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Fragmented QRS Predicts Heart Failure Progression in Patients With Hypertrophic Cardiomyopathy

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Background: Although fragmented QRS complex (frag-QRS) reflecting intra-ventricular conduction delay has been shown to be a prognostic marker for cardiac events, few data exist regarding the impact of frag-QRS on cardiac events in hypertrophic cardiomyopathy (HCM).

Methods and Results: Ninety-four HCM patients (56 male; mean age, 58±17 years) were retrospectively investigated. Frag-QRS was defined as the presence of various RsR' patterns in at least 2 contiguous ECG leads. Major arrhythmic events (MAE) were defined as sudden cardiac death, and combined sustained ventricular tachycardia/ventricular fibrillation. New-onset atrial fibrillation (AF) was diagnosed based on ECG during provisional or routine medical examination. Heart failure (HF) with hospitalization was defined as hospital admission due to subjective or objective symptoms. Frag-QRS was detected in 31 patients (33%). *TNNI3* was the most frequent disease-causing gene. Median follow-up was 4.6 years. The 4-year cumulative survival rates of cardiac death, MAE, new-onset AF and HF with hospitalization were 97.6%, 94.6%, 87.5% and 89.3%, respectively. On multivariate analysis, frag-QRS was significantly associated with HF with hospitalization (adjusted hazard ratios [95% confidence intervals]: 5.4 [1.2–36], P=0.03). Moreover, HF-free survival was significantly lower in the frag-QRS (+) group compared to the frag-QRS (–) group (79.0% vs. 95.1%, P=0.03).

Conclusions: Frag-QRS is associated with HF with hospitalization in HCM patients who had a unique distribution of gene mutations. (*Circ J* 2015; **79:** 136–143)

Key Words: Clinical outcome; Fragmented QRS complex; Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous myocardial disorder that can cause fatal cardiac events such as sudden cardiac death or progressive left ventricular (LV) systolic dysfunction.[1–4] Although more than half a century has passed since HCM was first described,[5] it is still challenging to prevent these life-threatening events in HCM patients using effective risk stratification methods. For primary prevention, high-yield non-invasive clinical findings are needed to identify potentially high-risk HCM patients effectively and economically. From this point of view, cardiac magnetic resonance imaging is useful for identifying massive LV hypertrophy (≥30 mm) and extensive late gadolinium enhancement (LGE), both of which have been considered as risk factors for cardiac events in HCM.[2,6] With regard to 12-lead electrocardiogram (ECG), however, the many specific abnormal ECG patterns (except multiple repetitive non-sustained ventricular tachycardia [VT]) have still failed to be a useful prognostic tool for risk stratification in HCM patients.[7]

Fragmented QRS complexes (frag-QRS), which are primarily defined as the presence of an additional R wave (R'), notching in the nadir of the S wave or the presence of >1 R' on 12-lead ECG,[8] reflect intra-ventricular conduction delay and have been shown to be a prognostic marker in coronary artery disease,[8] Chargas' disease,[9] arrhythmogenic right ventricular cardiomyopathy,[10] Brugada syndrome,[11] acquired long QT syndrome[12] and structural heart disease with implantable cardioverter defibrillator (ICD) implantation.[13,14] Regarding HCM, frag-QRS could be a predictor of life-threatening arrhythmic events,[15] especially in those with ICD implantation.[16]

