

Distribution and Prognostic Significance of Fragmented QRS in Patients With Brugada Syndrome

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Background—Fragmented QRS complexes (fQRS) in the right precordial leads are associated with occurrence of ventricular fibrillation (VF) in Brugada syndrome. Recently, epicardial mapping has revealed abnormal electrograms at the right ventricular (RV) outflow tract and inferior region of the right ventricle. fQRS may reflect the extent of the area of abnormal potentials, but whether the distribution of fQRS has prognostic value is not known.

Methods and Results—We evaluated the existence of fQRS in 456 patients with Brugada syndrome, including 117 patients with syncope and 23 patients with VF. The region of fQRS was defined as inferior (II, III, and aVF), lateral (I, aVL, and V5 and V6), anterior (V3 and V4), RV (V1 and V2), and RV outflow tract (V1 and V2 at the third intercostal space). fQRS were present in 229 patients (RV outflow tract in 175, inferior in 135, RV in 90, and lateral in 16 patients). During follow-up (mean 91 months), 39 patients experienced VF. In univariable analyses, fQRS in any distribution and fQRS in each region excluding the RV were associated with VF. Multivariable analysis showed that fQRS in the inferior (hazard ratio, 3.9; confidence interval, 1.9–8.5), lateral (hazard ratio, 3.5; confidence interval, 1.2–8.2), and RV outflow tract (hazard ratio, 2.5; confidence interval, 1.2–5.6) were associated with VF events. The presence of multiple regions of fQRS was associated with worse prognosis.

Conclusions—The distribution of fQRS is associated with prognosis in Brugada syndrome, further supporting the association of fQRS and arrhythmia substrate. (*Circ Arrhythm Electrophysiol.* 2017;10:e004765. DOI: 10.1161/CIRCEP.116.004765.)

Key Words: arrhythmia ■ Brugada syndrome ■ ECG ■ fragmented QRS ■ sudden cardiac death
■ ventricular fibrillation

ST elevation in the right precordial leads, consistent with a repolarization abnormality in the right ventricle (RV), is the main ECG finding in patients with Brugada syndrome (BrS); however, evidence of conduction delay is also common. For example, patients with BrS frequently have a wide QRS interval¹ that is associated with cardiac events.^{2,3} PQ interval prolongation,^{4,5} complete right bundle branch block,^{6,7} changes of the electric axis,^{8,9} and fragmented QRS complexes (fQRS)^{10–12} have also been reported, and these are found to be associated with occurrence of polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).

fQRS is a marker of depolarization abnormality.¹³ fQRS is associated with a scarred area of the ventricle¹⁴ and is associated with cardiac events in patients with coronary artery disease¹⁵ and cardiomyopathy.¹⁶ fQRS indicates changes in the direction of ventricular activation by a scar tissue that can be a substrate for reentrant arrhythmias.¹³ The diagnostic and prognostic impact of fQRS in various heart diseases has been reported.¹³

fQRS also appears in patients with BrS. fQRS usually appears at the right precordial leads, especially at the high intercostal space (leads V1, V2 at the third intercostal space) felt to reflect findings in the myocardium of the RV outflow tract (RVOT).¹⁰ fQRS is frequently observed in high-risk patients^{12,17} and is associated with the occurrence of VF in symptomatic patients¹⁰ and in patients without previous VF episodes.¹¹ Based on the observation that an arrhythmogenic region exists at the RVOT myocardium in BrS,¹⁸ fQRS in BrS has been defined as multiple spikes within the QRS complexes in right precordial leads.^{10,11}

Recently, epicardial mapping has revealed the existence of abnormal delayed potentials in the epicardium of the RVOT, and elimination of these potentials by radiofrequency catheter ablation normalizes the ECG and prevents VF recurrence.^{18–20} The source of fragmentation within the QRS complex is thought to be epicardial conduction disturbance.^{10,18} Delayed potentials are usually localized to the epicardium of the anterior RV and RVOT,^{18,20} but they can

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WHAT IS KNOWN

- Fragmented QRS (fQRS) is known to be a marker of myocardial injury and conduction delay. fQRS in the right precordial leads represents electrophysiological abnormality of the right ventricular outflow tract (RVOT) and is associated with lethal arrhythmic events in patients with Brugada syndrome.
- Epicardial mapping and ablation have revealed that the existence of delayed potential on the epicardium of RVOT is a substrate of ECG change and ventricular arrhythmia in Brugada syndrome, and it is also recorded outside of RVOT region.

