Diffuse Ventricular Fibrosis on Cardiac Magnetic Resonance Imaging Associates with Ventricular Tachycardia in Patients with Hypertrophic Cardiomyopathy

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Short Title Diffuse fibrosis predicts ventricular arrhythmia in HCM

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Abstract

Introduction

Non-sustained ventricular tachycardia (NSVT) is a risk factor for sudden cardiac death (SCD) in patients with hypertrophic cardiomyopathy (HCM). We aimed to assess whether diffuse ventricular fibrosis on cardiac magnetic resonance (CMR) imaging could be a surrogate marker for ventricular arrhythmias in patients with HCM.

Methods

100 patients with HCM (mean age 51 ± 13 years, septal wall thickness 20 ± 5 mm) underwent CMR with a 1.5T scanner to determine the presence of ventricular late gadolinium enhancement (LGE) for focal fibrosis, and post-contrast T_1 mapping for diffuse ventricular fibrosis. The presence of NSVT was determined by holter monitoring and a subset of high risk patients received an implantable cardioverter-defibrillator (ICD).

Results

NSVT was detected in 23 of 100 patients with HCM. Focal ventricular fibrosis (by LGE) was observed in 87%, with no significant difference between patients with (96%) or without NSVT (86%, $p=0.19$). However, LGE mass was greater in patients with (16.5 ± 19.1 g) versus without NSVT (7.6 ± 10.2 g, $p<0.01$). NSVT was associated with a significant reduction in ventricular T_1 relaxation time (422 ± 54 ms) versus patients without NSVT (512 ± 115 ms; $p<0.001$). There was significant reduction in ventricular T_1 relaxation time in patients with (430 ± 48 ms) versus without aborted SCD (495 ± 113 ms; $p=0.01$) over a mean follow-up of 40 ± 10 months. On multivariate analysis post-contrast ventricular T_1 relaxation time and septal wall thickness were the only predictors of NSVT.

Conclusion

Post-contrast T_1 relaxation time on CMR is associated with ventricular arrhythmias in patients with HCM. Diffuse ventricular fibrosis may be an important marker of arrhythmic risk in patients with HCM.

Keywords: cardiac magnetic resonance; hypertrophic cardiomyopathy; implantable cardioverter defibrillator; MRI; myocardial fibrosis; ventricular tachycardia

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List of Abbreviations

HCM	hypertrophic cardiomyopathy
CMR	cardiac magnetic resonance
LGE	late gadolinium enhancement
LVEF	left ventricular ejection fraction
VT	ventricular tachycardia
NSVT	non-sustained ventricular tachycardia
SCD	sudden cardiac death
ICD	implantable cardioverter-defibrillator
ROI	region of interest
GFR	glomerular filtration rate

Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited cardiomyopathy affecting approximately 1 in 500 people and is associated with an increased risk of sudden cardiac death (SCD)¹. Consensus guidelines identify the following risk factors for SCD in patients with HCM: 1) ventricular fibrillation, sustained VT, or SCD survivors; 2) family history of SCD; 3) unexplained syncope; 4) maximum left ventricular wall thickness > 30mm; 5) abnormal blood pressure response to exercise; and 6) presence of non-sustained VT. Unfortunately there is a low predictive value for all variables except prior cardiac arrest¹. Evidence to support NSVT as a risk factor in HCM patients has been mixed, and may depend on additional factors such as age, symptoms and exercise as a trigger²⁻⁶. Additional non-invasive markers may be useful to determine the risk of sudden death in patients with HCM.

An emerging tool for risk stratification of SCD in HCM is cardiac magnetic resonance (CMR) imaging, which may identify focal or diffuse ventricular fibrosis. Prior studies have demonstrated an association between ventricular late gadolinium enhancement (LGE) and NSVT on Holter monitoring^{7,8}, SCD and appropriate ICD therapy⁸⁻¹². However, LGE is present in the majority of patients with HCM. As such, the extent of LGE rather than its presence has variably been aligned with the risk of ventricular arrhythmias or SCD^{7,9,11}. LGE imaging requires a difference in signal intensity between fibrotic and normal tissue to be displayed¹³ and is insensitive to diffuse fibrosis. Diffuse myocardial fibrosis can be measured with CMR with contrast enhanced T₁ mapping and has been well validated histologically¹³⁻¹⁵. We hypothesized that quantification of diffuse ventricular fibrosis using post-contrast T₁ mapping on CMR may be associated with ventricular arrhythmias in patients with HCM.

