Assessment of the association between the presence of fragmented QRS and the predicted risk score of sudden cardiac death at 5 years in patients with hypertrophic cardiomyopathy

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ABSTRACT

Objective: It has been shown that the presence of fragmented QRS (fQRS) is associated with poor prognosis in many cardiovascular diseases and in patients with hypertrophic cardiomyopathy (HCM). However, no study has shown an association with the absolute risk score of sudden cardiac death. The aim of this study was to determine the relationship between QRS and the predicted risk score of sudden cardiac death at 5 years (HCM Risk-SCD) in HCM patients.
Methods: In total, 115 consecutive HCM patients were included in this prospective observational study. The patients were divided into two groups according to the presence [fQRS(+) group (n=65)] or absence [fQRS(−) group (n=50)] of fQRS on a 12-lead electrocardiogram (ECG).
Results: The HCM Risk-SCD (%) HCM Risk-SCD (>6%) values and some echocardiographic parameters, including ventricular extrasystole, ventricular tachycardia, cardiopulmonary resuscitation, implantable cardioverter defibrillator implantation, appropriate shock, and heart failure at the time of admission, were significantly higher in the fQRS(+) group than in the fQRS(−) group (all p<0.05). Both univariate and multivariate analyses revealed fQRS and New York Heart Association (NYHA) class as independent predictors of HCM Risk-SCD. In a receiver operating characteristic (ROC) curve analysis, an HCM Risk-SCD value of >4 was identified as an effective cut-off point in fQRS for HCM. An HCM Risk-SCD value of >4 yielded a sensitivity of 77% and a specificity of 76%.
Conclusion: fQRS is determined to be an independent high-risk indicator of HCM Risk-SCD. It seems to be associated with increased ventricular arrhythmias and some echocardiographic parameters. *(Anatol J Cardiol 2017; 18: 54-61)*
Keywords: fragmented QRS, hypertrophic cardiomyopathy, sudden cardiac death

Introduction

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic cardiac disorder. It can occur at any age; it is also a leading cause of sudden cardiac death (SCD), particularly at early ages (1). Current guidelines suggest the consideration of some clinical parameters that indicate the criticality of heart disease underlying HCM to determine the risk of sudden death; the ESC guideline recommends the use of the left ventricular outflow tract obstruction (LVOTO) gradient, left atrial (LA) diameter, syncope, family history of SCD at a young age, maximum left ventricular wall thickness, nonsustained ventricular tachycardia, and

age as risk factors for assessing the 5-year risk of sudden death in patients with HCM. According to this guideline, implantable cardioverter defibrillator (ICD) implantation should be considered in patients with a high risk who have a predicted risk score of SCD at 5 years (HCM Risk-SCD) of 6% and life expectancy of >1 year (2, 3).

Although it has been a long-time since HCM was first described and numerous studies have been conducted on the same, no risk stratification strategy will ever be able to predict SCD with absolute certainty in HCM patients (4, 5). The lack of assessment of the risk of SCD forced the researchers to search for a new risk assessment method that can be applied easily and

quickly. The fragmented QRS (fQRS) complex seen on a 12-lead electrocardiogram (ECG) is associated with myocardial fibrosis and ischemic scaring (6). The relationships between structural heart disease, cardiac arrhythmias, and the presence of fQRS on ECG have been shown in many studies (7–10). The relationship between fQRS on ECG and HCM Risk-SCD in HCM patients has not been evaluated yet.

The aim of this study was to investigate the association between fQRS and the absolute HCM Risk-SCD value according to the newly developed HCM SCD risk model and to identify high-risk patients who need the insertion of ICD (HCM Risk-SCD of >6%). In addition, we aimed to analyze whether the presence of fQRS is associated with a poor HCM prognosis and whether the presence of fQRS is associated with echocardiographic parameters, cardiac arrhythmias, or HCM Risk-SCD.

Methods

Study population
In total, 115 consecutive patients with HCM who presented to the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital and Bezmialem Vakıf University, School of Medicine between December 2012 and March 2016 were enrolled in this prospective observational study. The study was approved by the Ethics Committee, and the patients who gave informed consent were included. Long-term follow-up results of HCM patients were evaluated.

The study inclusion criteria were as follows: age over 17 years and echocardiography (ECHO) or cardiac magnetic resonance imaging (CMRI) revealing HCM, defined as a maximum left ventricular wall thickness of 15 mm in one or more LV myocardial segments (2), with lesser degrees of wall thickening (13–14 mm). Evaluation was performed for other factors, including family history or positive gene mutations and ECG abnormalities. Consequently, patients with a high possibility of HCM were included in the study (1).

