Fragmented QRS as a candidate marker for high-risk assessment in hypertrophic cardiomyopathy

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BACKGROUND The relationship between a fragmented QRS complex (fQRS) on 12-lead ECG and fatal arrhythmic events in hypertrophic cardiomyopathy (HCM) remains unclear.

OBJECTIVE The purpose of this study was to investigate whether fQRS is associated with ventricular arrhythmic events (VAEs) in HCM patients.

METHODS Of an initial cohort of 273 patients (57% male, mean age 55 years) diagnosed with HCM, 167 patients were included and divided into 2 groups: those with fQRS (n = 67) and those without fQRS (n = 100). fQRS was defined as notching of the R or S wave in 2 contiguous leads. VAEs were defined as nonsustained or sustained ventricular tachycardia (VT) or sudden cardiac death (SCD). Major arrhythmic events (MAEs) were sustained VT or SCD.

RESULTS During mean follow-up of 6.3 years, univariate analysis showed that fQRS was significantly associated with increased VAEs (unadjusted hazard ratio [HR] 6.17, 95% confidence interval [CI] 2.46–15.49, $P < .001$) and MAEs (unadjusted HR 5.12, 95% CI 1.38–19.01, $P = .014$). Multivariate analysis revealed that fQRS was a strong independent predictor of VAEs (adjusted HR 6.28, 95% CI 2.49–15.84, $P < .001$) and MAEs (adjusted HR 6.04, 95% CI 1.49–24.39, $P = .011$). fQRS in the inferior leads was most closely related to MAEs compared to fQRS in other myocardial territories, and its inclusion in a risk calculator for mortality in HCM patients increased the positive predictive value from 8% to 25% in low-risk patients.

CONCLUSION Presence of an fQRS may be a good candidate marker for prediction of VAE in patients with HCM.

KEYWORDS Hypertrophic cardiomyopathy; Fragmented QRS; Ventricular arrhythmic events; Major arrhythmic events; Sudden cardiac death

ABBREVIATIONS **CI** = confidence interval; **fQRS** = fragmented QRS; **HCM** = hypertrophic cardiomyopathy; **HR** = hazard ratio; **ICD** = implantable cardioverter-defibrillator; **LV** = left ventricle; **MAE** = major arrhythmic event; **PPV** = positive predictive value; **SCA** = sudden cardiac arrest; **SCD** = sudden cardiac death; **VAE** = ventricular arrhythmic event; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

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Introduction

A fragmented QRS complex (fQRS), defined as unexpected deviations in the QRS complex on 12-lead ECG, has recently been identified as an independent prognostic marker for sudden death.[1,2] An fQRS reflects regional conduction delay due to disorganized myocardial tissue or scar, which, in turn, provides an anatomic substrate by which ventricular arrhythmias may be generated.[3–6] An fQRS has been shown to predict fatal arrhythmic events such as ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients with acute myocardial infarction, dilated cardiomyopathy, Brugada syndrome, and arrhythmogenic right ventricular dysplasia.[7–9] However, little is known about the association of an fQRS complex and occurrence of ventricular tachyarrhythmias in patients with hypertrophic cardiomyopathy (HCM).

Risk stratification of sudden cardiac death (SCD) in patients with HCM is paramount when selecting patients for implantable cardioverter-defibrillator (ICD) placement. Selection of HCM patients to receive an ICD is guided by conventional risk factors such as family history of SCD, unexplained syncope, left ventricular (LV) wall thickness >30 mm, hypotension during exercise, and nonsustained or sustained VT.[10] Almost 50% of HCM patients have 1 or more risk factors for SCD, yet the annual mortality rate of SCD in clinically identified HCM patients is only approximately 1%, demonstrating that use of conventional risk factors suffers from a low positive predictive value (PPV) when attempting to identify those HCM patients who will go on to experience SCD. Most patients with HCM who undergo screening are at relatively low risk, so the decision

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for primary prevention is made according to individual clinical situation.[11] Here, clinicians must weigh the benefits of preventing SCD against the risks of unnecessary ICD placement. We hypothesized that fQRS would provide an additional marker to predict arrhythmic events in patients with HCM. Accordingly, we examined patients with HCM and investigated the presence of fQRS (as a surrogate marker of regional conduction delay) to ventricular arrhythmic events (VAEs), defined as nonsustained or sustained VT, and SCD. We then investigated whether fQRS can also predict major arrhythmic events (MAEs), defined as sustained VT and SCD.

