Original Article

Association between Left Ventricular Wall Thickness and Heart Rate Variability with Complex Ventricular Arrhythmia in Hypertrophic Cardiomyopathy

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Objective: To demonstrate the association between the maximal left ventricular (LV) wall thickness and the late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) and heart rate variability (HRV) with complex ventricular arrhythmia (VA) in patients with hypertrophic cardiomyopathy (HCM).

Materials and Methods: The present study was a retrospective study. Fifty-seven HCM patients who underwent CMR and Holter monitoring at Siriraj Hospital, Bangkok, Thailand, were identified and included. Complex VA was defined as Lown grading system type 4a or 4b as couplet or non-sustained ventricular tachycardia. Standard deviation of normal RR-interval (SDNN) was used to assess HRV.

Results: The authors studied 57 patients, 40 (70.2%) patients had LGE, and 13 (22.8%) patients had complex VA. Complex VA was demonstrated in 11 (27.5%) patients in the LGE group compared with two (11.8%) in those without (p=0.304), and four (57.1%), and nine (18.0%) in patients had a maximal LV wall thickness of 25 mm or more and less than 25 mm, respectively (p=0.041). SDNN was 100.98±29.82 ms versus 123.85±35.12 ms (p=0.015) in the LGE group compared with the no-LGE group, and 89.08±25.39 ms versus 113.34±33.06 ms (p=0.018) in patients with and without complex VA. Multivariate analysis showed significant associations of maximal LV wall thickness of 25 mm or more and SDNN of less than 105 ms with complex VA with odds ratios of 6.71 (95% confidence interval [CI] 1.09 to 41.14; p=0.040) and 5.15 (95% CI 1.14 to 23.30; p=0.033), respectively.

Conclusion: In HCM patients, increased LV wall thickness and a reduction in SDNN are associated with complex VA. The present study supports the utility of CMR and HRV for risk stratification of patients with HCM.

Keywords: Heart rate variability; Maximal left ventricular wall thickness; Complex ventricular arrhythmia; Hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a common inherited cardiomyopathy that affects about 1:500 in the general population[1]. Sudden cardiac death (SCD) is the major cause of death among patients with HCM[2]. Current guidelines describe the following SCD risk factors, 1) prior ventricular fibrillation, SCD, or sustained ventricular tachycardia (VT), 2) family history of SCD, 3) syncope, 4) maximum left ventricular (LV) wall thickness of 30 mm or greater, 5) non-sustained ventricular tachycardia (NSVT), and 6) abnormal blood pressure response during exercise to determine the need for an implantable cardioverter defibrillator (ICD) for prevention of SCD[3,4]. LV wall thickness has been shown to be a risk factor for SCD in patients with HCM[5]. Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging[1] is an emerging image modality for risk stratification in HCM patients and was recommended as a SCD risk modifier. Previous studies showed association between LGE and ventricular arrhythmia (VA)[6-8]. Current guideline recommends routine Holter monitoring as a class I indication for detection of atrial and VA[3]. The guideline also suggested CMR for the assessment of anatomy, function, and LGE in patients with HCM as class I for patients with an inadequate echocardiography window, and as class IIa for all patients. Although echocardiogram is usually the initial imaging evaluation in patients with HCM, CMR has been recommended as the gold standard for

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assessment of LV wall thickness due to lower intra- and inter-observer variability[9]. Contrast-enhanced echocardiography is more accurate than standard echocardiography for the assessment of LV wall thickness, and it has close to the same efficacy as CMR in this imaging setting[9]. In addition, heart rate variability (HRV) has been reported to be associated with VA in patients with HCM[10].

The objective of the present study was to investigate for association between maximal LV wall thickness and HRV with complex VA in patients with HCM.

Materials and Methods

Study population

The present study was a retrospective study conducted at Her Majesty Cardiac Center of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand between January 2012 and December 2019. The authors enrolled HCM patients who met the following inclusion criteria, 1) older than 18 years old, 2) both CMR and Holter monitoring had been performed, and 3) the duration between CMR and Holter monitoring was less than one year. The exclusion criteria were 1) congenital heart disease, 2) other cardiac diseases that can cause VA, such as coronary artery disease as confirmed by coronary angiogram or perfusion imaging, Brugada syndrome, long QT syndrome, and arrhythmogenic right ventricular cardiomyopathy, or 3) uninterpretable Holter results. The present study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 564/2019).

