represent fibrosis, that is, advanced stage injury.

Though not the primary aim of our study, our finding that patients with both LGE and HighT2 had the highest hs-cTnT concentrations is interesting, and requires further study. Hypothetically, in HCM LGE with HighT2 might indicate active, ongoing tissue injury, as compared with a more burnt-out phase in which active injury is no longer present and LGE occurs without HighT2. This would imply a potential clinical use of HighT2 in HCM for assessment of the stage of LGE resembling the current use of HighT2 in patients with ischaemic heart disease, in which HighT2 is able to discriminate acute

from chronic myocardial infarction.[23] Currently, LGE has been demonstrated to be associated with a detrimental disease course in HCM, but does not effectively discriminate low and high-risk patients, due to its high prevalence in HCM.[29] Hypothetically, HighT2 may allow for better differentiation of patients with LGE into higher and lower risk patients.

Finally, it should be appreciated that in the absence of HighT2, hs-cTnT was still detectable in two-thirds and even elevated in about one-eighth of the patients. One might speculate that hs-cTnT is more sensitive to injury and may serve as an early marker of active disease.

In this study, we have provided supportive evidence for the assumption that HighT2 is representative of recently sustained myocyte injury in patients with HCM. Additional insights may be provided by studies on the impact of exercise and by (CMR) follow-up studies. It has been suggested that exercise in patients with HCM may result in (additional) ischaemia with a troponin rise afterwards, which can be blunted or prevented with the use of β-blockers.[30] With CMR follow-up we would be able to study whether areas of HighT2—as a marker of active tissue injury—may evolve into (larger) areas of 'chronic injury', as represented by (the extent of) LGE. A first indication of this concept has been described in eight patients with HCM, which suggested that hs-cTnT is associated with an increase of LGE at CMR follow-up.[8] Given the association of LGE with adverse prognosis,[29] the next step would be to assess and compare the predictive value of HighT2 to other (much easier) promising markers, such as hs-cTnT for adverse clinical events, in a study adequately powered for clinical outcome.

Limitations

Although this is, as of yet, the largest HCM cohort with systematic T2-weighted CMR imaging, our results should be considered as pilot data. Both the assessment of HighT2 and LGE are subject to interpretation. First, T2-weighted image interpretation is often quite challenging due to a limited signal-to-noise ratio and artefacts such as the slow flow phenomenon. Unfortunately at the start of our study T2-mapping and T1-mapping sequences were not widely available, but these techniques seem very promising and may lead to more objective data. In analogy to previous studies in HCM, the presence of HighT2 was visually assessed by two independent observers (DHFG and JB).[9 13] In 14 out of 101 patients (14%) a third observer was necessary (Cohen's κ: 0.61). Although ancillary SI analysis demonstrated that there was marked contrast in SI between areas, visually identified as HighT2, and normal non-thickened myocardium (data not shown), the interpretation of an area of high SI remains subjective with moderate interindividual agreement. HighT2 was associated with an elevated hs-cTnT regardless of whether we used data on the presence of HighT2 of observer 1 or 2. Lastly, LGE extent was assessed according to a validated semiquantitative score, but quantitative analysis could have provided more detailed insights.[18]

CONCLUSIONS

In this CMR study on an outpatient cohort of patients with HCM, we observed HighT2 in a quarter of patients, and demonstrated that HighT2 was associated with a markedly higher risk of an elevated hs-cTnT. This observation, combined with the very high negative predictive value of an undetectable troponin for HighT2, provides supportive evidence for the hypothesis that HighT2 is indicative of recently sustained myocyte injury. Confirmative studies are warranted, as well as additional research with regard to the potential future role of HighT2 in HCM risk stratification and/or treatment.

Key messages

What is already known on this subject?
Areas of high signal intensity on T2-weighted cardiovascular MRI (HighT2) have been demonstrated in hypertrophic cardiomyopathy, and might be representative of a more active disease state.

What might this study add?
HighT2 was present in a quarter of our hypertrophic cardiomyopathy (HCM) population, and was associated with an elevated level of highly sensitive cardiac troponin T (hs-cTnT), independent of left ventricular mass. The presence of HighT2 increased the chance of an elevated hs-cTnT threefold. Moreover, in case of an undetectable hs-cTnT, we observed a very high negative predictive value for HighT2 (>95%). These observations support that HighT2 in HCM indicates recently sustained myocardial injury.

How might this impact on clinical practice?
With further cardiovascular magnetic resonance follow-up studies, HighT2 might demonstrate to be useful as a predictor of disease progression, indicated, for example, by an increase of late gadolinium enhancement. The next step would be to assess the predictive value of HighT2 for adverse clinical events.

Contributors All authors analysed data, developed the study protocol and design and read, commented on, contributed to and approved the submitted manuscript. DHFG, GEC and MAB were the main contributors to the writing of the manuscript. MAB and MJMK contributed to the planning and interpretation of the study. Our manuscript is not under consideration elsewhere and has not been published previously.