The patients for whom the implantation of ICD was absolutely essential because of a previous history of aborted SCD or those who had previously undergone ICD implantation were not included in the study because there was no need to calculate HCM Risk-SCD. The patients with a history of septal ablation or myomectomy were not included in the study. Further, patients with hypertension (HT) (n=8), renal failure (n=2), a history of MI (n=1), or aortic valve stenosis (n=1) were excluded. Patients with a history of storage disease were excluded as well. The maximum interventricular septum thickness (IVST) was 33 mm in the statistical evaluation. Thus, the final study population consisted of 115 patients. The patients were divided into two groups according to the presence or absence of fQRS. The group with the presence of fQRS (n=65) was termed the fQRS(+) group, while that with the absence of fQRS (n=50) was termed the fQRS(−) group. Complete and incomplete bundle branch blocks and paced rhythm were excluded from the definition of fQRS.

First evaluation on admission
On admission, the patients' medical histories, family history of SCD, and syncope were noted, and a special questionnaire on lifestyle and risk factors was administered. In addition, complete blood counts and other serum values were determined.

Family history of premature SCD
Unexpected nontraumatic premature death within 1 h after the onset of symptoms and without previous symptoms in relatives, including unwitnessed unexpected nocturnal death and equivalents such as successful resuscitation or appropriate ICD discharge.

Electrocardiography
A 12-derivation surface ECG was obtained from all the patients in the supine position. ECG recordings were taken using a Nihon Kohden-cardiofax S(ECG-1250K, filter range 0.5 Hz to 150 Hz, AC filter 60 Hz, speed 25 mm/s, amplitude 10 mm/mV; Nihon Kohden, Tokyo, Japan) on admission. Using ECG, we assessed the rhythm and speed as well as determined whether fQRS was present and calculated QRS, QT, and QTc durations.

fQRS measurement
Two independent readers who were blinded to the final comment evaluated the presence or absence of fQRS. The interindividual concordance interpretation on the presence of fQRS was 96.8% (j=0.93) If the presence or absence of fQRS was still unclear on ECG despite evaluations by two cardiologists, a third independent observer was included to make the final decision. We reached an agreement according to the majority decision. The assessment of fQRS was made on ECG taken at the patient's first outpatient clinic visit. fQRS was defined as the presence of an extra R wave (R1) with or without a Q wave on 12-lead ECG, the presence of notching on an R wave, the presence of notching on an S wave, or the presence of more than one R1 wave in two adjacent derivations corresponding to the feeding area of one of the major coronary arteries (6). An example of fQRS on 12-lead ECG is shown in Figure 1.

Echocardiography
In the first evaluation, a transthoracic echocardiographic study was performed using a Vivid S5 3S-RS probe (General Electric Vivid S5; GE Vingmend Ultrasound AS, Horten, Norway) with a 1.7/3.4 MHz phased-array transducer, and the left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method (11). The thickness of the left ventricular wall [IVST (mm), left ventricular posterior wall thickness (LVPWT) (mm)] was measured along the parasternal long axis. The left ventricular outflow tract obstruction gradient was measured using the apical five chamber view. In addition, left ventricular end-diastolic volume, end-systolic volume, left atrial diameter, left atrial volume (LAV), left atrial volume index (LAVI), left ventricular mass (LVM), and LVM index (LVMI) in grams were calculated according to De-
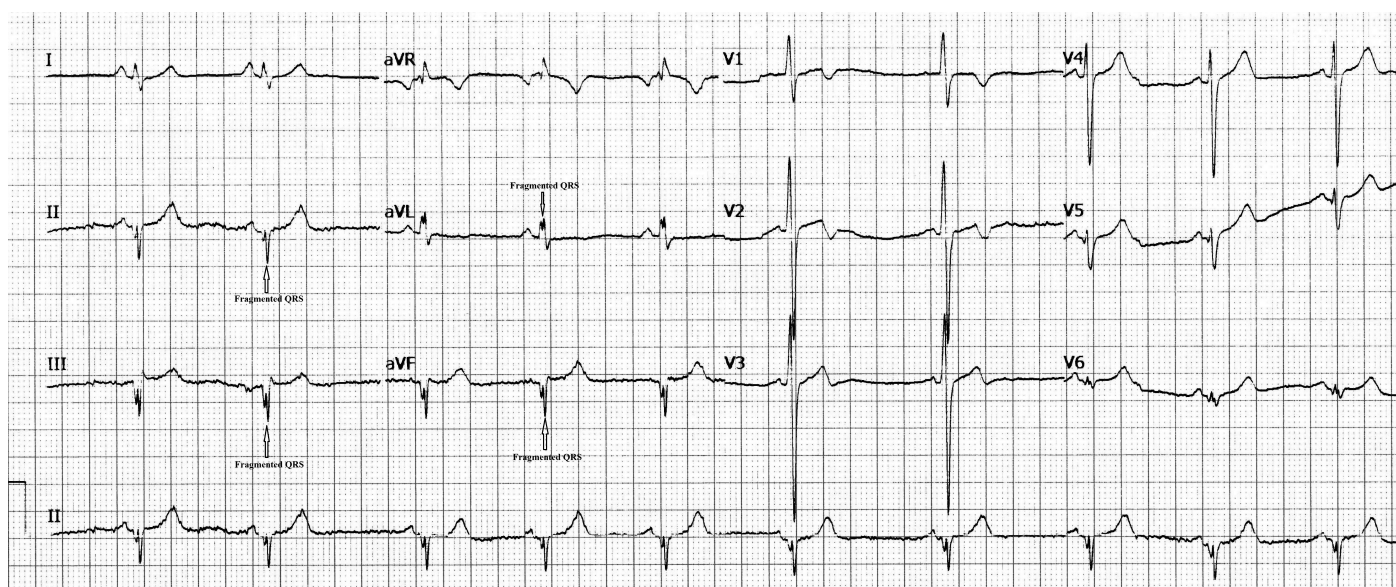
Figure 1. Fragmented QRS as shown on 12-lead ECG