Methods

Patient selection

This prospective observational study was undertaken at the Alfred Hospital, Melbourne, Australia, and approved by the institution's ethics committee. All patients gave informed consent. Patients were included in this research if they fulfilled diagnostic criteria for HCM (myocardial hypertrophy including asymmetric septal hypertrophy $\geq 1.5\text{mm}$; septal to posterior wall thickness ratio $\geq 1.3:1$; and absence of an alternate explanation for

hypertrophy). Exclusion criteria included ischaemic heart disease, contra-indication for CMR (pacemaker or defibrillator), and significant renal dysfunction ($\text{eGFR} < 50 \text{ mL/min/1.73m}^2$).

CMR Protocol

CMR sequences

A previously validated CMR protocol is described¹⁶. CMR was performed with a clinical 1.5-T scanner (Signa HD 1.5-T, GE Healthcare, Waukesha, Wisconsin, USA) during a breath-hold of 10–15 s. LV function was assessed by a steady-state free precession (SSFP) pulse sequence (repetition time [TR] = 3.8 ms, echo time [TE] = 1.6 ms, 30 phases, slice thickness 8 mm). Initial cine CMR sequences were performed in 3 standard long-axis (4-, 3- and 2-chamber views) and short-axis slices (basal, mid, and apical). LV volume and function were assessed using a contiguous short-axis SSFP stack (8 mm slice thickness, no gap), extending from the mitral valve annulus to the LV apex.

LGE was evaluated 10 minutes after a bolus of gadolinium-diethylene triamine penta-acetic acid (DTPA) (0.2 mmol/kg BW Magnevist, Schering, Germany) to identify regional fibrosis using a T_1 -weighted inversion recovery gradient echo technique (TR 7.1 ms, TE 3.1 ms, inversion time [TI] individually determined to null the myocardial signal, slice thickness 8 mm, matrix 256×192 , number of acquisitions = 2, inversion pulse every RR interval). LGE imaging was performed using both standard long-axis and short-axis views of the LV (including a contiguous stack of slices from the mitral valve annulus to the apex).

For the evaluation of diffuse myocardial fibrosis, T_1 mapping was used to acquire mid-left ventricular short-axis images over a range of inversion times. The sequence consisted of an electrocardiogram-triggered, inversion recovery prepared, 2-dimensional fast gradient echo sequence employing variable temporal sampling of k-space (VAST) (Global Applied Science Laboratory, GE Healthcare). Ten images were acquired sequentially at increasing inversion times (75 to 750 ms), commencing 20 minutes after the bolus of gadolinium-DTPA. Imaging parameters were TR/TE: 3.7 ms/1.2 ms, flip angle: 20° , 256×128 acquisition matrix, 36×27 cm field of view, slice thickness 8 mm, TI: 75–750 ms, trigger delay 300 ms, and views per segment = 24.

Assessment of left ventricular volumes, function, mass, and regional (focal) fibrosis

As previously described¹⁶, we performed volumetric analysis of the LV using the summation of disc method. Regional fibrosis was identified by LGE within the myocardium, defined quantitatively by a myocardial post-contrast signal intensity 6 SD above that within a reference region of remote myocardium (without LGE) within the same slice, confirmed in two orthogonal views. Given the frequency of insertion point LGE, LGE was also quantified as non-insertion point LGE. LGE quantity, expressed as a percentage of total LV mass, was calculated from all short-axis slices using the summation of disc method.

Assessment of diffuse left ventricular fibrosis using T₁ mapping

The ten short-axis images of varying inversion times were transferred to an external computer for analysis using a dedicated research software package (Cinetool, Global Applied Science Laboratory, GE Healthcare)¹⁷. For each short-axis image, a ROI was drawn around the entire LV myocardium (excluding papillary muscles and areas of regional LGE) to calculate post-contrast myocardial T₁ time. The post-contrast T₁ times were corrected using a formula previously reported by Gai et al that accounts for variation in eGFR (standardized to 90ml/min), acquisition time of T₁ mapping images post gadolinium contrast (standardized to 15 minutes), height and weight¹⁸.

Echocardiography

Transthoracic echocardiography was performed on all patients immediately prior to CMR, and included assessment of LV systolic and diastolic function including E/e' (mean of septal and lateral measurements) for assessment of LV filling pressure.

All CMR and echocardiography images were analysed by two experienced CMR physicians blinded to analysis of arrhythmic outcomes.