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REFERENCES

1 Maron BJ, McKenna WJ, Danielson GK, *et al*. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003;42:1687–713.
2 Gersh BJ, Maron BJ, Bonow RO, *et al*. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;124:e783–831.
3 Basso C, Thiene G, Corrado D, *et al*. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. *Hum Pathol* 2000;31:988–98.
4 Petersen SE, Jerosch-Herold M, Hudsmith LE, *et al*. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. *Circulation* 2007;115:2418–25.
5 Cramer G, Bakker J, Gommans F, *et al*. Relation of highly sensitive cardiac troponin T in hypertrophic cardiomyopathy to left ventricular mass and cardiovascular risk. *Am J Cardiol* 2014;113:1240–5.
6 Kubo T, Kitaoka H, Yamanaka S, *et al*. Significance of high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2013;62:1252–9.
7 Moreno V, Hernández-Romero D, Vilchez JA, *et al*. Serum levels of high-sensitivity troponin T: a novel marker for cardiac remodeling in hypertrophic cardiomyopathy. *J Card Fail* 2010;16:950–6.
8 Kawasaki T, Sakai C, Harimoto K, *et al*. Usefulness of high-sensitivity cardiac troponin T and brain natriuretic peptide as biomarkers of myocardial fibrosis in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2013;112:867–72.
9 Abdel-Aty H, Cocker M, Strohm O, *et al*. Abnormalities in T2-weighted cardiovascular magnetic resonance images of hypertrophic cardiomyopathy: regional

distribution and relation to late gadolinium enhancement and severity of hypertrophy. *J Magn Reson Imaging* 2008;28:242–5.
10 Melacini P, Corbetti F, Calore C, *et al*. Cardiovascular magnetic resonance signs of ischemia in hypertrophic cardiomyopathy. *Int J Cardiol* 2008; 128:364–73.
11 Hen Y, Iguchi N, Machida H, *et al*. High signal intensity on T2-weighted cardiac magnetic resonance imaging correlates with the ventricular tachyarrhythmia in hypertrophic cardiomyopathy. *Heart Vessels* 2013;28:742–9.
12 Tyan CC, Armstrong S, Scholl D, *et al*. Stress hypoperfusion and tissue injury in hypertrophic cardiomyopathy: spatial characterization using high-resolution 3-tesla magnetic resonance imaging. *Circ Cardiovasc Imaging* 2013;6:229–38.
13 Hueper K, Zapf A, Skrok J, *et al*. In hypertrophic cardiomyopathy reduction of relative resting myocardial blood flow is related to late enhancement, T2-signal and LV wall thickness. *PLoS One* 2012;7:e41974.
14 Todiere G, Pisciella L, Barison A, *et al*. Abnormal T2-STIR magnetic resonance in hypertrophic cardiomyopathy: a marker of advanced disease and electrical myocardial instability. *PLoS One* 2014;9:e111366.
15 Amano Y, Aita K, Yamada F, *et al*. Distribution and clinical significance of high signal intensity of the myocardium on T2-weighted images in 2 phenotypes of hypertrophic cardiomyopathy. *J Comput Assist Tomogr* 2015;39:951–5.
16 D'Agostino RB Sr, Vasan RS, Pencina MJ, *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743–53.
17 Schulz-Menger J, Bluemke DA, Bremerich J, *et al*. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post Processing. *J Cardiovasc Magn Reson* 2013;15:35.
18 Doesch C, Huck S, Böhm CK, *et al*. Visual estimation of the extent of myocardial hyperenhancement on late gadolinium-enhanced CMR in patients with hypertrophic cardiomyopathy. *Magn Reson Imaging* 2010;28:812–19.
19 Lehrke S, Lossnitzer D, Viertler D, *et al*. T2 abnormalities in patients with hypertrophic cardiomyopathy characterized by cardiovascular magnetic resonance imaging- an indicator of myocardial injury as assessed by the high sensitive cardiac troponin T assay. *J Cardiovasc Magn Reson* 2012;14:O100.
20 Chen S, Chen Y, Zhang Q, *et al*. Is tissue edema a potential cause of myocardial injury in HCM patients: a CMR study. *Cardiology* 2014;129:122.
21 Scholz TD, Fleagle SR, Burns TL, *et al*. Nuclear magnetic resonance relaxometry of the normal heart: relationship between collagen content and relaxation times of the four chambers. *Magn Reson Imaging* 1989;7:643–8.
22 Takeuchi M, Sekino M, Iriguchi N, *et al*. Dependence of the spin-spin relaxation time of water in collagen gels on collagen fiber directions. *Magn Reson Med Sci* 2004;3:153–7.
23 Abdel-Aty H, Zagrosek A, Schulz-Menger J, *et al*. Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. *Circulation* 2004;109:2411–16.
24 Eitel I, Friedrich MG. T2-weighted cardiovascular magnetic resonance in acute cardiac disease. *J Cardiovasc Magn Reson* 2011;13:13.
25 Konno T, Hayashi K, Fujino N, *et al*. High sensitivity of late gadolinium enhancement for predicting microscopic myocardial scarring in biopsied specimens in hypertrophic cardiomyopathy. *PLoS One* 2014;9:e101465.
26 de Lemos JA, Drazner MH, Omland T, *et al*. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010;304:2503–12.
27 Tanaka M, Fujiwara H, Onodera T, *et al*. Quantitative analysis of narrowings of intramyocardial small arteries in normal hearts, hypertensive hearts, and hearts with hypertrophic cardiomyopathy. *Circulation* 1987;75:1130–9.
28 Maron BJ, Wolfson JK, Epstein SE, *et al*. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1986;8:545–57.
29 Briasoulis A, Mallikethi-Reddy S, Palla M, *et al*. Myocardial fibrosis on cardiac magnetic resonance and cardiac outcomes in hypertrophic cardiomyopathy: a meta-analysis. *Heart* 2015;101:1406–11.
30 Pop GA, Cramer E, Timmermans J, *et al*. Troponin I release at rest and after exercise in patients with hypertrophic cardiomyopathy and the effect of betablockade. *Arch Cardiol Mex* 2006;76:415–18.

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High T2-weighted signal intensity is associated with elevated troponin T in hypertrophic cardiomyopathy

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