vereux formula using M-mode echocardiogram images (12). Mitral valve regurgitation (systolic anterior motion of the mitral valve) and left ventricular diastolic dysfunction were also evaluated.

Holter electrocardiography

Analyses were performed using 12-channel recordings obtained from the ambulatory Holter monitors. Ambulatory electrocardiographic recordings (DMS 300-7 Holter Reader; DSM, Stateline, NV, USA) were obtained for a period of 24 h in all the patients. Before automatic analysis, the tapes were analyzed using the Holter program (CardioScan 12.0 DM software, DSM). The recordings were evaluated for rhythm, premature atrial contraction (PAC), supraventricular tachycardia (SVT), paroxysmal atrial fibrillation (PAF), ventricular extra-systole (VES), nonsustained and/or sustained ventricular tachycardia (NSVT), and atrioventricular (AV) block with pauses.

Measurement of HCM Risk-SCD

The probability of HCM Risk-SCD in an individual patient can be calculated using the following equation derived from the Cox proportional hazards model: PSCD at 5 years=1 – S0 (t) exp (prognostic index), where S0 (t) is the average survival probability at time t (i.e., at 5 years) and the prognostic index is the sum of the products of the predictors and their coefficients (1, 2). The patients with HCM Risk-SCD were divided into two groups based on percentage, as follows: the ≤5.9% group and >6% group.

Statistical analysis

In this study, statistical analysis was performed using SPSS (Version 15.0, SPSS Inc., Chicago, IL, USA) for Windows software package program. The study population was divided into two groups on admission according to the presence of fQRS: (+) (n=65) and (–) (n=50). The quantitative variables are expressed as the mean±SD, and the qualitative variables are expressed as a percentage (%). Data were evaluated using the Kolmogorov–Smirnov test. If the distribution of data was parametric, Student's t-test was performed. If the distribution of data was not non-parametric, Mann–Whitney U test was performed. Chi-square and Fisher's exact tests were performed to compare the rates between the groups. Pearson's correlation coefficient analysis was performed to evaluate the relationship between two types of quantitative data. Backward stepwise multiple logistic regression analysis, which included variables with a p value less than 0.1, was performed to identify independent predictors of high risk (>6%). The accuracy of relevant variables from the regression analysis to differentiate between the groups was assessed with receiver operating characteristic (ROC) curves to determine the area under the curve and the optimal sensitivity and specificity. A p value of <0.05 was considered statistically significant.

Study end-point and follow-up

On admission, the patients' medical histories, family history of SCD, and syncope were noted, and a special questionnaire on lifestyle and risk factors was administered. The patients were regularly followed during outpatient visits in the HCM outpatient clinic at regular 3-month intervals. If any change occurred in the patients' clinical status, it was noted. ECG was performed every 3 months. Further, 24-h Holter monitoring was performed at least once in all patients and at least twice in those with more than one risk factor for SCD. This was also performed when patients had any possible arrhythmic symptoms, including dizziness, light headedness, palpitations, and syncope. The primary end-point of the study was ventricular arrhythmic events. The secondary end-point was the occurrence of major arrhythmic events. Follow-up for clinical endpoints was performed by a telephonic interview and review of outpatient and inpatient medical records.