WHAT THE STUDY ADDS

- fQRS appeared in various ventricular region; the frequency of fQRS was highest at the RVOT, followed by the inferior region and RV, and appearance of fQRS in any ventricular region was associated with occurrence of lethal arrhythmic events in patients with and without symptoms.
- Appearance of fQRS in multiple regions was associated with easily induced ventricular fibrillation by programmed electric stimulation and a marker of early occurrence of lethal arrhythmic events.

also appear at the inferior wall of the ventricle.²¹ Although extension of the delayed potential region is associated with ECG abnormality in corresponding leads,^{13,14,22} and fQRS in the right precordial leads that represents RV/RVOT has been established,^{12,23} there has been no report showing the distribution of fQRS and clinical significance in patients with BrS. We, therefore, assessed the existence of fQRS beyond the RVOT leads and evaluated the prognostic value of extension of fQRS to these regions for predicting the occurrence of VT/VF.

Methods

Subjects of the Study

This study was approved by the Ethics Committee on Human Research and Epidemiology of Okayama University. Analysis of the *SCN5A* gene was performed in 179 patients in compliance with guidelines for human genome studies of the Ethics Committee of Okayama University. Analysis of *SCN5A* mutation was performed as we reported previously.²⁴

The subjects of this study are 467 patients with Brugada-type ECG who visited our hospital. We excluded 11 patients because of low quality of ECG recording (n=2) and lack of ECG recording of leads V1 and V2 at the third intercostal spaces (n=9), leaving 456 patients (mean age, 47±14 years). The diagnosis of BrS was made according to the criteria of expert consensus statements.^{25,26} The symptoms at the first visit to our hospital were VF/aborted cardiac arrest (n=23) and syncope (n=117), and the rest of the patients had mild symptoms (such as palpitation, chest discomfort, and chest pain; n=39) or no symptoms (n=277). These mild symptoms were not associated with ventricular tachyarrhythmias, and we consider these 316 patients to be asymptomatic from the standpoint of BrS. The subjects included 20 patients from 9 families, but the other patients were not related to each other. Echocardiography and chest roentgenography were performed in all patients, and no abnormalities were found.

ECG Recording and Definition of fQRS

Standard 12-lead ECGs (with a 0–150 Hz filter) and additional V1 through V3 leads at the third intercostal space were recorded simultaneously. ECGs acquired prior to initiation of drug therapy were used for analysis. We evaluated the digital ECG at 400% size on a PC monitor and measured each parameter and fragmentation of the QRS complex.

We defined abnormal fragmentation within the QRS complex as (1) ≥4 positive spikes in one of the leads V1 through V3 or (2) ≥8 positive spikes in all of leads V1, V2, and V3, according to a previous study. When patients had one of these criteria, we considered them positive for fQRS¹⁰ (fQRS 2008 criterion).

To evaluate the distribution of fQRS in BrS, we defined a new criterion based on the definition of fQRS for a wide QRS complex²² because right bundle branch block can appear in BrS: the QRS complex with >2 positive spikes within the QRS complex in 2 contiguous leads. The regions exhibiting fQRS were defined as (1) inferior (leads II, III, and aVF), lateral (leads I, aVL, and V5 and V6), anterior (leads V3 and V4), RV (leads V1 and V2), and RVOT (leads V1 and V2 located at the third intercostal space). ECGs were reviewed blindly by 3 cardiologists (Drs Morita, Watanabe, Nakagawa).

Evaluation of Late Potential and Inducibility of VF

The presence of late potential was evaluated by using a signal-averaged electrogram (ART 1200EPX or Nihon Koden ECG-2500 with QP-180D software, noise level <0.3 μV, high-pass filtering of 40 Hz using a bidirectional 4-pole Butterworth) in 437 patients. The filtered QRS duration, the root mean square voltage of the terminal 40 ms in the filtered QRS complex (RMS40), and the duration of low-amplitude signals <40 μV in the terminal-filtered QRS complex (LAS40) were measured using a signal-averaged electrogram. A late potential was considered to be present when 2 criteria were met (RMS40<20 μV and LAS40>38 ms).²⁷

Electrophysiological study was performed in 225 patients. Written informed consent was obtained before the study. Induction of ventricular arrhythmia was attempted without the use of antiarrhythmic drugs. We performed programmed electric stimulation (PES) from the RV apex, and RVOT was performed at 2 basic cycle lengths using ≤3 extra stimuli with a minimal coupling interval of 180 ms.

Statistics

Continuous data are expressed as mean±SD values. Fisher exact test or the χ^2 test was used for categorical variables. Comparison of 2 groups was made with Student's *t* test for unpaired data, as appropriate. Arrhythmic events were defined as occurrence of VT/VF or aborted cardiac arrest or sudden death. The mean events rate per year was evaluated by the number of events occurring during the follow-up period divided by the number of patients multiplied by the average duration of follow-up periods. Survival curves were plotted by the Kaplan–Meier method and analyzed by the long-rank test. Time from initial visit to the hospital to the first event was analyzed with Cox's proportional hazards model. Hazard ratios (HRs) and confidence intervals are presented for results of univariable analysis and only with significant *P* values in multivariable analysis. Multivariable analysis was performed with regions of fQRS and symptoms (syncope and VF). Significance was defined as *P*<0.05. All statistics were performed with the use of the JMP, version 12.2.0 (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data.