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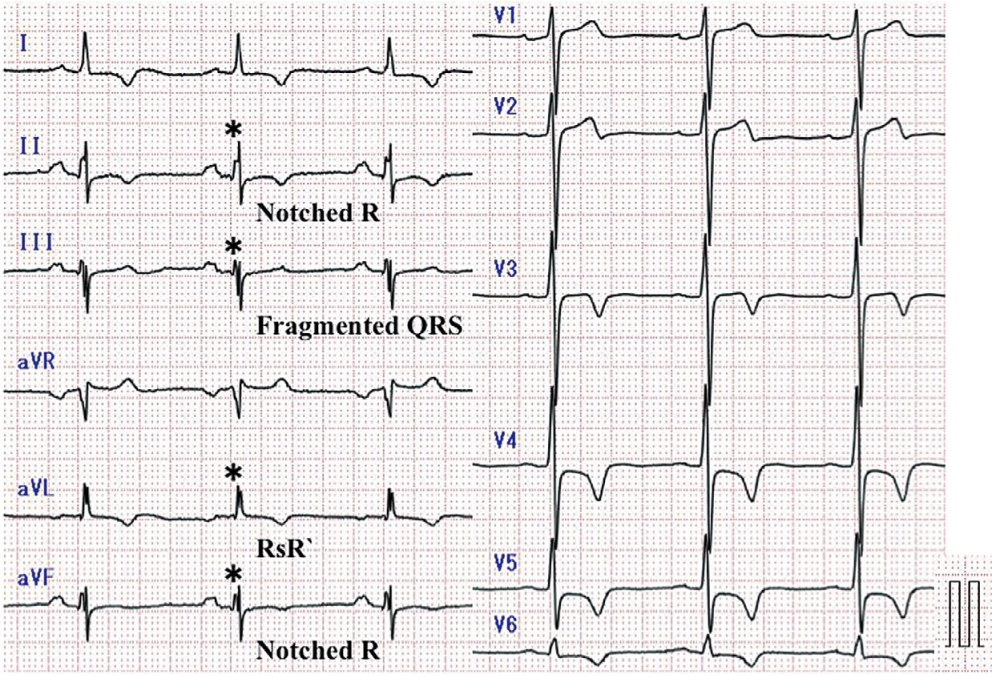

Figure 1. Representative case of hypertrophic cardiomyopathy showing fragmented QRS complexes (frag-QRS). The 12-lead electrocardiogram shows various frag-QRS patterns (notched R, notched S and RsR' with QRS duration <120 ms) in inferior leads and aVL. Inferior frag-QRS was positive because inferior leads had >1 contiguous frag-QRS pattern, where myocardial scarring is thought to exist. Posterior frag-QRS, however, was negative because the posterior leads had only 1 frag-QRS pattern.

It remains uncertain, however, whether frag-QRS could also predict other cardiac events such as new-onset atrial fibrillation (AF) or heart failure (HF) with hospitalization.

The aim of this study was to evaluate whether frag-QRS could be used as a potential risk stratification tool to predict cardiac events including cardiac death, life-threatening arrhythmic events, new-onset AF and HF with hospitalization in patients with HCM.

Methods

Patient Selection

From September 2008 to March 2010, 240 patients (HCM, n=193; hypertensive heart disease, n=47) had been registered in the Left Ventricular Hypertrophy Multicenter Registration Study in Japan.[17] The institutional Ethics Committee for Medical Research approved the study protocol, and all patients provided written informed consent before registration. Of the 193 HCM patients in the Registration Study, 100 HCM patients followed at the Kanazawa University Hospital and its affiliated hospitals were enrolled. Of those 100 patients, 6 were excluded for the following reasons: unable to obtain appropriate ECG data at registration (n=4), clinical data missing (n=1), and diagnosed with cardiac sarcoidosis after registration (n=1). Finally, 94 patients who were diagnosed with HCM were retrospectively evaluated in this study. All clinical information was collected from the patient's hospital records or telephone contact with the patients, their family members or the primary care physician.

HCM Definitions

HCM was diagnosed based on the 2011 guideline of the American College of Cardiology Foundation/American Heart Association.[1] In brief, patients whose maximum LV wall was >13 mm thick (usually involving asymmetric septal hypertrophy) without extra-cardiac or metabolic findings based on echocardiography or cardiovascular magnetic resonance were diagnosed with HCM. Carriers harboring at least one sarcomere gene mutation were diagnosed as HCM even if ventricular hypertrophy was absent (genotype-positive, phenotype-negative preclinical HCM).

LV outflow tract (LVOT) obstruction (LVOTO) was defined as peak instantaneous LVOT pressure gradient >30 mmHg. Maximum LV wall thickness was defined as the greatest thickness within the chamber. Other echocardiographic parameters were evaluated according to the guidelines recommended by American Society of Echocardiography.[18]

HCM coexisting with hypertension was not an exclusion criterion in the study. Hypertension was diagnosed when systolic blood pressure (BP) was ≥140 mmHg and/or diastolic BP was ≥90 mmHg. Diabetes mellitus was diagnosed when a patient was treated with insulin or oral hypoglycemic drugs, when casual plasma glucose was >200 mg/dl, fasting plasma glucose was >126 mg/dl or glycosylated hemoglobin was >6.5% in patients without need for treatment with insulin or oral hypoglycemic drugs. Dyslipidemia was diagnosed when a patient was treated with lipid-lowering agents, or when the casual total cholesterol was >220 mg/dl. Medication and a device implantation (such as pacemaker or ICD) during the study period were performed according to the guidelines of the Japanese Society of Cardiology.