Definition

HCM is defined as 1) wall thickness of 15 mm or more in one or more LV myocardial segments, or 2) wall thickness of 13 mm or more in first-degree relatives of HCM patients or typical LV morphology on CMR in the absence of another cause of hypertrophy[3]. Complex VA is defined as ventricular couplets, triplets, or NSVT, according to the Lown grading system for VA type 4a or 4b[11]. Combining ventricular couplets and NSVT increased the odds ratio for prediction of SCD in patients with HCM from 1.9 to 2.4[12]. The analysis of CMR and Holter monitoring were blinded for the presence or absence of the interested outcomes.

CMR protocol

CMR for LV function, volume, and mass was performed using a Philips Gyroscan NT 1.5T MRI Scanner (Philips Medical Systems, Best, the Netherlands). Images were acquired in 4-chamber, vertical long-axis, horizontal long-axis, and multiple-slice short-axis series cine images, and spin echo images were performed using a steady-state free-precession (SSFP) technique. Functional images were developed according to the following parameters, echo time/repetition time/number of excitations=1.8/3.7/2; 256×240 matrix; 390×312 mm field of view; 8 mm slice thickness; 1.52×1.21 reconstruction pixel; and, 70° flip angle in standard long-axis, 4-chamber, and short-axis views. LGE images were acquired in the long-axis, 4-chamber, and short-axis views approximately 10 minutes after gadolinium injection.

CMR images were analyzed with the IntelliSpace Portal (ISP) workstation (Philips Medical Systems). LGE images were analyzed by visual assessment according to the 17-segment LV wall system.

Holter monitoring and HRV

Cardiac arrhythmia and parameter for heart rate variation were analyzed using a Philips DigiTrak XT and Philips Holter 2010 Plus Ver. 3.0.1 (Philips Medical Systems). Non-sustained ventricular tachycardia was defined as three or more consecutive ventricular beats, and HRV was analyzed by standard deviation of all normal RR intervals (SDNN), which is a time domain variable.

Statistical analysis

The PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA) was used to perform all data analyses. Continuous data were reported as mean ± standard deviation (SD), and categorical data were reported as number and percentage. Continuous data were compared using independent t-test, and categorical data were compared using chi-square test or Fisher's exact test. Univariate and multivariate logistic regression analysis were applied for the identification of factors independently associated with the outcome measures. For binary data, the authors used an LV wall thickness cut-off of 25 mm, which was reported to be associated with an increased risk of SCD[5]. For the SDNN cut-off, the authors used 105 ms, which was the median value in the present study. For LV mass index, the authors used a previously reported cut-off for males and females[13]. A p-value of less than 0.05 was considered statistically significant.

Results

Patient demographic and clinical characteristics

Table 1. Baseline demographic and clinical data

	All patients (n=57)	Patients without complex VA (n=44)	Patients with complex VA (n=13)	p-value
Age (years); mean±SD	62.1±16.7	61.6±16.6	64.1±17.8	0.640
Sex: male; n (%)	31 (54.4)	25 (56.8)	6 (46.2)	0.498
Comorbidity; n (%)				
DM	14 (24.6)	11 (25.0)	3 (23.1)	0.887
HTN	31 (54.4)	24 (54.5)	7 (53.8)	0.965
DLP	23 (40.4)	19 (43.2)	4 (30.8)	0.423
CKD	8 (14.0)	5 (11.4)	3 (23.1)	0.285
HF	5 (8.8)	4 (9.1)	1 (7.7)	0.876
AF	16 (28.1)	11 (25.0)	5 (38.5)	0.343
Medication; n (%)				
Beta-blocker	35 (61.4)	26 (59.1)	9 (69.2)	0.509
NH-CCB	21 (36.8)	16 (36.4)	5 (38.5)	0.890
Amiodarone	6 (10.5)	3 (6.8)	3 (23.1)	0.093
Statin	28 (49.1)	20 (45.5)	8 (61.5)	0.308
ACEIs/ARBs	21 (36.8)	15 (34.1)	6 (46.2)	0.428