Results

Characteristics of Patients

Ninety-five percent of the patients were male (n=434), and 306 patients (67%) had a spontaneous type 1 ECG. Fourteen percent of the patients had a family history of sudden death (<45 years old). An *SCN5A* mutation was detected in 27 (15%) of

179 patients. Late potentials by a signal-averaged electrogram were present in 267 patients (63%). PES induced VT/VF in 105 (47%) of the 225 patients. During follow-up (89.5±62.1 months), 39 patients experienced arrhythmic events (asymptomatic patients, n=12 [3.8%]; patients with syncope, n=13 [11%]; patients with VF, n=14 [61%]). We implanted a cardioverter defibrillator in 93 patients (20%) because of the occurrence of VT/VF (n=24) or arrhythmic syncope (n=39) or because of the result of PES (n=30). We administered anti-arrhythmic drugs to prevent VF episodes in 20 patients with frequent VF attacks after the ECG recording for evaluation of fQRS (bepidil, 6 patients; disopyramide, 6 patients; quinidine, 7 patients; cilostazol, 1 patient).

Incidence and Distribution fQRS

fQRS defined by the 2008 criterion was present in 144 patients (32% of overall, 26% of asymptomatic patients, 39% of patients with syncope, and 70% of patients with VF; $P<0.0001$). Existence of fQRS in any ventricular region defined by the new criterion was observed in 229 patients (50% of overall patients, 46% of asymptomatic patients, 53% of patients with syncope, and 100% of patients with VF; Table). The frequency of fQRS was highest at the RVOT, followed by the inferior region and RV. The appearance of fQRS at lateral regions was rare (Figure 1A). Ninety-nine patients had fQRS only in a single region (RVOT, inferior, RV, anterior, and lateral: 59, 32, 8, 3, and 2 patients, respectively), whereas 131 patients had fQRS in

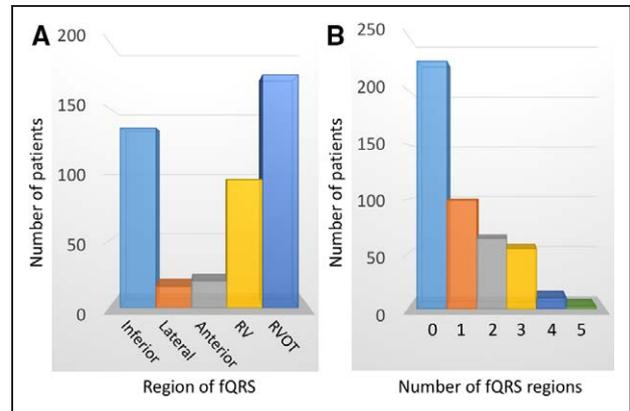


Figure 1. Distribution of fragmented QRS (fQRS). **A**, Distribution of fQRS in each region. Incidence of fQRS was highest at the right ventricular outflow tract (RVOT), followed by the inferior region and right ventricle (RV). Appearance of fQRS in the lateral region was rare. **B**, Number of regions with fQRS. Ninety-nine patients had fQRS in a single region, and 131 patients had fQRS in multiple regions (2–5 regions).

multiple regions (Figure 1B). A combination of the RVOT and inferior region or RV was frequently observed in patients with fQRS in multiple regions (Figure 2).

Characteristics of Patients With Newly Defined fQRS in Any Leads

The percentage of males was high in both the patients with and those without fQRS (Table). Patients with fQRS were more often symptomatic and frequently experienced arrhythmic events during follow-up, and cardioverter defibrillator implantation was, therefore, more frequent in patients with fQRS than in patients without fQRS. The existence of fQRS was associated with spontaneous type 1 ECG, late potential, and PES-induced VF. There was no relationship of family history of sudden death or *SCN5A* mutation with existence of fQRS. Appearance of fQRS can increase over time (Figure 2B through 2D). We performed catheter ablation on the epicardial surface of the anterior RV extending to the RVOT in a case with drug-refractory VF. Epicardial ablation eliminated Brugada-type ST elevation and also diminished QRS fragmentation (Figure 2E).

Results of PES and fQRS in Any Leads

VF was induced by PES in 105 (47%) of the 225 patients with 1 extrastimulus in 8 patients, 2 extrastimuli in 58 patients, and 3 extrastimuli in 39 patients. Univariable analysis showed that PES-induced VF was associated with VF events during follow-up (HR, 2.18; confidence interval, 1.09–4.60; $P=0.0283$). fQRS defined by the 2008 criterion was not associated with PES-induced VF, but newly defined fQRS in any leads was associated with PES-induced VF (Table). PES-induced VF was frequently observed in patients with inferior fQRS and was not associated with fQRS in the lateral, anterior, and RV regions. PES frequently induced VF in patients with fQRS in the RVOT leads, but it did not reach statistical significance. Although VF was induced by 2 or 3 extrastimuli, it was not induced by 1 extrastimulus in patients without fQRS in any leads. VF was induced by 1 or 2 extrastimuli in most