Assessment of NSVT and ventricular arrhythmias

Patients were enrolled in this research at the time of cardiac MRI, and subsequently Holter monitoring was performed in 93 of 100 patients after study enrollment and not in 7 who underwent ICD implantation immediately after CMR (5 secondary prevention and 2 primary prevention). NSVT was defined as ≥ 3 beats of NSVT at > 120 beats per minute. Number of

NSVT episodes in 24 hours, maximum number of beats of NSVT, and heart rate during NSVT was recorded. Sustained VT was defined as > 30 seconds of VT. Atrial fibrillation (AF) was documented if persistent for more than 30 seconds. We pre-specified a secondary endpoint of aborted sudden cardiac death that included patients with ICD reversion of VF.

All ICD interrogations were analyzed for the presence of NSVT, and for appropriate or inappropriate device therapy (antitachycardia pacing ATP, or defibrillation). Defibrillator programming was according to physician preference, with the routine programming of a monitor zone from 150bpm, VT zone from 170bpm, and VF zone from 200 bpm.

Interpretation of CMR and Holter monitoring

Analysis of CMR, Holter monitoring, or ICD interrogation was performed by senior CMR or electrophysiology-pacing cardiologists blinded to clinical parameters including presence of NSVT, ICD therapy or CMR data, respectively. ICD therapy terminating sustained VT or VF was independently reviewed by two electrophysiology-pacing cardiologists before being classified as aborted SCD.

Statistics

Scalar data are expressed as mean $\pm$ standard deviation (SD); and median (interquartile range). After assessment of normal distribution with the Kolmogorov–Smirnov test, two-group comparisons were made using Student's t test for continuous variables, or the Chi-squared test for categorical variables. The independent samples Mann-Whitney U test was used for non-normally distributed variables. Results are presented for the entire cohort as well as for patients with Holter monitoring only, and for patients with ICD. Logistic regression analysis was utilized to assess the association of continuous and categorical variables with the presence of NSVT in univariable and multivariable models. Logistic regression was not performed for the secondary endpoint of aborted SCD due to the low number of events. Receiver Operating Characteristic (ROC) curves were generated across a range of post-contrast ventricular T₁ relaxation times (that had been transformed into

binary variables) to define the T_1 time that performed best regarding area under the curve (AUC) for the identification of 1) NSVT or 2) aborted SCD; Chi-squared test was used to assess the association of this post-contrast ventricular T_1 time and the presence of NSVT or aborted SCD, respectively. A two-tailed p value of <0.05 was considered significant. Analyses were conducted using SPSS software (version 22, SPSS, Chicago, Illinois).

Results

Baseline characteristics

We included all 100 patients with HCM (mean age 51 ± 13 years; BMI $28 \pm 5 \text{ kg/m}^2$; CMR LVEF $69 \pm 8\%$, septal wall thickness $20 \pm 5 \text{ mm}$, septal: posterior wall ratio 2.4 ± 0.7 , left ventricular mass index $83 \pm 31 \text{ g/m}^2$, left atrial area $29 \pm 7 \text{ cm}^2$) who underwent contrast-enhanced CMR for evaluation of both focal (by LGE) and diffuse (by T_1 mapping) ventricular fibrosis at our institution between August 2010 and September 2013 (Table 1).

Cardiac MRI – focal and diffuse fibrosis: impact on NSVT

LGE was identified in 87 patients (insertion point 71%, septum 46%, apex 13%), with no difference in the presence of LGE between patients with (96%) or without NSVT (84%, $p=0.16$). In the 63 patients with non-insertion point LGE, 18 (29%) had NSVT; and in the 37 patients without non-insertion point LGE, 5 (14%) had NSVT ($p=0.08$). However, LGE mass and LGE mass as a percentage of total LV mass were greater in HCM patients with NSVT (Table 2, Figure 1). Post-contrast ventricular T_1 relaxation time in the whole cohort was $491 \pm 111 \text{ ms}$; the T_1 time was significantly shorter in patients with NSVT ($422 \pm 54 \text{ ms}$) versus without NSVT ($512 \pm 115 \text{ ms}$, $p<0.001$, Figure 2).

Rhythm analysis

The mean time from CMR to holter monitoring assessment of NSVT was 7 ± 16 months and the mean time from CMR to ICD assessment of NSVT was 17 ± 10 months ($p<0.01$). Holter monitoring was performed in 93 patients and not in 7 patients, as an ICD had been implanted soon after CMR and study enrollment (table 3). A further 13 patients underwent

ICD implant over the follow-up period. The indications for ICD were primary prevention in 15 and secondary prevention in 5.