VA=ventricular arrhythmia; DM=diabetes mellitus; HTN=hypertension; DLP=dyslipidemia; CKD=chronic kidney disease; HF=heart failure; AF=atrial fibrillation; NH-CCB=non-dihydropyridine calcium channel blocker; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; SD=standard deviation

A p<0.05 indicates statistical significance

Table 2. Association between patients with or without complex VA and CMR findings and Holter monitoring findings

Variables	All patients (n=57)	Without complex VA (n=44)	With complex VA (n=13)	p-value
CMR variables				
Presence of LGE; n (%)	40 (70.2)	29 (65.9)	11 (84.6)	0.304
Maximum LV wall thickness (mm); mean±SD	18.8±4.8	18.3±4.5	20.8±5.5	0.095
Maximum LV wall thickness ≥25 mm; n (%)	7 (12.3)	3 (6.8)	4 (30.8)	0.041
LV mass index (g/m^2); mean±SD	78.4±36.4	72.7±34.1	97.5±38.9	0.029
LV mass index (males ≥91 g/m^2; females ≥69 g/m^2); n (%)	21 (36.8)	13 (29.5)	8 (61.5)	0.051
LVEF (%); mean±SD	75.3±9.9	77.2±6.7	68.6±15.4	0.069
LVEF <65%; n (%)	5 (8.8)	2 (4.5)	3 (23.1)	0.010
Apical type HCM; n (%)	19 (33.3)	17 (38.6)	2 (15.4)	0.183
Holter monitoring				
Average heart rate (/minute); mean±SD	67.8±10.4	67.5±8.7	68.9±15.2	0.684
SDNN (ms); mean±SD	105.9±35.6	113.3±33.1	89.1±25.4	0.018
SDNN <105 ms; n (%)	28 (49.1)	18 (40.9)	10 (76.9)	0.022

CMR=cardiac magnetic resonance; VA=ventricular arrhythmia; LGE=late gadolinium enhancement; LV=left ventricular; LVEF=left ventricular ejection fraction; HCM=hypertrophic cardiomyopathy; SDNN=standard deviation of all normal RR intervals; SD=standard deviation

A p<0.05 indicates statistical significance

are shown in Table 1. The mean age of patients was 62.1±16.7 years, and 54.4% were male. No significant difference between those with and without complex VA was observed for age, gender, comorbidities, or medications.

Forty (70.2%) patients had LGE, and thirteen (22.8%) patients had complex VA including seven with NSVT with or without couplets, and six with couplet only (Table 2). Complex VA was demonstrated in eleven (27.5%) versus two (11.8%), p=0.195 in the LGE group compared with the no-LGE group, and four (57.1%) versus nine (18.0%), (p=0.041) in patients with maximal LV wall thickness of 25 mm or more compared with less than 25 mm, respectively. Regarding analysis of Holter monitoring and heart rate variation, SDNN in time domain was 100.98±29.82 ms versus 123.85±35.12 ms (p=0.015) in the LGE group compared with the no-LGE group, and 89.08±25.39 ms versus 113.34±33.06 ms, p=0.018 in patients with and without complex VA, respectively.

Table 3. Univariate and multivariate analysis for factors predicting complex ventricular arrhythmia

Factors	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Amiodarone use	4.10 (0.72 to 23.43)	0.113		
Presence of LGE on CMR	2.85 (0.56 to 14.53)	0.209		
Maximum wall thickness ≥25 mm	6.07 (1.15 to 32.00)	0.033	6.71 (1.09 to 41.14)	0.040
Increased LV mass index*	3.82 (1.05 to 13.88)	0.042		
LVEF <65%	6.30 (0.93 to 42.87)	0.060		
Apical type HCM	0.29 (0.06 to 1.47)	0.134		
SDNN <105 ms	4.82 (1.16 to 19.99)	0.030	5.15 (1.14 to 23.30)	0.033

OR=odds ratio; CI=confidence interval; LGE=late gadolinium enhancement; CMR=cardiac magnetic resonance; LV=left ventricular; LVEF=left ventricular ejection fraction; HCM=hypertrophic cardiomyopathy; SDNN=standard deviation of all normal RR intervals

* Increased LV mass index=LV mass index ≥91 g/m^2 in males, and ≥69 g/m^2 in females