Table. Characteristics of Patients With and Without fQRS in Any Leads

	fQRS (–)	fQRS (+)	P Value
Number of patients	227	229	
Age, y	46±14	47±14	0.5178
Male	212 (93%)	222 (97%)	0.0768
Symptom			
Asymptomatic*	172 (76%)	144 (63%)	<0.0001
Syncope	55 (24%)	62 (27%)	
VF	0 (0%)	23 (10%)	
Family history of sudden death†	36 (15%)	28/226 (12%)	0.3418
<i>SCN5A</i> mutation	9/71 (13%)	18/108 (14%)	0.4655
Spontaneous type 1	138 (61%)	168 (73%)	0.0043
fQRS (2008 Criterion)	23 (10%)	121 (53%)	<0.0001
LP by SAECG	125/216 (58%)	150/221 (68%)	0.0387
PES induced VF	37/97 (38%)	68/128 (53%)	0.0257
Follow-up, mo	85.6±59.4	93.4±64.6	0.1813
VT/VF during follow-up	2 (1%)	37 (16%)	<0.0001
ICD implantation	25 (11%)	68 (30%)	<0.0001

fQRS indicates fragmented QRS; ICD, implantable cardioverter–defibrillator; PES, programmed electric stimulation; LP, late potential; SAECG, signal-averaged electrogram; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Asymptomatic included asymptomatic patients and patients with mild symptoms (chest pain, chest discomfort, and palpitation).

†Family history of sudden death include only victims of age <45 y.