NSVT was documented in 23 patients (holter monitor in 12 and on ICD in 13 including 2 patients with NSVT detected on both Holter and ICD interrogation). In patients with NSVT the mean number of NSVT episodes was 2 ± 2 (range minimum-maximum, 1-5); the maximum number of continuous NSVT beats was 12 ± 10 beats (range, 4-29); and the NSVT rate was 169 ± 40 beats per minute (range, 120-260 beats per minute).

Post-contrast ventricular T_1 relaxation time was significantly shorter in patients with NSVT on either Holter or ICD (422 ± 54 ms) versus patients without NSVT on either Holter or ICD (512 ± 115 ms, $p < 0.001$). The post-contrast ventricular T_1 relaxation time remained significantly shorter in patients with NSVT on Holter only (424 ± 45 ms) versus patients without NSVT on Holter only (506 ± 116 ms, $p < 0.001$).

Predictors of NSVT

On logistic regression analysis, significant univariable predictors of NSVT included post-contrast ventricular T_1 relaxation time, septal wall thickness on CMR, LGE mass (grams), and LGE % of total LV mass (supplementary table 1). On multivariable analysis confined to significant univariable predictors, post-contrast T_1 relaxation time ($p = 0.004$) and septal wall thickness remained significant ($p = 0.04$).

On ROC analysis, the best performing post-contrast ventricular T_1 relaxation time for the prediction of NSVT was 490ms, with 1 of 38 (3%) of patients having NSVT if the ventricular T_1 relaxation time was > 490 ms, versus 22 of 62 (36%) if < 490 ms ($p < 0.001$).

Aborted Sudden Cardiac Death

Seven patients had aborted SCD, including 5 patients with aborted SCD prior to ICD implant and a further 2 patients with primary prevention devices who had ICD reversion of VF. The post-contrast ventricular T_1 relaxation time was significantly shorter in the aborted SCD group (430 ± 48 ms) versus non SCD group (495 ± 113 ms; $p = 0.01$) over a mean follow-up of 40 ± 10 months (Figure 3).

On ROC analysis, the best performing post-contrast ventricular T_1 relaxation time for the prediction of aborted SCD was 440ms, with 2 of 66 (3%) patients having aborted SCD if the T_1 relaxation time was >440ms, versus 5 of 34 (15%) if <440ms ($p=0.03$) (Figure 4).

All patients with aborted SCD had presence of LGE, compared with 87% of patients without aborted SCD ($p=0.31$). In the 63 patients with non-insertion point LGE group, aborted SCD occurred in 7 compared with no aborted SCD in the 37 patients with absence of non-insertion point LGE ($p=0.04$). Patients with aborted SCD had significantly increased LGE mass (23 ± 27 g) compared to patients without aborted SCD (9 ± 11 g, $p=0.03$) (figure 5). There was no difference in LGE mass as a percentage of LV mass between patients with ($7\pm 5\%$) versus without aborted SCD ($5\pm 7\%$, $p=0.12$) (figure 5).

AF was identified in 16 patients, with no difference in post-contrast ventricular T_1 relaxation time between patients with (465 ± 107 ms) versus without AF (495 ± 112 ms, $p=0.31$). One patient received inappropriate ICD therapy for AF with a rapid ventricular response.

Discussion

Patients with hypertrophic cardiomyopathy have an increased risk of sudden cardiac death; however, determining an individual's risk remains a challenge despite recognized factors associated with sudden cardiac death. CMR can provide diagnostic and prognostic information in HCM. While the extent of LGE as a marker of focal fibrosis is increasingly recognized as a marker of sudden death, there are no such data on T_1 mapping, a measure of diffuse fibrosis. In the present study we demonstrated the following preliminary findings in patients with HCM who underwent CMR and cardiac monitoring:

1. Post-contrast ventricular T_1 relaxation time was significantly reduced in patients with NSVT and patients with aborted SCD;
2. The quantity, rather than presence of LGE was associated with NSVT and aborted SCD;

3. Following multivariate analysis, post-contrast ventricular T_1 relaxation time and septal wall thickness on CMR were predictors of NSVT;
4. NSVT was identified in 36% of patients with a post-contrast ventricular T_1 relaxation time cut-off of less than 490ms versus 3% if more than 490ms ($p<0.01$). Aborted SCD was identified in 15% of patients with a T_1 time less than 440ms versus 3% if more than 440ms ($p=0.02$);