Table 1. Subject Characteristics

Clinical characteristics	
No. patients	94
Age (years)	58±17
Male	56 (60)
Hypertension	32 (35)
Diabetes mellitus	8 (9)
Dyslipidemia	14 (15)
Previous VT/VF	7 (7)
Family history of SCD	11 (12)
LVOTO	17 (18)
ICD	7 (7)
Sarcomere gene mutation	45 (48)
TNNI3	23
MYBPC3	17
MYH7	4
TNNT2	1
Electrocardiography	
Sinus rhythm	79 (84)
Chronic AF	9 (10)
LBBB	2 (2)
RBBB	11 (12)
Pacemaker	2 (2)
Q wave	16 (17)
Giant negative T wave	14 (15)
QRS interval (ms)	110±26
QRS axis (degrees)	35±50
QTc interval (ms)	436±36
Frag-QRS positive	31 (33)
Anterior	12
Posterior	3
Inferior	21
Echocardiography	
MWT (mm)	17±5
IVS (mm)	15±5
PW (mm)	10±2
LVDd (mm)	46±6
LVEF (%)	67±10
E/e'	16±8
Medication at registration	
ACEI/ARB	33 (35)
β-blocker	34 (36)
Calcium channel blocker	30 (32)
Diuretics	24 (26)
Warfarin	17 (18)
Amiodarone	4 (4)
Statin	5 (5)

Data given as mean±SD or n (%). ACEI, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; E/e', E to E prime ratio; frag-QRS, fragmented QRS complex; ICD, implantable cardioverter defibrillator; IVS, intraventricular septum; LBBB, left bundle branch block; LVDd, left ventricular diameter at end diastole; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; *MYBPC3*, myosin-binding protein C; MWT, maximum wall thickness; *MYH7*, myosin heavy chain; PW, posterior wall; RBBB, right bundle branch block; SCD, sudden cardiac death; *TNNI3*, troponin I; *TNNT2*, troponin T; VF, ventricular fibrillation; VT, ventricular tachycardia.

Genetic Testing

Genetic screening tests were performed for all the study patients using polymerase chain reaction and direct DNA sequencing for mutations in 9 common HCM sarcomere genes (myosin binding protein C, *MYBPC3*; myosin heavy chain, *MYH7*; regulatory myosin light chain, *MYL2*; essential myosin light chain, *MYL3*; troponin I, *TNNI3*; troponin T, *TNNT2*; tropomyosin, *TPM1*; titin, *TTN*; and cardiac actin, *ACTC1*), as previously reported.[17]

Event Collection

Cardiac death was defined as any death from a cardiovascular cause. Ventricular fibrillation (VF) was defined as an irregular, random waveform with no clearly identifiable QRS complexes or P waves. VT was defined as the presence of ≥3 consecutive premature ventricular beats at a rate >100 beats/min.[19] Major arrhythmic events (MAE) were defined based on the occurrence of sudden cardiac death, apparent records of the occurrence of sustained VT (>30 s) and VF from an automated external defibrillator, ICD, 24-h Holter ECG or continuous ECG monitoring, which were performed at annual regular clinical visits. New-onset AF was diagnosed based on a standardized ECG obtained during provisional or routine medical examination. HF with hospitalization was defined as hospital admission due to subjective or objective symptoms (eg, severe dyspnea or pulmonary edema).