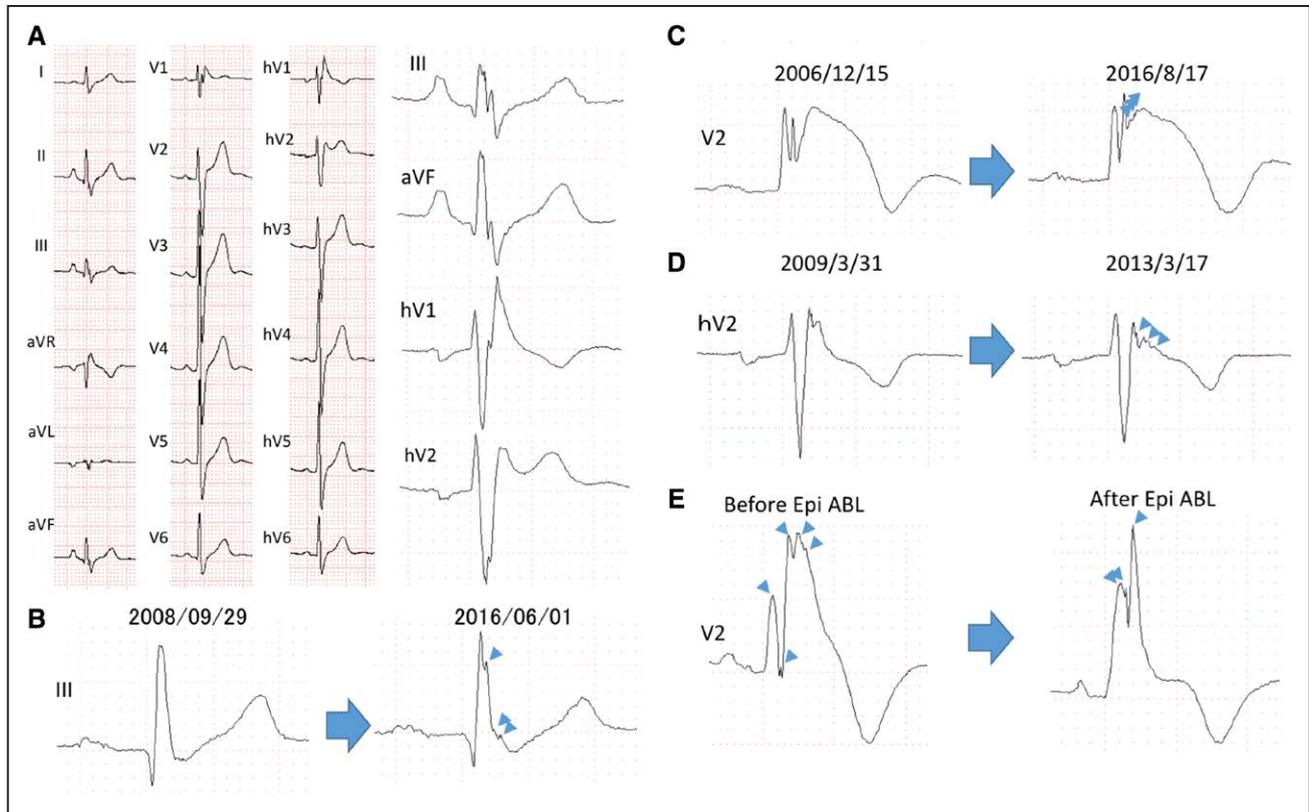


Figure 2. Fragmented QRS (fQRS) in the right ventricular outflow tract (RVOT) and inferior region. **A**, ECG recorded in a 61-year-old male who experienced syncope at night. Ventricular fibrillation (VF) was detected 57 months after ICD implantation. hV1–hV6 represents ECG lead positions 1 intercostal space higher than the regular lead positions (V1–V6). Multiple R waves existed in leads II, III, aVF, V1, hV1, and hV2, and fQRS were present in leads reflecting the inferior and RVOT regions. No fQRS was observed in lead V2, and fQRS in the right ventricle (RV) region was, thus, judged as being negative. **B–D**, Progressive increment of QRS fragmentation (**B**, fQRS in the inferior region; **C**, fQRS in the RV; **D**, fQRS in the RVOT). Arrowheads indicate new QRS spikes that appeared during follow-up. **E**, Effect of radio-frequency catheter ablation on the RV epicardial surface. Before ablation, 5 spikes (arrowheads) were observed within QRS complex in lead V2. Epicardial ablation decreased number of the spikes (3 spikes, arrowheads) and ST elevation.

of the patients with fQRS in any leads (Table in the [Data Supplement](#)).

Prognostic Significance of fQRS in Any Leads

Patients with fQRS defined by the 2008 criterion had a shorter time to arrhythmic events than did patients without fQRS (occurrence of events: 0.46%/year in patients without fQRS versus 2.77%/year in patients with fQRS; $P < 0.0001$; Figure 3A). Sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of fQRS for detecting patients having VT/VF were 70.2%, 72.9%, 22.9%, and 95.5%, respectively.

Using our new criteria, patients with fQRS in any leads also had a shorter time to arrhythmic events than did patients without fQRS (occurrence of events: 0.12%/year in patients with fQRS versus 2.33%/year in patients without fQRS; $P < 0.0001$; Figure 3B). The new criterion decreased specificity but improved sensitivity and NPV compared with the 2008 criterion: sensitivity, specificity, positive predictive value, and NPV of fQRS for predicting VT/VF were 95.7%, 55.0%, 19.7%, and 99.1%, respectively.

Patients with nonspontaneous type 1 ECG had a benign prognosis, regardless of the presence or absence of fQRS (Figure 4A). In patients with spontaneous type 1 ECG, fQRS in

any leads predicted arrhythmic events (Figure 4B). In asymptomatic patients and patients with syncope, patients with fQRS in any leads had a shorter time to arrhythmic events than did patients without fQRS (Figure 5A and 5B). All of the patients who experienced VF or aborted cardiac arrest at the initial visit to the hospital had fQRS in at least 1 region (Figure 5C).

Patients with fQRS in multiple regions (>1 region) had a shorter time to the occurrence of arrhythmic events than did patients with fQRS in a single region (Figure 6). Univariable analysis showed that the existence of fQRS by the 2008 criterion was associated with VF events (HR, 5.84; confidence interval, 2.99–12.24; $P < 0.0001$), and the existence of fQRS in any leads by the new criterion was associated with VF events (HR, 17.91; confidence interval, 5.48–110.14; $P < 0.0001$). Univariable analysis showed that fQRSs in inferior, lateral, anterior, and RVOT regions were risk factors for VF events (Figure 7A). Multivariable analysis adjusted by symptoms (syncope or VF) showed that fQRSs in inferior, lateral, and RVOT regions were significantly associated with VF events (Figure 7B).

Comparison of 2008 and New Criteria of fQRS

The new criterion increased the percentage of patients with positive fQRS (50%) compared with that for the 2008 criterion

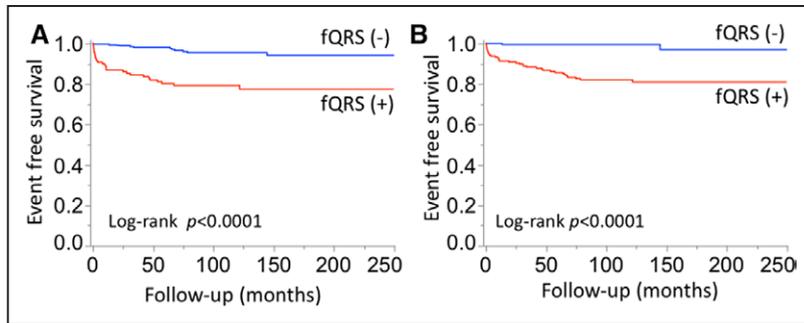


Figure 3. Event-free survival with existence of fragmented QRS (fQRS). **A**, Event-free survival according to existence of fQRS (2008 criterion). Patients with fQRS had a shorter time to arrhythmic events than did patients without fQRS (annual event ratio, 0.46%/y without fQRS vs 2.77%/y with fQRS). **B**, Event-free survival according to the existence of fQRS in any leads. Patients with fQRS in any leads had a shorter time to arrhythmic events than did patients without fQRS (annual event ratio, 0.12%/y without fQRS vs 2.33%/y with fQRS). Event rate was significantly lower in patients negative for fQRS.