NSVT and SCD in patients with HCM

NSVT has variably been reported as a risk factor for SCD in patients with HCM, and may be modified by factors such as age, symptoms, and association with exercise²⁻⁶. In the current study only patients with NSVT required ICD therapy, although this was non-significant due to the low number of events. Maron et al performed 24-hour Holter monitoring in 99 patients with HCM with an incidence of NSVT of 19% translating to an 8%/year risk of SCD vs 1% in patients without NSVT². In a larger series of 531 patients, Monserrat et al reported a similar prevalence of NSVT; however, this was only a risk factor for SCD in younger patients⁵.

The role of LGE on arrhythmic outcomes in HCM

LGE is present in the vast majority of patients with HCM. Several reports suggest the amount or proportion of LGE is associated with ventricular arrhythmias^{7,8,11}. O'Hanlon and colleagues reported the presence of focal ventricular LGE in 63% of 213 patients with HCM. Although both LGE and NSVT predicted ventricular tachyarrhythmia on univariate analysis, only NSVT was a multivariable predictor⁹. Similarly, Rubinstein et al identified LGE in 56% of 424 HCM patients, with LGE patients more likely to have NSVT, with both NSVT and LGE multivariable predictors of SCD⁸. Adabag et al reported a 7-fold increase in the risk of NSVT in HCM patients with LGE; however, the amount of LGE as a % of total LV myocardium was not associated with NSVT⁷. In contrast, Chan et al identified a significant correlation between LGE as a percent of LV mass with the risk of SCD¹¹. Our results are more in keeping with the latter study, in that the presence of LGE (87%) was not associated with NSVT or SCD in the current study; however, there was an association between the proportion of LGE and

ventricular arrhythmias. The differences may be explained by the very high prevalence of focal LGE in our cohort (87% vs 41% in Adabag et al) that may be secondary to the higher rate of insertion point LGE in our cohort compared to other studies¹⁹, and highlights the limitation of using LGE in a binary fashion for prediction of sudden cardiac death. When excluding patients with insertion point LGE, 63% of the cohort had delayed enhancement that was significantly associated with SCD. In patients without non-insertion point LGE, there were no cases of aborted SCD. Due to the small sample size of the present study, we are unable to ascertain whether diffuse ventricular fibrosis on CMR offers incremental prognostic benefit regarding ventricular arrhythmia in HCM compared to ventricular LGE alone.

Previous studies assessing the impact of T₁ mapping on arrhythmic outcomes

In the present study, we demonstrated an association between diffuse ventricular fibrosis as measured by post-contrast T₁ mapping on CMR and NSVT and aborted SCD. A smaller study of 25 patients only including patients with the apical HCM variant did not observe an association between T₁ mapping and ventricular arrhythmias²⁰. We have previously reported a strong correlation between post-contrast ventricular T₁ relaxation time and histologic fibrosis, left ventricular filling pressures, and freedom from atrial fibrillation in patients undergoing catheter ablation^{13, 14, 17, 21}. In patients with HCM, Ellims et al have previously demonstrated multivariable predictors of post-contrast ventricular T₁ time include body mass index and left ventricular filling pressure (as measured by E/e' on echocardiography)¹⁴.

Limitations

Although this study presents a novel method (T₁ mapping) for the prediction of ventricular arrhythmias in patients with HCM, the results of this study are exploratory rather than conclusive and we await the outcome of larger multicenter studies. Holter monitoring was performed for 24 hours, and it is possible the prevalence of NSVT (23%) would have increased if monitoring had been extended; however, clinical practice in risk assessment of HCM patients generally employs a similar period of monitoring. Given the low rate of SCD, NSVT was utilized as a surrogate marker of ventricular arrhythmias; as such, the association of diffuse fibrosis with NSVT is inconclusive for SCD risk and should be regarded as

hypothesis generating. The post-contrast T_1 method may be affected by confounders such as acquisition time post contrast, eGFR, and patient height and weight; accordingly, we utilized a correction formula previously reported by Gai and colleagues to account for these factors¹⁸. Last, there were 7 aborted SCD events in this cohort and the impact of diffuse ventricular fibrosis on this outcome should be regarded as hypothesis generating rather than definitive, providing a platform for further research in a larger cohort with extended duration of follow-up.