A p<0.05 indicates statistical significance

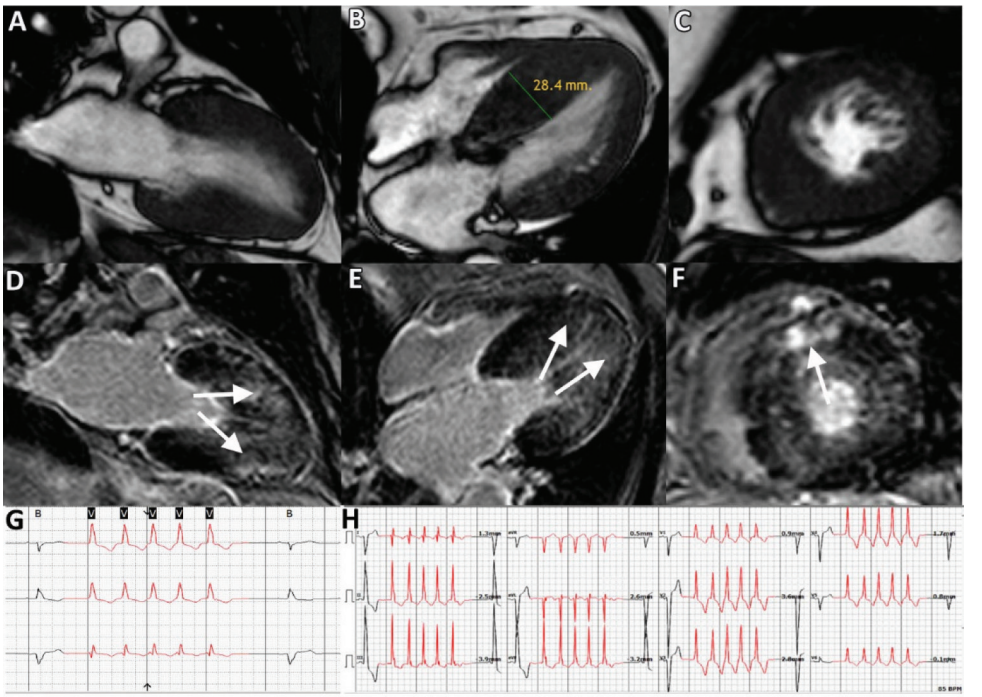

Figure 1. Cardiac magnetic resonance (CMR) images and electrocardiograph of a patient with hypertrophic cardiomyopathy. Steady-state free precession CMR in long-axis (A), 4-chamber (B), and short-axis (C) views demonstrated a maximal left ventricular wall thickness of 28.4 mm. Late gadolinium enhancement in the same views (D-F) showed myocardial scarring (arrow). Holter monitoring showed non-sustained ventricular tachycardia (G) originating from the left ventricle (H). Standard deviation of N-N interval was 87.6 ms.

Maximal LV wall thickness of 25 mm or more and LV mass index in males greater than 91 g/m² and females greater than 69 g/m² were associated with complex VA from univariate logistic regression analysis with odds ratios of 6.07 (95% confidence interval [CI] 1.15 to 32.00, p=0.033) and 3.8 (95% CI 1.05 to 13.88, p=0.042), respectively (Table 3). From multivariate logistic regression analysis, maximal LV wall thickness of 25 mm or more had a significant association with the adjusted odds ratio and 95% CI of 6.71 (1.09 to 41.14). Figure 1 and 2 demonstrates two cases with NSVT and increased LV wall thickness, reduced SDNN, and myocardial fibrosis by LGE.

Sensitivity analysis was performed to determine the relation of LV wall thickness and SDNN for the prediction of complex VA by treating LV wall