(32%; Table). The use of the new criterion decreased specificity but increased sensitivity and NPV for detection of patients having VT/VF compared with fQRS of the 2008 criterion. fQRS by the 2008 criterion was not associated with PES-induced VF, but fQRS by the new criterion was associated with PES-induced VF, especially VF induced by less extrastimuli beats (Table in the [Data Supplement](#)). HR for predicting arrhythmic events was 5.84 by the 2008 criterion and was 17.91 by the new criterion. Among 312 patients who were negative for fQRS by the 2008 criterion, fQRS by the new criterion was positive in 108 patients. Occurrence of VT/VF events during follow-up was observed in 9 patients (8.3%) who were negative for fQRS by the 2008 criterion but were positive by the new criterion.

Discussion

New Observations

In BrS, fQRS appears in various ventricular regions, especially in the RVOT and inferior region. The existence of fQRS in any group of leads was associated with PES-induced VF and the occurrence of VT/VF events during follow-up. fQRSs in the RVOT, inferior, and lateral regions were significant risk factors for VF events after adjusting for symptoms. Patients who had fQRS in multiple regions had a shorter time to arrhythmic events than did patients with fQRS in a single region.

fQRS in Brugada Syndrome

fQRS was initially reported to be associated with myocardial scar and to improve accuracy of the diagnosis of old myocardial infarction.^{14,22} The significance of fQRS was then expanded to prediction of cardiac and arrhythmic events in

patients with ischemic heart disease and nonischemic cardiomyopathy.¹⁶ The existence of fQRS has been evaluated in various heart diseases, and it has been reported that fQRS is related to prognosis,^{13,28,29} especially to sudden cardiac death.^{30,31}

In patients with BrS, we initially reported that fQRS appeared in the right precordial leads and was associated with VT/VF events in symptomatic patients.¹⁰ A prospective study revealed that fQRS was a predictor of prognosis in patients without a previous history of cardiac arrest.¹¹ A paced fQRS³² and the combination of fQRS and early repolarization^{12,17} were also useful for identifying high-risk patients. The appearance of fQRS was evaluated in the right precordial leads in those studies.

It has been thought that ST elevation in the right precordial leads is closely associated with arrhythmogenesis in BrS³³ and that it indicates electrophysiological abnormality in the RVOT. Premature ventricular contractions, which can be a precursor of VT/VF events,³⁴ usually occur from the RVOT, but origin of premature ventricular contractions outside the RVOT region, such as the inferior right ventricle or left ventricle, is not rare.^{35,36} Epicardial delayed potentials are recorded at the RVOT, and radiofrequency catheter ablation to this area can eliminate ST elevation and prevent recurrent VT/VF.^{19,20} Epicardial delayed potential have also been recorded at the inferior epicardium and were associated with VT/VF.²¹ Epicardial conduction delay at the RVOT can be a source of fQRS in the right precordial leads,¹⁰ and delayed potentials in other ventricular regions can cause fQRS in corresponding leads. Indeed, epicardial ablation on the RV surface diminished QRS fragmentation in a patient with frequent VF episodes (Figure 2E). Moreover, appearance of fQRS

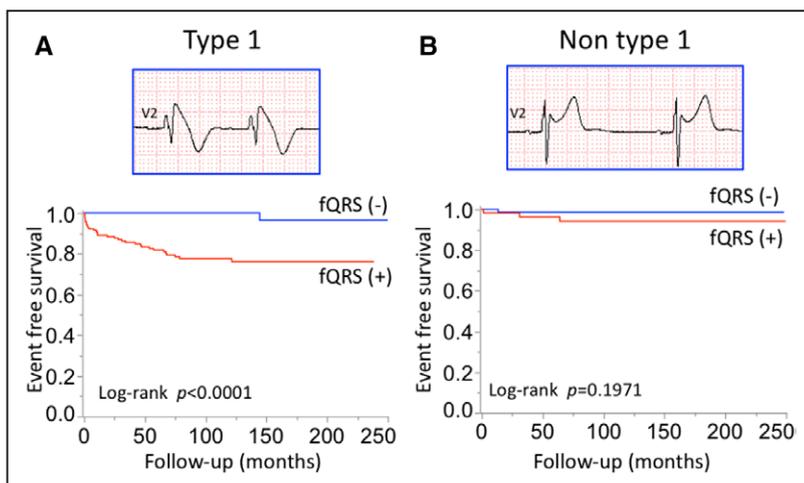


Figure 4. Prognostic significance of fragmented QRS (fQRS) in any leads in patients with different ECG types. **A**, Event-free survival in patients with spontaneous type 1 ECG. Existence of fQRS in any region increased the incidence of arrhythmic events (annual event ratio: 0.09%/y without fQRS vs 2.81%/y with fQRS). **B**, Event-free survival in patients with nonspontaneous type 1 ECG. Event rate was slightly higher in patients with fQRS than in patients without fQRS, but the difference did not reach statistical significance (annual event ratio: 0.16%/y without fQRS vs 0.52%/y with fQRS).