Table 1. Baseline and clinical characteristics

Variabilities		All (n: 115)	Fragmented QRS(+) (n: 65)	Fragmented QRS(−) (n: 50)	P
Age, years		46.5±15.3	44.7±15.1	48.7±15.3	0.167
Gender	Male, %	67(58)	43(37.4)	24(20.9)	0.051
	Female, %	48(42)	22(19.1)	26(22.6)	
BMI, kg/m²		26.8±3.5	26.3±3.0	27.4±3.0	0.104
History of family SCD, %	(+)	48(41.7)	35(30.4)	13(11.3)	**0.003**
	(−)	66(57.3)	30(26)	36(31.3)	
Presyncope, %	(+)	36(32)	26(23)	10(9)	**0.026**
	(−)	78(68)	39(34)	39(34)	
Syncope, %	(+)	13(11.9)	12(11)	1(0.9)	**0.006**
	(−)	102(88.1)	53(46.1)	48(42)	
NYHA, % class	I	37(32)	13(11.4)	24(21.1)	**<0.001**
	II	54(47)	31(27.1)	22(19.3)	
	III	24(21)	21(18.4)	3(2.6)	
Beta blockers, %	(+)	65(57)	61(53.5)	4(3.5)	0.145
	(−)	49(42.9)	42(36.8)	7(6.1)	
Amiodarone, %	(+)	4(3.5)	3(2.6)	1(0.9)	0.460
	(−)	110(96.5)	62(54.4)	48(42.1)	
Dysopyramide, %	(+)	8(7)	7(6.1)	1(0.9)	0.071
	(−)	106(93)	58(50.9)	48(42.1)	
Calcium channel blocker, %	(+)	5(4.4)	3(2.6)	2(1.8)	0.890
	(−)	109(95.6)	62(54.4)	47(41.2)	
HCM Risk-SCD, %		5.7±0	7.5±4.6	3.3±1.7	**<0.001**
HCM Risk-SCD	(>6%)(%)	40(34.7)	35(30.4)	5(4.3)	**<0.001**
	(<6%)(%)	75(65.3)	30(26.1)	45(39.2)	
LAAPD, mm		41.9±4.3	42.6±4.6	41.1±3.8	0.073
LAV, mL		52.6±15.9	56.5±15.8	47.3±14.7	**0.002**
LAVI, mL/m²		29.5±9.0	31.8±9.2	26.6±7.9	**0.002**
LV EF, %		66.4±7.0	66.5±8.3	66.1±5.0	0.766
IVST, mm		21.9±4.4	23.3±4.7	2.0±3.3	**<0.001**
LVPWT, mm		12.7±3.0	13.2±3.6	12.0±1.8	**0.036**
LVEDD, mm		42.9±5.8	42.7±6.3	43.2±5.1	0.661
LVM, g		329.6±84.0	355.1±83.9	295.8±72.1	**<0.001**
LVMI, g/m²		178.6±52.7	189.8±60.8	172.7±47.4	**0.001**
LVOTO, mm Hg		25.5±29.4	28.4±31.2	21.5±26.5	0.220
Paroxysmal atrial fibrillation, %	(+)	12(10.5)	8(7)	4(3.5)	0.454
	(−)	103(89.5)	57(49.5)	46(40)	
Ventricular extrasystole, %	(+)	75(65.2)	54(47)	21(18.2)	**<0.001**
	(−)	40(34.8)	11(9.6)	29(25.2)	
Ventricular tachycardia, %	(+)	24(20.9)	20(17.4)	4(3.5)	**0.003**
	(−)	91(79.1)	45(39.1)	46(40)	
Cardiopulmonary rescuscitation, %	(+)	13(11.3)	12(10.4)	1(0.9)	**0.006**
	(−)	102(88.7)	53(46.1)	49(42.6)	
ICD implantation, %	(+)	11(9.6)	10(8.7)	1(0.9)	**0.016**
	(−)	104(90.4)	55(47.8)	49(42.6)	
Shock, %	apropriate	8(18)	7(2.6)	1(15.4)	0.050
	inappropriate	3(2.6)	3(2.6)	0	
Heart failure at the time of admission, %	(+)	33(28.7)	25(21.7)	8(7)	**0.008**
	(−)	82(71.3)	40(34.8)	42(36.5)	

Values are the mean±SD or percentage (%). EF - ejection fraction; ICD - implantable cardioverter defibrillator; IVST - interventricular septum thickness; LAAPD - left atrial anterior–posterior dimension; LAV - left atrial volume; LAVI - left atrial volume index; LVEDD - left ventricular end-diastolic dimension; LVESD - left ventricular end-systolic dimension; LVM - left ventricular mass; LVMI - left ventricular mass index; LVPWT - left ventricular posterior wall thickness; LVOTO - left ventricular outflow tract obstruction; NYHA - New York Heart Association; HCM Risk-SCD - predicted risk score of sudden cardiac death at 5 years; RWTI - relative wall thickness index