Conclusion

Diffuse ventricular fibrosis as measured by CMR is a predictor of NSVT in patients with HCM. The identification of diffuse ventricular fibrosis by T_1 mapping may be an important prognostic tool for ventricular arrhythmias in patients with HCM, but requires further validation with a large scale prospective study.

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Legends to figures

Figure 1: The presence or absence of non-sustained VT as determined by LGE mass (left panel) and LGE as a percentage of LV mass (right panel).

Figure 2: A shorter post-contrast ventricular T_1 relaxation time was associated with non-sustained VT.

Figure 3: Post-contrast ventricular T_1 relaxation time in patients with versus without aborted SCD defined as survivors of cardiac arrest or ICD reversion of VF.

Figure 4: A ventricular T_1 time greater than 440ms was associated with freedom from aborted sudden cardiac death (SCD) in 97%.

Figure 5: The association between LGE mass (left panel) and LGE mass as a percentage of LV mass (right panel) and aborted sudden cardiac death.

Tables

Table 1: Patient characteristics and non-sustained VT

	COHORT (n=100)			HOLTER (n=93)			ICD (n=20)		
	Without NSVT (n=77)	With NSVT (n = 23)	P value	Without NSVT (n=81)	With NSVT (n = 12)	P value	Without NSVT (n = 7)	With NSVT (n = 13)	P value
Age (years)	51±14; 55 (17)	49±11; 50 (19)	0.93	51±14; 53(17)	51±12; 54 (24)	0.90	61±11; 59 (20)	49 (11); 50 (17)	0.03
Male sex	47 (61)	18 (78)	0.13	51 (63)	10 (83)	0.17	3 (43)	10 (77)	0.13
BMI (kg/m2)	27±5; 27 (7)	29±5; 30 (6)	0.14	28±5; 27 (7)	29±5; 30 (9)	0.26	28±6; 27 (9)	29±5; 30 (7)	0.67
eGFR (mL/min)	82±10; 83 (13)	84±10; 91 (10)	0.48	82±10; 84 (13)	82±11; 86 (18)	0.90	80±11; 81 (12)	84±8; 91 (11)	0.36
Syncope	7 (9)	4 (17)	0.26	7 (9)	2 (17)	0.38	2 (29)	3 (23)	0.79
Presyncope	29 (38)	5 (22)	0.16	30 (37)	3 (25)	0.42	3 (43)	3 (23)	0.36
Chest pain	20 (26)	9 (39)	0.22	20 (25)	7 (58)	0.02	4 (57)	3 (23)	0.13
Family history SCD	23 (30)	6 (26)	0.73	24 (30)	3 (25)	0.74	2 (29)	4 (31)	0.92
NYHA	1.5±0.5	1.5±0.5	0.42	1.5±0.6	1.6±0.5	0.44	1.3±0.5	1.4±0.5	0.76
Hypertension	23 (30)	3 (13)	0.11	24 (30)	1 (8)	0.12	0 (0)	2 (15)	0.27

Diabetes	2 (3)	1 (4)	0.67	2 (3)	1 (8)	0.28	0 (0)	0 (0)	-
Medications									
Beta-blocker	36 (47)	14 (61)	0.24	38 (47)	7 (58)	0.46	5 (71)	8 (62)	0.66
Calcium-channel blocker	15 (20)	5 (22)	0.81	17 (21)	1 (8)	0.30	0 (0)	3 (23)	0.17
ACE-i	14 (18)	5 (22)	0.70	15 (19)	3 (25)	0.60	0 (0)	3 (23)	0.17
AT2R-blocker	9 (12)	1 (4)	0.30	9 (11)	0 (0)	0.22	0 (0)	1 (8)	0.45

All values are mean±standard-deviation; median (interquartile range), or number and (percentage).

ICD implantable cardioverter-defibrillator; BMI body mass index; eGFR estimated glomerular filtration rate; SCD sudden cardiac death; NYHA New York Heart Association; ACE-I angiotensin converting enzyme inhibitor; AT2R angiotensin type 2 receptor blocker.