ECG

Standard 12-lead ECG (0.5–150 Hz, 25 mm/s, 10 mm/mV) was recorded in the supine position during quiet respiration. The frag-QRS was defined as previously described,[8,20] as follows: (1) in patients with QRS duration <120 ms, (a) an additional R wave (R prime: R'), or (b) notching in nadir of the S wave, (c) notching of R wave, or (d) the presence of >1 R' in 2 contiguous leads corresponding to major coronary artery territory; (2) in patients with right or left bundle branch block (QRS duration ≥120 ms), (a) various RsR' pattern with or without a Q wave with >2 R', or (b) >2 notches in the R wave, or (c) >2 notches in the downstroke or upstroke of the S wave, in 2 contiguous leads corresponding to major coronary artery territory; and (3) in patients with mechanical pacing (QRS duration ≥120 ms), the presence of >2 R' or >2 notches in the S waves in 2 contiguous leads corresponding to major coronary artery territory. A representative case of HCM with frag-QRS on 12-lead ECG is shown in **Figure 1**.

Pathological Q waves were defined as follows based on previous studies: Q wave >1/4 of the ensuing R wave in depth and/or >40 ms in duration in at least 2 leads except aVR.[21] Giant negative T waves >10 mm in depth in any leads were defined as giant negative T waves.[22]

Statistical Analysis

In this study, the incidences of cardiac death, MAE, new-onset AF, and HF with hospitalization were evaluated. Potential risk factors were also analyzed for each category.

Continuous variables are presented as mean±SD or as median (interquartile range [IQR]) and were compared using the Student's unpaired t-test or Wilcoxon rank sum test depending on their distributions, respectively. Categorical variables were presented as count and percentage and were compared with Fisher's exact test. Survival curves were generated using the Kaplan-Meier method, and were evaluated with the log-rank test.

To adjust for a range of potential confounders, multivariate analysis of independent predictors of each cardiac event (MAE,

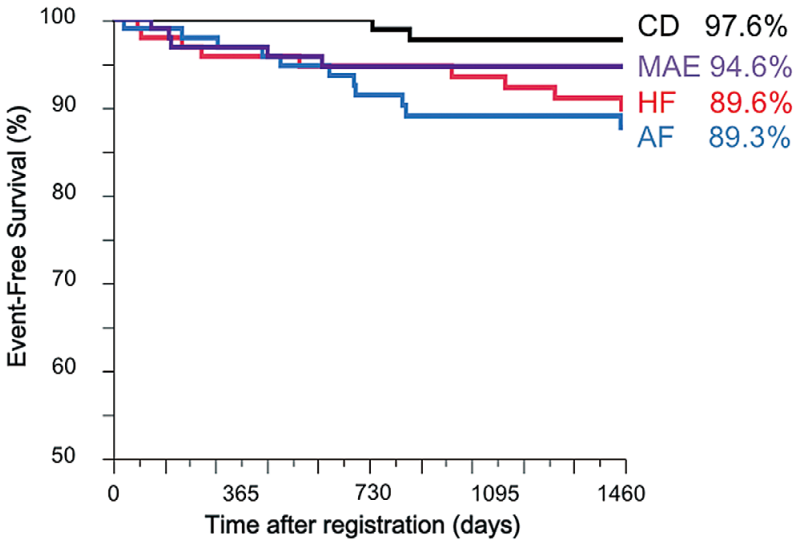

Figure 2. Kaplan-Meier estimates of event-free survival rates of cardiac death (CD), major arrhythmic events (MAE), heart failure (HF) with hospitalization and new-onset atrial fibrillation (AF). At 4 years, the CD-free survival was 97.6%; MAE, 94.6%; HF with hospitalization-free survival, 89.3%; and new-onset AF-free survival, 87.5%.

Table 2. Multivariate Predictors of MAE, New-Onset AF and HF With Hospitalization

	MAE (n=5/94)			New-onset AF (n=11/94)			HF with hospitalization (n=9/94)		
	Adjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Age	0.96	0.88–1.1	0.40	1.01	0.97–1.06	0.68	1.1	0.99–1.2	0.10
Male gender	0.61	0.02–17	0.74	0.62	0.16–2.4	0.48	0.09	0.008–0.64	0.01*
Hypertension	–	–	–	–	–	–	0.07	0.003–0.64	0.02*
Previous VT/VF	27	3.2–570	0.003*	–	–	–	2.2	0.09–31	0.60
QTc interval	–	–	–	0.98	0.96–1.0	0.053	1.0	0.98–1.02	0.80
LVEF	0.94	0.85–1.0	0.22	0.94	0.88–0.99	0.046*	0.88	0.79–0.97	0.01*
ACEI/ARB	3.0	0.18–150	0.46	–	–	–	–	–	–
Diuretics	1.5	0.11–27	0.77	–	–	–	0.80	0.09–6.0	0.83
Amiodarone	–	–	–	–	–	–	0.78	0.03–18	0.88
Sarcomere gene mutation	–	–	–	0.78	0.18–3.2	0.73	0.15	0.01–1.1	0.06
Frag-QRS(+)	1.7	0.05–53	0.74	2.1	0.56–7.5	0.26	5.4	1.2–36	0.03*