Results

Baseline characteristics and fQRS results

The mean follow-up period in this study was 31.7±12.7 months. A comparison of the results for patients in the fQRS(+) and fQRS(−) groups is shown in Table 1. No significant differences were found in terms of age, gender, body mass index (BMI) (kg/m²), diabetes mellitus (DM) (%), hyperlipidemia (HL) (%), LVEF (%), LVOTO gradient (mm Hg), C-reactive protein (CRP) level (mg/dL), white blood cell (WBC) count (x109 /L), blood urine nitrogen (BUN) level (mg/dL), creatinine level (mg/dL), and PAF (%) at admission between the two groups (all p>0.05). In the fQRS(+) group, HT (4.3% vs. 0%), cigarette smoking (14.7% vs. 4.3%), family history of SCD (30.4% vs.11.3%), syncope (11% vs. 0.9%), presyncope (23% vs. 9%), NYHA class (I: 11.4% vs. 21.1%, II: 27.1% vs. 19.3%, III: 18.4% vs. 2.6%) class, HCM Risk-SCD (7.5±4.6% vs. 3.3±1.7%), HCM Risk-SCD (>6%) (30.4% vs. 4.3%), VES (47% vs. 18.2%), VT (17.4% vs. 3.5%), cardiopulmonary resuscitation (CPR) (10.4% vs. 0.9%), ICD implantation (8.7% vs. 0.9%), and heart failure at the time of admission (21.7% vs. 7%) were more frequent than those in the fQRS(−) group, and the results were significant (all p<0.05). LAV (mL) (56.5±15.8 vs. 47.3±14.7), LAVI (mL/m²) (31.8±9.2 vs. 26.6±7.9), IVST (mm) (23.3±4.7 vs. 20.0±3.3), and LVPWT (mm) (13.2±3.6 vs. 12.0±1.8) were significantly higher in the fQRS(+) group than in the fQRS(−) group (all p<0.05). LVMI (g/m²) (189.8±60.8 vs. 172.7±47.4) and LVM (g) (355.1±83.9 vs. 295.8±72.1) were significantly higher in the fQRS(+) group than in the fQRS(−) group (all p<0.05). There was no significant difference in beta blocker, amiodarone, disopyramide, and calcium channel blocker drug use between the two groups (all p>0.05).

Sixty-five patients were treated with beta blockers. Calcium channel blocker treatment was added on case of five patients in whom beta blocker therapy was contraindicated. If beta blockers or calcium channel blockers alone were ineffective, disopyramide added to the treatment. Amiodarone was added in case of four patients who had nonsuppressed ventricular tachycardia attacks with other medical treatment. Symptom improvement was observed in three patients with disopyramide, but in one patient, treatment was discontinued because of increased incidence of ventricular tachycardia attacks.

Correlation between fQRS and other parameters

A significant correlation was observed between fQRS and the family history (%) (r=0.274, p=0.003), presyncope (%) (r=0.209, p=0.026), syncope (%) (r=0.256, p=0.006), NYHA class (%) (r=0.378, p<0.001), HCM Risk-SCD (%) (r=0.497, p<0.001), LAV (mL) (r=0.287, p=0.002), LAVI (mL/m²) (r=0.285, p=0.002), IVST (mm) (r=0.369, p<0.001), LVPWT (mm) (r=0.196, p=0.036), LVM (g) (r=0.351, p<0.001), LVMI (g/m²) (r=0.320, p=0.001), VES (%) (r=0.428, p<0.001), VT (%) (r=0.278, p=0.003), CPR (%) (r=0.258, p=0.005), and ICD implantation (%) (r=0.226, p=0.015) (Table 2). No significant correlation was found between fQRS and other parameters.

Table 2. Correlation between fragmented QRS and other parameters

Variabilities	Fragmented QRS	
	r	**P**
Age, years	-0.130	0.167
Gender	0.182	0.051
History of family SCD, %	**0.274**	**0.003**
Presyncope, %	**0.209**	**0.026**
Syncope, %	**0.256**	**0.006**
NYHA, % class (I,II,III)	**0.378**	**<0.001**
HCM Risk-SCD, %	**0.497**	**<0.001**
LAAPD, mm	0.168	0.073
LAV, mL	**0.287**	**0.002**
LAVI, mL/m²	**0.285**	**0.002**
LV EF, %	0.028	0.766
IVST, mm	**0.369**	**<0.001**
LVPWT, mm	**0.196**	**0.036**
LVEDD, mm	**0.351**	**<0.001**
LVM, g	**0.351**	**<0.001**
LVMI, g/m²	**0.320**	**0.001**
LVOTO, mm Hg	0.060	0.527
PAF, %	0.070	0.458
VES, %	**0.428**	**<0.001**
Ventricular tachycardia, %	**0.278**	**0.003**
CPR, %	**0.258**	**0.005**
ICD implantation, %	**0.226**	**0.015**

Values are the mean±SD or percentage (%), CPR - cardiopulmonary resuscitation; EF - ejection fraction; HF - heart failure; ICD - implantable cardioverter defibrillator; IVST - Interventricular septum thickness; LAAPD - left atrium anterior-posterior dimension; LAV - left atrium volume; LAVI - left atrial volume index; LVEDD - left ventricular end-diastolic dimension; LVESS - left ventricular end-systolic dimension; LVM - left ventricular mass; LVMI - left ventricular mass index; LVOTO - left ventricular outflow tract obstruction; LVPWT - left ventricular posterior wall thickness; NYHA - New York heart association; PAF - paroxysmal atrial fibrillation; RWTI - relative wall thickness index; HCM Risk-SCD - predicted risk score of sudden cardiac death at five years; VES - ventricular extra systole; VT - ventricular tachycardia

Univariate analysis (UVA) and multivariate analysis (MVA)

Findings of UVA and MVA for independent high-risk indicators of HCM Risk-SCD are shown in Table 3. Both in UVA and MVA, fQRS [UVA: odds ratio (OR): 10.500, 95% confidence interval (CI): 3.694–29.848, p<0.001; MVA: OR: 0.162, 95% CI: 0.042–0.625, p=0.008] and NYHA class [UVA: OR: 0.127, CI: 0.057–0.288, p<0.001; MVA: OR: 0.271, 95% CI: 0.104–0.703, p=0.007] revealed that HCM Risk-SCD is an independent predictor of high risk. In ROC curve analysis, an HCM Risk-SCD value of >4 was identified as an effective cut-off point in fQRS for HCM (area under curve=0.845, 95% CI=0.776–0.914, p<0.001). An HCM Risk-SCD value of >4 yielded a sensitivity of 77% and a specificity of 76% (Fig. 2).