Methods

Study population

Between February 2001 and April 2007, the records of 273 patients diagnosed with HCM via echocardiography were reviewed. All patients underwent routine clinical examination, 2-dimensional echocardiography, and standard 12-lead ECG. HCM was diagnosed if there was unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of other cardiac or systemic disease capable of producing maximal LV wall thickness ≥ 15 mm.[2] Exclusion criteria included reduced LV function (ejection fraction $<50\%$, n = 11), QRS ≥ 120 ms, left or right bundle branch block (n = 87), previous ICD placement (n = 7), and age <18 years (n = 1). The remaining 167 patients who gave informed consent were enrolled in the study.

The study protocol adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System. Clinical information was obtained by electronic medical records search.

ECG analysis

Resting 12-lead ECGs, obtained at the time of HCM diagnosis, were recorded at a paper speed of 25 mm/s (filter range 0.15–100 Hz, AC filter, 60 Hz, 10 mm/mV) and stored using a Marquette MAC 5000 (GE Marquette Medical Systems, Milwaukee, WI) recording system.

Several morphologies of fQRS were observed (Figure 1).[5] fQRS was defined by the presence of an additional R wave (R′), notching in the nadir of the R or S wave, or the presence of >1 R′ (fragmentation), present in 2 contiguous leads that corresponded to a single myocardial territory.[1,3,12] Myocardial territories were defined as anteroseptal (V_1–V_3), anterior (V_4–V_6), lateral (I, aVL) or inferior (II, III, aVF) leads. The presence of early repolarization also was analyzed. Early repolarization pattern was defined as J-point elevation in at least 2 consecutive leads (≥ 0.1 mV in inferior or lateral leads, >0.2 mV in precordial leads) with upward concavity of the ST segment, or distinct notch or slur on the downstroke of the R wave in any of leads V_3 to V_6.[13,14] ST-segment depression/inversion was defined as ≥ 1mV descending or horizontal depression of the ST segment within 100 ms of the J point or concave portion of the ST segment.

ECGs were reviewed by 2 cardiologists and separately by 2 cardiac electrophysiologists, who were blinded to the final interpretation. The concordance of interindividual interpretation on fQRS was 98% between the cardiologists and the electrophysiologists. Ambiguous notching in QRS, time-to-

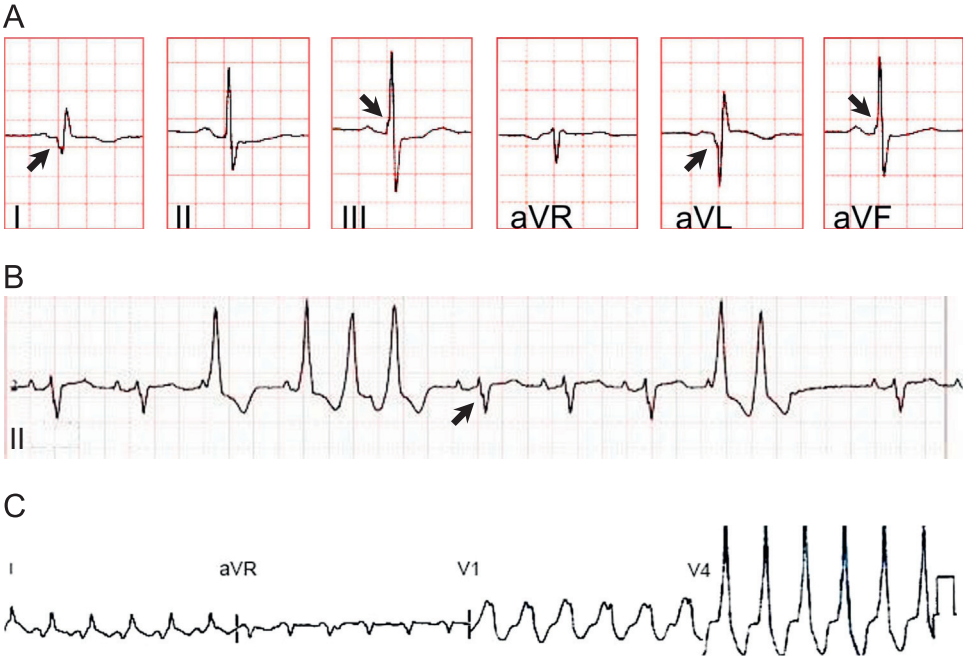

Figure 1 Representative ECG of fragmented QRS (fQRS). **A:** fQRS present on 12-lead ECG of a 47-year-old patient. **B:** Coexistence of fQRS and nonsustained ventricular tachycardia on ECG of a 71-year-old patient. **C:** Sustained ventricular tachycardia occurred 3 years after the diagnosis of hypertrophic cardiomyopathy. *Arrow* indicates fQRS.