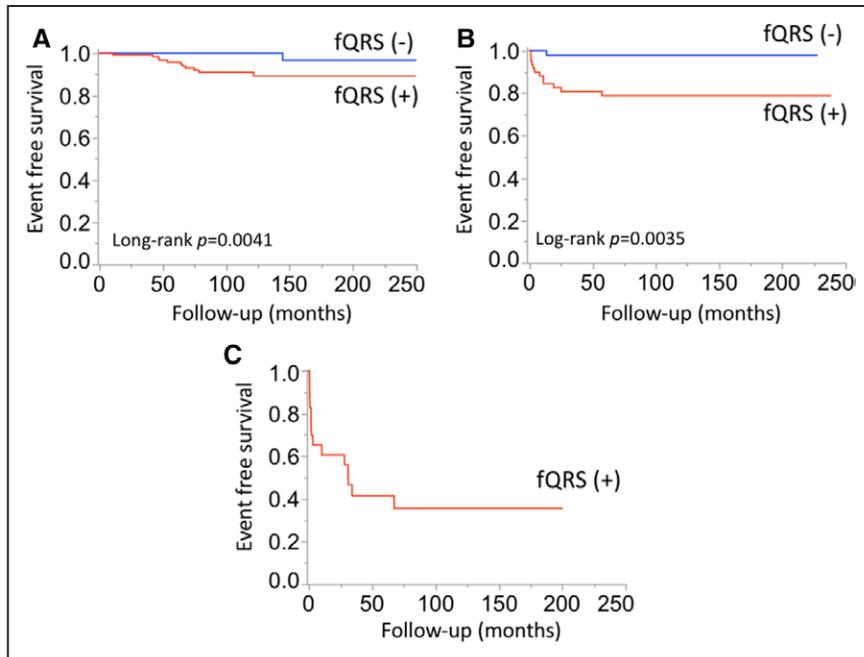


Figure 5. Event-free survival of patients with fragmented QRS (fQRS) in any region according to symptoms. Event-free survival of asymptomatic patients (A) and that of patients with syncope (B). Patients with fQRS had worse prognosis than did patients without fQRS. In asymptomatic patients, annual event ratios were 0.08%/y in patients without fQRS and 0.89%/y in patients with fQRS. Annual event rate in patients with syncope who did not have fQRS was 0.25%/y and that in patients with fQRS was 2.66%/y. C, Patients with ventricular fibrillation (VF). All patients who had a history of VF or aborted cardiac arrest at the first visit to the hospital had fQRS, and the event rate in these patients was 14.29%/y.

can be progressive (Figure 2B through 2D) and might indicate widening of the arrhythmic substrate over time. A case report also showed that progression of the electric substrate was associated with an electrical storm,³⁷ suggesting that increase in prominence of fQRS might indicate increased risk of arrhythmia.

In the present study, we evaluated the distribution of fQRS in patients with BrS. An inferior distribution of fQRS was not rare, and anterior and lateral distributions of fQRS were also observed in some cases. Although fQRS at the RVOT was dominant, fQRS outside the RVOT was also associated with arrhythmic events. fQRS in any region was a significant risk factor for VF events even after adjusting the symptoms, and fQRS in any group of leads, thus, is consistent with the existence of an arrhythmogenic substrate in BrS. The highest incidence of fQRS in the RVOT region is compatible with observations in previous studies of the existence of an abnormal electric substrate at the RVOT epicardium.^{18–20} Using the criterion of fQRS in any leads, sensitivity for detection of patients with VT/VF increased and specificity decreased from those in fQRS of the 2008 criterion. NPV was significantly improved using the criterion of fQRS in any leads. The occurrence of VT/VF in patients who did not have fQRS in any leads was remarkably rare. Although the existence of fQRS in any leads itself is not an indication for cardioverter defibrillator implantation, patients without fQRS in any leads are at low risk.

We observed fQRS in the lateral region in a small number of patients. fQRS in the lateral region represents left ventricular abnormality, but extension of the abnormal potential to the left ventricle has not been reported in patients with BrS. Mapping on the left ventricular epicardium may be required to eliminate VT/VF events in such a case.

Limitations

We evaluated fQRS by quadruple magnification of the digital ECG wave on a PC monitor with a low-pass filter of 150 Hz.

Evaluation of fQRS with no magnification would decrease the incidence of fQRS. Different filter settings would also likely influence the incidence of fQRS.