Table 3. Univariate and multivariate analyses for independent high-risk predictors of predicted risk score of sudden cardiac death at 5 years

	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Fragmented QRS	**10.500**	**3.694–29.848**	**<0.001**	**0.162**	**0.042–0.625**	**0.008**
NYHA	**0.127**	**0.057–0.288**	**<0.001**	**0.271**	**0.104–0.703**	**0.007**
PAF	4.437	1.245–15.812	0.022			
VT	9.409	3.322–26.650	<0.001			
LAVI	0.938	0.896–0.983	0.007			
IVST	0.846	0.768–0.931	0.001			
LVM	0.992	0.985–1.000	0.044			
LVMI	1.008	1.000–1.015	0.001			
Presyncope	3.625	1.579–8.321	0.002			
Heart failure at the time of admission	0.141	0.058–0.343	<0.001			

CI - confidence interval; IVST - interventricular septum thickness; LAVI - left atrial volume index; LVM - left ventricular mass; LVMI - left ventricular mass index; NYHA - New York Heart Association functional class; OR - odds ratio; PAF - paroxysmal atrial fibrillation; VT - ventricular tachycardia
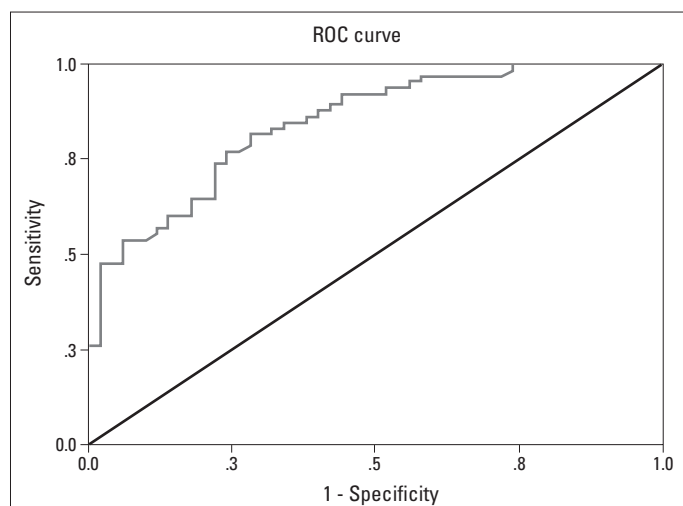

Figure 1. In a receiver operating characteristic (ROC) curve analysis, a predicted risk score of sudden cardiac death at 5 years (the HCM Risk-SCD) value of >4 was identified as an effective cut-off point in FQRS for HCM (area under curve=0.845, 95% CI=0.776–0.914, *P*<0.001). An HCM Risk-SCD value of more than 4 yielded a sensitivity of 77% and a specificity of 76%

Discussion

In this present study, the most important finding was that fQRS seems to be associated with ventricular arrhythmic events and predicts HCM Risk-SCD. Moreover, fQRS and NYHA class were determined to be independent high-risk indicators of HCM Risk-SCD. Family history, presyncope, syncope, need for CPR or ICD implantation, and heart failure at the time of admission to the hospital were significantly more common in patients with fQRS.

Inhomogeneous activation of the ventricles because of partially depolarized and depressed action potential upstroke velocities due to regional slow activation of the islands of chronically ischemic ventricular myocardium manifests itself as fQRS on 12-lead ECG (13, 14). Actually, fractionated ECGs consisting of multiple discrete deflections have been observed in regions where "islands" of viable myocardial tissue are interspersed with abundant fibrous tissue (15). fQRS has been demonstrated to be a more sensitive marker with a higher predictive value for myocardial scarring than Q waves on 12-lead ECGs (6, 8). Furthermore, fQRS is a useful marker for predicting events that may develop in patients with coronary artery disease. Akgül et al. (9) proved that the presence of fQRS on ECG is a reliable and easily applicable prognostic indicator for the follow-up of patients after acute myocardial infarction. On the other hand, fQRS is not specific for coronary artery disease and has also been observed in other myocardial diseases associated with arrhythmias, such as dilated cardiomyopathy (16, 17), Chagas' disease (18), ion channel disease such as Brugada (19) and long QT syndrome (20), some congenital heart diseases such as tetralogy of Fallot (21), and arrhythmogenic right ventricular cardiomyopathy (10). Consequently, whole anatomical or electrophysiological substrates that give rise to the development of conduction disturbances in the myocardium predispose the heart to ventricular tachyarrhythmias. In this present study, the percentage of VES/VT, presyncope, syncope, and requirement of CPR were significantly higher in the fQRS(+) group than in the fQRS(−) group. Similarly, Femenía et al. (22) found that the presence of fQRS is associated with a worse prognosis predicting arrhythmic events in patients receiving ICD for primary or secondary prophylaxis of SCD. They also showed that the localization of fQRS in the lateral area of the left ventricule is associated with increased ICD requirement (22). In situations like this, myocyte disarray and myocardial fibrosis provide the anatomical substrate for ventricular arrhythmia (23). In the present study, a significant correlation was observed between fQRS and the percentage of ICD implantation.