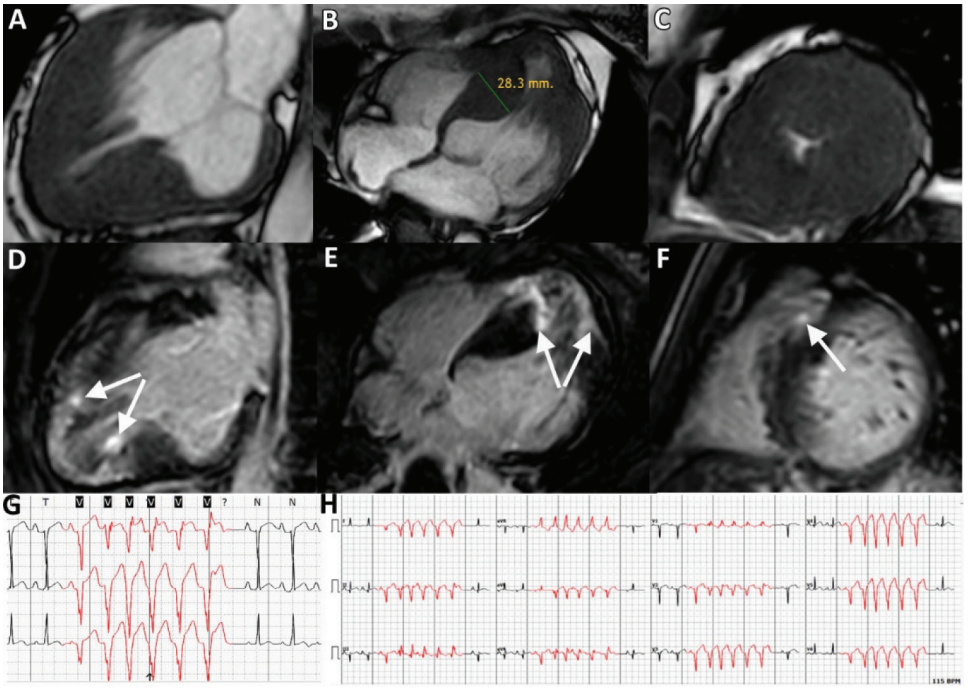

Figure 2. Cardiac magnetic resonance (CMR) images and electrocardiograph of another patient with HCM. Steady-state free precession CMR in long-axis (A), 4-chamber (B), and short-axis (C) views demonstrated a maximal left ventricular wall thickness of 28.3 mm. Late gadolinium enhancement in the same views (D-F) showed myocardial scarring (arrow). Holter monitoring showed non-sustained ventricular tachycardia (G) originating from the left ventricle (H). Standard deviation of N-N interval was 41.0 ms.

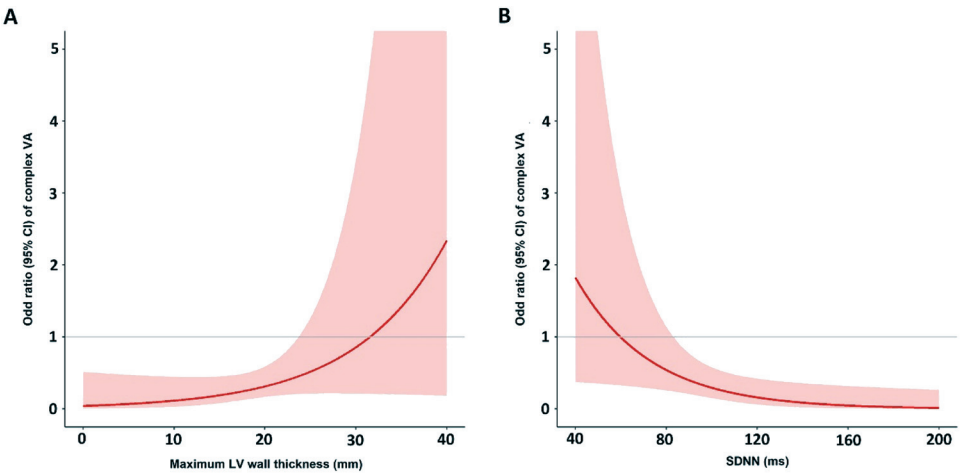

Figure 3. The association of complex ventricular arrhythmia (VA) and [A] maximum left ventricular (LV) wall thickness (X-axis) and [B] standard deviation of normal-normal interval (X-axis). Y-axis is the Odds ratio and 95% confidence interval (CI) of complex VA.

thickness and SDNN as continuous variables. Results of the analysis are displayed in Figure 3A and 3B. From Figure 3, the risk of complex VA increased when LV wall thickness more than 30 mm and SDNN was below 60 msec and the risk increased exponentially when the LV wall thickness increased and SDNN decreased.