*P<0.05. CI, confidence interval; HF, heart failure; HR, hazard ratio; MAE, major arrhythmic event. Other abbreviations as in Table 1.

new-onset AF or HF with hospitalization) was performed using a Cox-proportional hazard regression model. Variables with P<0.1 on univariate analysis in addition to age, male gender, sarcomere gene mutation and frag-QRS were selected in each final model considering confounding variables. Adjusted hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) are shown in the relevant tables. All statistical analysis was performed using JMP Pro version 11 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

Baseline subject characteristics are listed in Table 1. The median follow-up period of the 94 eligible HCM patients was 4.6 years (IQR, 4.1–4.8 years), mean age was 58±17 years, and 56 patients (60%) were male. Seventeen patients (18%) had LVOTO; 9 patients (10%) presented with chronic AF; 11 patients (12%) had a family history of sudden cardiac death; 7 patients (7%) had already been implanted with an ICD according to the guidelines; and 4 patients (4%) were prescribed amiodarone. Sarcomere gene mutations were detected in 45 patients (48%) and *TNNI3* was the most frequent disease-causing gene (23 patients) followed by *MYBPC3* (17 patients), *MYH7* (4 patients) and *TNNT2* (1 patient). Of those 45 patients, 11 patients (12%) had genotype-positive, phenotype-negative preclinical HCM. The number of patients with positive frag-QRS was 31 (33%).

Clinical Outcome

During the follow-up period of 4 years, cardiac death, MAE, new-onset AF, and HF with hospitalization occurred in 2 (2.4%), 5 (5.4%), 11 (12.5%), and 9 (10.7%) of the 94 patients, respectively. Thus, cardiac death-free survival was 97.6%; MAE-free survival, 94.6%; new-onset AF-free survival, 87.5%; and HF with hospitalization-free survival, 89.3%, respectively (Figure 2).

Potential confounders of each cardiac event (MAE, new-

Table 3. Subject Characteristics in Accordance With the Presence of Frag-QRS

	Frag-QRS (+), n=31	Frag-QRS (–), n=63	P-value
Clinical characteristics			
Age (years)	63±13	55±19	0.02*
Male	20 (65)	36 (57)	0.51
Hypertension	15 (48)	17 (27)	0.06
Diabetes mellitus	4 (13)	4 (6)	0.43
Dyslipidemia	4 (13)	10 (16)	1.00
Previous VT/VF	4 (13)	3 (5)	0.21
Family history of SCD	4 (13)	7 (11)	1.00
LVOTO	8 (26)	9 (14)	0.25
Chronic AF	4 (13)	5 (8)	0.47
ICD	3 (10)	4 (6)	0.68
Sarcomere gene mutation	14 (45)	31 (49)	0.83
Echocardiography			
MWT (mm)	17±4	16±5	0.84
IVS (mm)	16±4	15±5	0.57
PW (mm)	11±2	10±2	0.21
LVDd (mm)	47±7	46±6	0.78
LVEF (%)	65±10	68±10	0.23
E/e'	18±9	15±7	0.28
Medication at registration			
ACEI/ARB	15 (48)	18 (29)	0.07
β-blocker	14 (45)	20 (32)	0.26
Calcium channel blocker	12 (39)	18 (29)	0.35
Diuretics	12 (39)	12 (19)	0.048*
Warfarin	8 (26)	9 (14)	0.25
Amiodarone	3 (10)	1 (2)	0.10
Statin	1 (3)	4 (6)	1.00

Data given as mean±SD or n (%). *P<0.05, frag-QRS(+) vs. frag-QRS(–). Abbreviations as in Tables 1,2.