Abnormal and overmuch myocyte hypertrophies along with progressive fibrous tissue accumulation in the cardiac interstitium are pathological processes affecting the myocardial structure in HCM patients (24). Because of these alterations, the ho-

mogenous myocardial tissue becomes heterogeneous. Kadı et al. (25) observed a significant relationship between fQRS and LV hypertrophy. They interpreted that the presence of fQRS on ECG may reveal myocardial fibrosis. In the present study, fQRS seemed to be associated with increased LVM, LVMI, IVST, and PWT. In addition to these, fQRS is related to a higher adverse cardiac event, decreased life span, and impaired quality of life in patients with a large number of cardiovascular diseases (26, 27). Nomura et al. (16) found that fQRS is significantly higher in case of hospitalization for heart failure. Fibrous tissue promotes ventricular stiffness. For example, pathological evaluation revealed that microscopic fibrosis is greater in the hearts of patients with a dilated phase of HCM than in those with a nondilated phase. In present study, we observed that patients with NYHA class 3–4 heart failure symptoms were significantly higher in fQRS(+) group.

Nonsustained ventricular tachycardia, severe hypertrophy, unexplained syncope, family history of SCD, and abnormal blood pressure response to exercise have been used in clinical practice to guide ICD therapy for a long-time; however, these approaches only provide a very crude estimate of the relative risk of SCD and not of the absolute risk and they fail to account for the differences in the size of the effects of individual risk factors (22, 23). Current clinical guidelines for HCM in Europe recommend a practical risk prediction model for SCD in patients with HCM (2). This newly developed prediction model for SCD is uncomplicated, is not time-consuming, and is a good method for guiding the therapy used to treat the condition. According to this guideline, HCM Risk-SCD over 6% indicates that the patient belongs to the high-risk group and ICD should be considered. In this study, we observed that fQRS was significantly higher in patients in the high\-risk group with HCM Risk-SCD over 6%. fQRS is determined as an independent high-risk indicator of HCM Risk-SCD. Ventricular tachycardia attacks caused by irregular myocardial fibrosis may be responsible for the increased 5-year risk of SCD. The predictive value of fQRS and arrhythmic events are warranted before. Investigation of the presence of fQRS is seems to be a simple and quick parameter for predicting HCM Risk-SCD in patients, particularly those in the high-risk group.

Study limitations

This is not an epidemiological or randomized study exploring new associations with SCD. A relatively small sample size (n=115) of HCM patients was included in the study. The duration of the study was not long enough for following patients. Genetic and screening tests were performed for patients with another suspected disease. Genetic test for HCM was performed in only three patients, and screening test for Anderson–Fabry disease was performed in 35 patients. We did not evaluate the relationship between the fQRS localized area and frequency of ventricular arrhythmias. Instead, we investigated whether fQRS could be a potential predictor of cardiac events, including arrhythmic

events as well as HCM Risk-SCD in patients with HCM. This is the first series that reports this association, and it was difficult to collect information from patients from two medical centers. We included only adult HCM patients in the present study. We did not quantitative modalities other than magnetic resonance imaging to view the myocardial fibrous tissue all our patients; some of them just refused to undergo imaging.

Conclusion

In the present study, we demonstrated that the presence of fQRS on 12-lead ECG seems to be significantly associated with increasing percentages of the predicted HCM Risk-SCD value in HCM patients. fQRS is an independent high-risk indicator of HCM Risk-SCD. Ventricular arrhythmias and some echocardiographics parameters are significantly higher in HCM patients with fQRS.

References

1. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008; 29: 270-6.
2. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014; 35: 2733-79.
3. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, et al. Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy(HCM Risk-SCD). Eur Heart J 2014; 35: 2010-20.
4. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J 1958; 20: 1-8
5. Chatterjee S, Changawala N. Fraqmented QRS complex: a novel marker of cardiovascular disease. Clin Cardiol 2010; 33: 68-71.
6. Das MK, Suradi H, Maskoun W, Michael MA, Shen C, Peng J, et al. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. Circ Arrhythm Electrophysiol 2008; 1: 258-68.
7. Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation 2006; 113: 2495-501.
8. Das MK, Maskoun W, Shen C, Michael MA, Suradi H, Desai M, et al. Fragmented QRS on twelve-lead electrocardiogram predicts ar-

rhythmic events in patients with ischemic and nonischemic cardiomyopathy. Heart Rhythm 2010; 7: 74-80.