Table 2: Imaging characteristics

COHORT (n=100)	HOLTER (n=93)	ICD (n=20)
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	Without NSVT (n=77)	With NSVT (n = 23)	P value	Without NSVT (n=81)	With NSVT (n = 12)	P valu e	Without NSVT (n = 7)	With NSVT (n = 13)	P valu e
CMR									
Septal wall thickness (mm)	18.7±4.2; 18.0 (5)	22.0±5.2; 21.0 (6)	0.002	19.0±4.5; 18.0 (5.0)	20.6±4.0; 20.0 (5.8)	0.25	19.3±3.5; 18.0 (7)	23.9±5.7; 23.0 (8)	0.07
Posterior wall thickness (mm)	8.3±1.8; 8.0 (3)	8.6±1.9; 8.0 (3)	0.58	8.4±1.8; 8.0 (3)	8.3±2.1; 8.0 (2.8)	0.83	7.0±1.5; 7.0 (3)	9.2±1.8; (9.0 (3)	0.02
Septal: Posterior wall ratio	2.3±0.7; 2.3 (0.9)	2.6±0.6; 2.7 (0.8)	0.05	2.3±0.7; 2.3 (0.9)	2.6±0.5; 2.6 (0.8)	0.25	2.8±0.4; 2.8 (0.4)	2.7±0.7; 2.5 (1.2)	0.67
LV mass index (g/m ²)	80.2±29.4 ; 75.5 (28)	93.5±33.5 ; 90.5 (30.8)	0.07	80.7±28.7 ; 78.0 (28.6)	83.1±22.0 ; 89.3 (42.4)	0.78	74.8±24.7; 63.8 (48.6)	106.4±37. 3; 93.6 (29.0)	0.06
LVEF (%)	68.6±8.4; 71.0 (10)	68.5±5.6; 68.0 (7)	0.94	68.5±8.3; 71.0 (10.0)	68.9±5.1; 68.5 (8.5)	0.87	67.7±11.8; 69.0 (6)	67.9±4.8; 66.0 (6.5)	0.96
LVEDVI (ml/m ²)	78.6±15.0 ; 77.7 (19)	81.7±15.1 ; 80.4 (20.1)	0.38	78.5±14.8 ; 77.7 (18.6)	79.2±12.4 ; 83.3 (24.3)	0.87	77.0±12.9; 77.5 (23.5)	85.5±16.5 ; 83.9 (15.4)	0.25
Post-contrast ventricular T ₁ relaxation time (ms)	512±115; 488 (110)	422±54; 429 (83)	<0.001	506±116; 487 (110)	424±45; 426 (83)	<0.01	480±148; 456 (243)	429±38; 429 (64)	0.37
LGE (yes/no) [#]	65 (84)	22 (96)	0.16	68 (84)	12 (100)	0.14	7 (100)	12 (92)	0.45
Non-insertion point LGE (yes/no)	45 (58)	18 (78)	0.08	48 (59)	9 (75)	0.30	4 (57)	11 (85)	0.18
LGE mass (g)	7.6±10.2; 3.4 (10)	16.5±19.1 ; 8.6 (19)	<0.01	8.1±11.5; 3.4 (10)	12.2±9.8; 10.6 (19)	0.24	10.3±8.6; 9.8 (14)	17.8±21.2 ; 8.6 (22)	0.38
LGE (%/LV mass)	4.2±6.3; 2.1 (5)	7.4±7.0; 5.6 (9)	0.01	4.4±6.5; 2.1 (5)	6.2±4.7; 6.5 (8)	0.36	7.2±8.5; 6.4 (7)	7.5±7.2; 5.0 (12)	0.94
LA area (cm ²)	27.7±6.4; 27.0 (9)	32.2±6.8; 32.0 (9)	<0.01	27.9±6.4; 28.0 (9)	31.4±8.3; 29.5 (14.8)	0.09	32.7±5.5; 34.0 (9)	31.9±7.1; 31.0 (10)	0.80
Echocardiography									
Septal wall thickness (mm)	17.6±4.3; 17.0 (4)	18.4±2.8; 18.0 (3)	0.51	17.5±4.3; 17.0 (4)	18.0±2.3; 19.0 (4)	0.75	20.7±3.8; 19.0	18.3±1.2; 18.5 (2)	0.19
Posterior wall thickness (mm)	11.2±2.9; 11.0 (2)	10.5±1.5; 11.0 (3)	0.43	11.2±2.9; 11.0 (2)	10.3±1.7; 11.0 (4)	0.38	7.7±2.5; 8.0	11.3±0.5; 11.0 (1)	0.13
LV mass index (g/m ²)	137.8±42. 7; 136.0 (55)	112.7±15. 4; 111.5 (12)	0.07	136.7±42. 2; 135.0 (54)	113.7±18. 7; 112.0 (28)	0.16	185.0±100. 4; 185.0	116.2±12. 9; 111.0 (17)	0.14
LVEF (%)	65.1±12.9 ; 68.5 (11)	70.2±6.9; 72.0 (11)	0.26	65.3±12.7 ; 69.0 (10)	71.6±6.3; 73.0 (9)	0.22	61.5±14.8; 61.5	68.6±6.4; 72.0 (12)	0.38
E/e'	11.9±4.1; 10.4 (6)	13.9±5.9; 11.5 (8)	0.30	12.2±4.3; 10.8 (6)	12.2±5.6; 10.4 (5)	0.99	15.4±9.5; 11.7	14.9±5.8; 12.6 (10)	0.92
LA volume indexed (ml/m ²)	48.8±13.7 ; 47.8 (21)	58.5±26.0 ; 52.4 (22)	0.39	48.9±13.5 ; 47.8 (21)	56.8±22.3 ; 52.4 (22)	0.19	51.6±26.8; 43.9	74.0±30.1 ; 60.7 (58)	0.33