onset AF and HF with hospitalization) were investigated using the Cox-proportional hazard regression model (Table 2). Cardiac death was excluded from the analysis because there was no event during the follow-up period in the frag-QRS (–) group. After adjustment for potential confounders, previous VT/VF episode was significantly associated with MAE (adjusted HR, 27; 95% CI: 3.2–570; P=0.003), and LV ejection fraction was significantly associated with new-onset AF (adjusted HR, 0.94; 95% CI: 0.88–0.99; P=0.046) and HF with hospitalization (adjusted HR, 0.88; 95% CI: 0.79–0.97; P=0.01). In addition, frag-QRS was significantly associated with HF with hospitalization (adjusted HR, 5.4; 95% CI: 1.2–36; P=0.03).

Frag-QRS

Clinical and echocardiographic features in relation to frag-QRS are shown in Table 3. Mean age (63±13 years vs. 55±19 years, P=0.02) and the number of patients prescribed diuretics (39% vs. 19%, P=0.048) were significantly higher in the frag-QRS (+) than frag-QRS (–) group; there was no statistically significant difference between any other variable.

Kaplan-Meier estimates of each cardiac event are shown in Figure 3. At 4 years, HF-free survival was significantly lower in the frag-QRS (+) group compared to frag-QRS (–) group (79.0% vs. 95.1%, P=0.03) at 4 years.

Discussion

In the present study, we investigated whether frag-QRS could be a potential predictor of cardiac events including not only arrhythmic events but also HF in patients with HCM. The most important findings are as follows: (1) event-free survival rates for cardiac death, MAE, HF with hospitalization, and new-onset AF were 97.6%, 94.6%, 89.3% and 87.5%, respectively; (2) at 4 years, frag-QRS was significantly associated with HF with hospitalization in the multivariate model; and (3) HF-free survival was significantly lower in the frag-QRS (+) group compared with the frag-QRS (–) group.

At 4 years, the individual event rates of each clinical event were as follows: cardiac death, 2.4%; MAE, 5.4%; HF with hospitalization, 10.7%; and new-onset AF, 12.5%, respectively. Previous studies reported that the annual mortality rate is approximately 1–5% in overall HCM patients,[23] and on analysis of stored ECG from ICD the mechanism of sudden death in HCM patients is mainly primary VT or VF.[2] Appropriate ICD shock interventions for VT/VF occurred in 5% of HCM patients annually who had undergone ICD implantation for primary prevention.[24] Exacerbation of HF occurs in approximately 15–20%, and paroxysmal or chronic AF is detected in approximately 20–25% during the patient's lifetime.[23] Also, Femenía et al observed new-onset AF in 32.4% of HCM patients with an ICD during the follow-up period (mean duration, 4 years).[16] Although the rate of new-onset AF observed in our study might be relatively low for 4 years, other event-free survival rates were similar to previous data.[2,16,23,24] In addition, although AF is a potential risk factor for stroke, no cerebrovascular diseases occurred during the 4-year period of