9. Akgül O, Uyarel H, Pusuroğlu H, Sürgit O, Türen S, Ertürk M, et al. Predictive value of a fragmented QRS complex in patients undergoing primary angioplasty for ST elevation myocardial infarction. Ann Noninvasive Electrocardiol 2015; 20: 263-72.

10. Peters S, Trümmel M, Koehler B. QRS fragmentation in standard ECG as a diagnostic marker of arrhythmogenic right ventricular dysplasia-cardiomyopathy. Hearth Rhythm 2008; 5: 1417-21.

11. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two- Dimensional Echocardiograms. J Am Soc Echocardiogr 1989; 2: 358-67.

12. Devereux RB, Koren MJ, de Simone G, Okin PM, Kligfield P. Methods for detection of left ventricular hypertrophy: application to hypertensive heart disease. Eur Heart J 1993; 14: 8-15.

13. Das MK, El Masry H. Fragmented QRS and other depolarization abnormalities as a predictor of mortality and sudden cardiac death. Curr Opin Cardiol 2010; 25: 59-64.

14. Zhang L, Mmagu O, Liu L, Li D, Fan Y, Baranchuk A, et al. Hypertrophic cardiomyopathy: Can the noninvasive diagnostic testing identify high risk patients? World J Cardiol 2014; 6: 764-70.

15. Lesh MD, Spear JF, Simson MB. A computer model of the electrogram: what causes fractionation? J Electrocardiol 1988; 21: S69-S73.

16. Nomura A, Konno T, Fujita T, Tanaka Y, Nagata Y, Tsuda T, et al. Fragmented QRS predicts heart failure progression in patients with hypertrophic cardiomyopathy. Circ J 2015; 79: 136-43.

17. Sha J, Zhang S, Tang M, Chen K, Zhao X, Wang F. Fragmented QRS is associated with all-cause mortality and ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy. Ann Noninvasive Electrocardiol 2011; 16: 270-5.

18. Baranchuk A, Femenia F, López-Diez JC, Muratore C, Valentino M, Retyk E, et al. Fragmented surface ECG was a poor predictor of appropriate therapies in patients with Chagas' cardiomyopathy and ICD implantation (Fragmented ECG in CHAgas' Cardiomyopathy Study). Ann Noninvasive Electrocardiol 2014; 19: 43-9.

19. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, et al. Risk stratificationin Brugada syndrome: results of the PRELUDE(PRogrammed ELectrial stimUlation preDictive valuE) registry. J Am Coll Cardiol 2012; 59: 37-45.

20. Haraoka K, Morita H, Saito Y, Toh N, Miyoshi T, Nishii N, et al. Fragmented QRS is associated with torsadesde pointes in patients with acquired long QT syndrome. Heart Rhythm 2010; 7: 1808-14.

21. Shanmugam N, Yap J, Tan RS, Le TT, Gao F, Chan JX, et al. Fragmented QRS complexes predict right ventricular dysfunction and outflow tract aneurysms in patients with repaired tetralogy of Fallot. Int J Cardiol 2013; 167: 1366-72.

22. Femenía F, Arce M, Van Grieken J, Trucco E, Mont L, Abello M, et al. Fragmented QRS in Hypertrophic Obstructive Cardiomyopathy (FHOCM) Study Investigators. Fragmented QRS as a predictor of arrhythmic events in patients with hypertrophic obstructive cardiomyopathy. J Interv Card Electrophysiol 2013; 38: 159-65.

23. Gray B, Ingles J, Medi C, Semsarian C. Prolongation of the QTc interval predicts appropriate implantable cardioverter-defibrillator therapies in hypertrophic cardiomyopathy. JACC Heart Fail 2013; 1: 149-55.

24. Gardner PI, Ursell PC, Fenoglio JJ Jr, Wit AL. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. Circulation 1985; 72: 596-611.

25. Kadı, H, Kevser, A, Öztürk, A, Koç F, Ceyhan K. Fragmented QRS complexes are associated with increased left ventricular mass in patients with essential hypertension. Ann Noninvasive Electrocardiol 2013; 18: 547-54.

26. Başaran Y, Tigen K, Karaahmet T, Işıklar I, Çevik C, Gürel E, et al. Fragmented QRS complexes are associated with cardiac fibrosis and significant intraventricular systolic dyssynchrony in nonischemic dilated cardiomyopathy patients with a narrow QRS interval. Echocardiography 2011; 28: 62-8.

27. Kang KW, Janardhan AH, Jung KT, Lee HS, Lee MH, Hwang HJ. Fragmented QRS as a candidate marker for high-risk assessment in hypertrophic cardiomyopathy. Heart Rhythm 2014; 11: 1433-40.