All values are mean±standard-deviation; median (interquartile range), or number and (percentage).
ICD implantable cardioverter-defibrillator; LV left ventricle; LVEF left ventricular ejection fraction;

LVEDVI left ventricular end diastolic volume indexed (to body surface area); LGE late gadolinium enhancement; LA left atrium. # including 24 patients with only insertion point LGE.

Table 3: Rhythm analysis

	COHORT (n=100)			HOLTER (n=93)			ICD (n=20)		
	Without NSVT (n=77)	With NSVT (n = 23)	P value	Without NSVT (n=81)	With NSVT (n = 12)	P value	Without NSVT (n = 7)	With NSVT (n = 13)	P value
Electrocardiogram									
Heart rate (bpm)	66±13; 66 (17)	61±11; 60 (18)	0.18	65±13; 66 (16)	60±12; 59 (24)	0.19	60±16; 57 (31)	60±6; 59 (10)	0.97
PR duration (ms)	172±27; 172 (30)	177±32; 172 (40)	0.54	171±26; 172 (32)	173±32; 168 (40)	0.84	171±30; 176 (57)	179±32; 178 (35)	0.69
QRS duration (ms)	98±18; 96 (16)	102±23; 96 (18)	0.47	98±17; 95 (16)	106±28; 95 (27)	0.20	111±19; 106 (34)	98±11; 101 (19)	0.16
Bundle-branch block	5 (6)	1 (4)	0.81	5 (6)	1 (8)	0.78	0 (0)	0 (0)	-
Holter monitoring									
Holter performed	77 (100)	16 (70)	<0.001	81 (100)	12 (100)	-	6 (86)	7 (54)	0.15
NSVT on Holter	-	12 (52)	-	-	12 (100)	-	-	-	-
NSVT (beats per minute)	-	169±40; 164 (47)	-	-	169±40; 164 (47)	-	-	-	-
Longest NSVT run (beats)	-	12±10; 7 (17)	-	-	12±10; 7 (17)	-	-	-	-
Number of NSVT runs (mean)	-	2±2; 2 (1)	-	-	2±2; 2 (1)	-	-	-	-
Atrial fibrillation	11 (14)	5 (22)	0.36	10 (12)	1 (8)	0.69	3 (43)	2 (15)	0.18
ICD									
ICD implantation	3 (4)	17 (74)	<0.001	6 (7)	7 (58)	<0.001	7 (100)	13 (100)	-
ICD primary prevention*	3 (100)	12 (71)	0.28	6 (100)	6 (86)	0.34	6 (86)	9 (69)	0.42
NSVT on ICD	0	13 (57)	0.01	3 (50)	4 (57)	0.80	0 (0)	13 (100)	-
Therapy (ATP or shock)	0	4 (17)	0.35	1 (17)	1 (14)	0.91	0 (0)	5 (39)	0.06

All values are mean±standard-deviation; median (interquartile range), or number and (percentage). NSVT non-sustained ventricular tachycardia; ICD implantable cardioverter-defibrillator; ATP anti-tachycardia pacing. * (percentage) in this row is of patients with an ICD implanted.

Figure 1

NSVT and Ventricular LGE in HCM

Author A

Figure 2

Authc

Figure 3

Authc

Figure 4

Ventricular T1 time and aborted sudden cardiac death

Author M

Figure 5

Aborted sudden cardiac death and Ventricular LGE in HCM

Author M

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