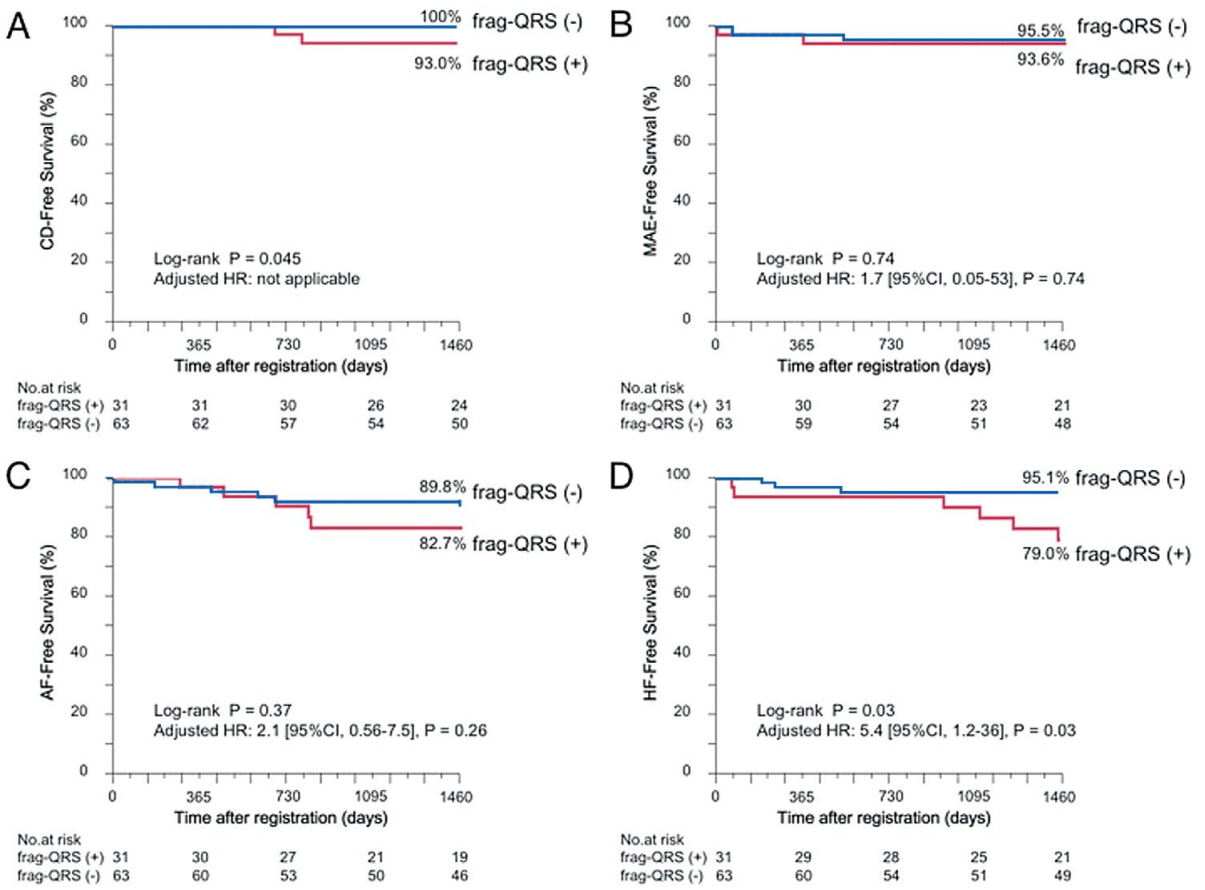

Figure 3. Freedom from (**A**) cardiac death (CD), (**B**) major arrhythmic events (MAE), (**C**) new-onset atrial fibrillation (AF), and (**D**) heart failure (HF) with hospitalization in patients with or without fragmented QRS complexes (frag-QRS). (**D**) At 4 years, the HF-free survival was significantly lower in the frag-QRS (+) group compared to the frag-QRS (–) group (79.0% vs. 95.1%, P=0.03).

our study.

Frag-QRS was significantly associated with HF with hospitalization in the present study, even though the many ECG findings such as T-wave alternans or late potential recorded in HCM patients have failed to reliably predict outcome over the years.[25,26] Fragmentation of QRS occurs as a consequence of an alternation to the normal depolarization of the ventricles. Morphological examination in HCM patients with sudden cardiac death has confirmed that they had patchy, multiple fibrous scarring in mainly the mid-septal hypertrophic regions.[27–29] These fibrous regions could cause slow activation as a result of partially depolarized and depressed action potential upstroke velocities, which could invoke inhomogeneous activation of the ventricles. This feature is thought to explain the fragmentation of QRS complexes on ECG.[20,30] Myocardial fibrosis detected on LGE in HCM patients has been associated with cardiac death,[31] systolic dysfunction[27] and nonsustained VT.[32] This indicates that frag-QRS might have worked as a surrogate marker of myocardial scarring, and thus was significantly associated with cardiac events. In addition to previous data, which showed that frag-QRS could be a prognostic tool for predicting sudden cardiac death and life-threatening VT/VF,[15,16] we found that frag-QRS was significantly associated with HF with hospitalization (**Table 2**). Moreover, on Kaplan-Meier estimate the HF-free survival was significantly lower in the frag-QRS (+) group compared to the frag-QRS (–) group at 4 years (**Figure 3**). O'Hanlon et al reported that myocardial scarring was associated with the development of HF in HCM patients,[33] and it is reasonable that frag-QRS that could predict myocardial scarring might be a prognostic marker of hospitalization-required HF in patients with HCM. Although HF is possibly influenced by the occurrence of AF, there was no association between chronic AF and HF with hospitalization (crude HR, 2.85; 95% CI: 0.42–12; P=0.24). Also, the rates of HF with hospitalization were similar between patients who developed new-onset AF and those without new-onset AF (11% [1/11] in patients with new-onset AF vs. 9% [8/83] in patients without new-onset AF, P=1.0).