Discussion

The results of the present study demonstrated significant association between complex VA and both maximum LV wall thickness of 25 mm or more and altered autonomic nervous system function shown by a reduction in SDNN, which is a time domain variable of HRV. Unlike prior study[7,14], the authors

were unable to demonstrate association between LGE and complex VA.

Among patients with HCM who have an elevated risk of sudden cardiac death, clinical variables and investigations were used for risk stratification of sudden cardiac death[3]. The extent of LGE on CMR can provide information for diagnosis and prognosis in HCM. LGE is a marker of focal fibrosis that increasingly recognized as a marker of sudden death[1,15]. CMR has become a standard evaluation imaging modality in patients with HCM. In addition to assessing cardiac anatomy, LV wall thickness, and LGE, emerging techniques, such as feature tracking and T1 mapping, might improve risk stratification in patients with HCM[14-16]. T1 mapping, which indicates diffuse myocardial fibrosis, may be even better prognostic marker than the presence of LGE[15]. The present study focused on LGE and LV wall thickness. Although echocardiography is the initial imaging evaluation, CMR provides additional tissue characterization information, such as LGE[16]. CMR is also a gold standard imaging technique for assessment of LV wall thickness due to lower inter- and intra-observer variation, which makes it appropriate for comparisons between groups and to track changes over time[9]. The results of the present study demonstrated a significant association between LV wall thickness and complex VA. However, the authors could not demonstrate significant association between LGE and complex VA in the present study.

Holter monitoring has been recommended as a class I indication for the assessment of HCM patients[3]. The reported prevalence of NSVT on Holter was 25% to 30%[5,12,17]. The prevalence in the present study, which also included couplets, was 23%, which is lower than previous reports. Most previous studies were retrospective in nature, and the prevalence of VA may depend on patient management, which may vary among cardiologists. Moreover, the detection rate of NSVT by Holter monitoring may be varied. The previous data suggested that 48 to 72 hours of recording may increase the yield for detection of NVST in HCM patients[18]. Although NSVT by Holter monitoring had an association with SCD, and it had a high negative predictive value (95%) for the prediction of SCD, the positive predictive value is low (9%). However, predictive value data also depends on the risk of the study population.

Previous studies have demonstrated that autonomic function might play a role in arrhythmia and sudden death in patients with HCM[10,19,20]. A study in HCM patients with and without unexplained syncope demonstrated that patients with syncope had lower parasympathetic activity compared to those without syncope[19]. A reduction in HRV was observed not only in patients with HCM, but also demonstrated in their first-degree relative[20]. However, Uemura et al compared HRV in 21 HCM patients and 10 controls and found that parasympathetic activity was reduced, and that sympathetic activity was increased in HCM patients with NSVT. However, HCM patients without NSVT were similar to control subjects[10]. The results of the present study showed that HCM patients with complex VA had a reduced SDNN, which is a marker of parasympathetic activity, compared to those without complex VA. The present study results confirmed that abnormal autonomic function may be the underlying or precipitating factor in complex VA and may be for SCD in patients with HCM. The present study finding also emphasizes the role of Holter monitoring as a routine non-invasive investigation in patients with HCM, not only for the detection of atrial and VA, but also for the assessment of HRV. This finding may be the reason behind the efficacy of beta blocker in the reduction of SCD in HCM[17]. However, in HCM patients at risk for SCD, ICD is the standard treatment[4].

The present study has limitations. In addition to retrospective design, the size of the present study population needed to have both CMR and Holter monitoring was small. Due to the small sample size, the authors included all patients who fitted in the inclusion and did not have exclusion criteria. Another limitation is that the data were extracted from the database of only one center. Lastly, the present study did not have follow-up data, so the relationship between the findings and the clinical outcomes could not be assessed.

Conclusion

In HCM patients, maximal LV wall thickness from CMR and a reduction in SDNN from Holter monitoring are associated with complex VA. The present study supports the utility of CMR for the risk stratification and prevention of sudden cardiac death in patients with HCM.

What is already known on this topic?

HCM increases risk of sudden cardiac death. Parameters have been proposed as the risk predictors.

What this study adds?

LV wall thickness and HRV may be useful as an integrated risk predictor for sudden cardiac death in

patients with HCM.

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Conflicts of interest

Both authors declare no personal or professional conflicts of interest relating to any aspect of the present study.

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