We did not evaluate fQRS in healthy control subjects. A previous study showed that fQRS in right precordial leads was rare in control subjects with right bundle branch block who did not have obvious heart disease.¹⁰ A study in which patients with a wide QRS complex were evaluated showed that a fragmented wide QRS was a sign of myocardial scar.²² The incidence of fQRS in any leads was lower in asymptomatic patients than in symptomatic patients, and the incidence of fQRS in any leads in healthy controls would, thus, be low.

The percentage of male patients was high in this study (95%) compared with the percentages in previous US and European studies ($\approx 80\%$).^{2,5,9,11,12} Previous Japanese studies also had a high percentage of male patients (93%–95%).^{3,27,38,39}

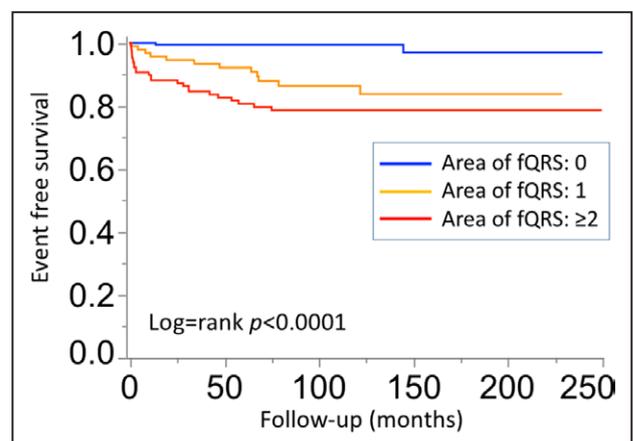


Figure 6. Extension of fragmented QRS (fQRS) and prognosis. Patients with fQRS in multiple regions had a worse prognosis than did patients with fQRS in a single region. Annual event rates in patients without fQRS, patients with fQRS in a single region, and patients with fQRS in multiple regions were 0.12%/y, 1.49%/y, and 2.55%/y, respectively.

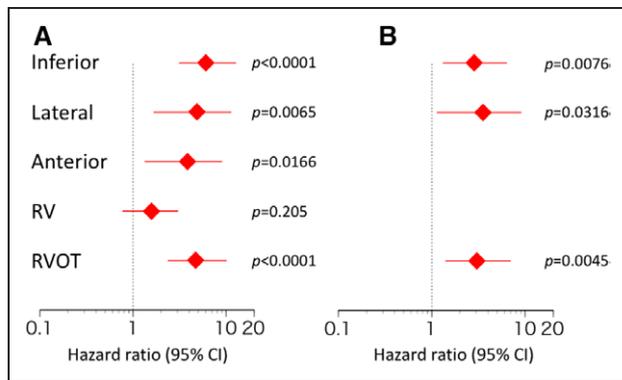


Figure 7. Univariable and multivariable analyses of fragmented QRS (fQRS) for predicting ventricular tachycardia (VT)/ventricular fibrillation (VF) events. **A**, Univariable analysis of fQRS in each region. fQRSs in inferior, lateral, anterior, and right ventricular outflow tract (RVOT) regions were associated with VF events. **B**, Multivariable analysis adjusted by symptoms. fQRSs in inferior, lateral, and RVOT regions were risk factors for VF events.

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Disclosures

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Distribution and Prognostic Significance of Fragmented QRS in Patients With Brugada Syndrome

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SUPPLEMENTAL MATERIAL

Supplementary Table fQRS and PES-induced VF

			PES-Induced VF+	<i>p</i> value
fQRS (2008 criterion)				
	fQRS +		45/84 (54%)	0.1091
	fQRS -		60/141 (43%)	
fQRS (new criaterion)				
	fQRS +		68/128 (53%)	0.0257
	fQRS -		37/97 (38%)	
Region of fQRS				
	Inferior	fQRS+	47/85 (55%)	0.0433
		fQRS-	58/140 (41%)	
	Lateral	fQRS+	4/9 (44%)	0.8915
		fQRS-	101/216 (47%)	
	Anterior	fQRS+	6/10 (60%)	0.3873
		fQRS-	99/215 (46%)	
	RV	fQRS+	37/58 (47%)	0.9838
		fQRS-	78/167 (47%)	
	RVOT	fQRS+	53/99 (54%)	0.0672
		fQRS-	52/126 (41%)	
Number of fQRS areas				
	fQRS area 0		37/97 (38%)	0.0722
	fQRS area 1		25/46 (54%)	
	fQRS areas 2-5		44/83 (53%)	
Number of extrastimuli those induced VF: 1/2/3				
	fQRS area 0	(pts)	0/15/22	0.0080
		(%)	(0/41/59)	
	fQRS area 1	(pts)	3/13/6	
		(%)	(14/59/27)	
	fQRS areas 2-5	(pts)	5/28/11	
		(%)	(11/64/25)	

fQRS: fragemented QRS, PES: programmed electrical stimulation