In contrast to previous reports,[15,16] frag-QRS was not significantly associated with MAE. The reasons for this discrepancy were thought to be the lower MAE rate and shorter follow-up period compared to previous reports. The subjects in the Femenía et al study were HCM patients with ICD implantation, who were considered to be in a high-risk group, and the event rate (appropriate ICD therapy) was up to 40.2%,[16] which might provide sufficient statistical power to evaluate the correlation between frag-QRS and cardiac events. Also, the MAE rate in the Kang et al study[15] was higher than the present one

(13.4% vs. 5.4%), and the occurrence of MAE was more apparent after 4 years follow-up in their study. Moreover, the subjects in our study might have had different genetic background compared to those in the two previous studies. A further large cohort study with long-term follow-up is needed to validate the correlations between frag-QRS and each cardiac event.

Although we have previously reported that having sarcomere gene mutations could be a prognostic factor in the elderly (>50 years old) patient group with HCM,[17] it was not associated with any of the cardiac events in the present study (Tables 2,3). One reason could be that the present subjects were much younger than the previous study cohort (mean age, 58 years vs. 69 years). Another reason could be that the present subjects included 11 preclinical HCM patients (11%), which could have influenced the results. Moreover, the present subjects had a unique distribution of sarcomere gene mutations: *TNNI3* was the most frequent disease-causing gene (51%). Generally, almost 90% of sarcomere gene mutations in HCM patients can be detected in *MYBPC3* or *MYH7* genes, whereas *TNNI3* mutations are rarely identified (approximately 5%).[34–36] The most prevalent mutation in the present study, *TNNI3 Lys183del*, is a founder mutation identified in families living in an isolated rural area in Japan, thus resulting in accumulation of this specific mutation carriers in the present HCM patients. *TNNI3* mutation could be a risk factor for early onset and severe clinical presentation in patients with HCM.[37] The results might be also influenced by this specific distribution of sarcomere gene mutations.

Study Limitations

This study had some limitations. First, the patients were enrolled in a tertiary referral center, therefore creating a selection bias regarding the severity of the disease. Specifically, 17 patients with LVOTO and 7 patients with ICD were included in this study, although LVOTO and ICD were not associated with any cardiac events on multivariate analysis. Also, 9 patients already had chronic AF at registration. Second, even though the number of each event was low, all the variables with P<0.1 were enrolled in each final model. This might have affected the accuracy of the findings. Third, the present subject group was extremely unique: *TNNI3* was the most frequent sarcomere gene mutation, and the group included 11 sarcomere gene mutation-positive patients without apparent HCM phenotype. The results might be influenced by these conditions, and their application to general practice should be done with caution. Fourth, cardiac magnetic resonance imaging with LGE was not performed for all patients. It might be necessary to validate the cardiac fibrosis on LGE and the correlation between LGE and frag-QRS. Fifth, fragmented premature ventricular complexes, which were recently reported to be associated with LV fibrosis in HCM patients,[38] were not evaluated. Also, indices derived from single-averaged ECG were not included in the regression models because single-averaged ECG was not performed for all patients. Sixth, the time relationship between HCM diagnosis and the occurrence of frag-QRS, or LVOTO and the occurrence of frag-QRS, were also not investigated in the present study.

Conclusions

Frag-QRS was significantly associated with HF with hospitalization in HCM patients who had a unique distribution of gene mutations. Furthermore, HF-free survival was significantly lower in the frag-QRS (+) group compared to the frag-QRS (–) group. These findings suggest that frag-QRS might be a non-invasive prognostic tool for predicting HF progression in HCM patients.

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Disclosures

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