Fragmented QRS Complex in Adult Patients With Ebstein Anomaly and Its Association With Arrhythmic Risk and the Severity of the Anomaly

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Background—Fragmented QRS complex (fQRS) on 12-lead ECG, a marker of myocardial scar, is a predictor of arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. We investigated whether the presence of fQRS is associated with the severity of the anomaly and with increased arrhythmic events in adult patients with Ebstein anomaly (EA).

Methods and Results—In 51 consecutive adult patients with EA (median age, 37 years; 18 males), the severity index of EA calculated from echocardiographic data and clinical arrhythmic events were analyzed. The extent of fQRS in each patient was measured by counting the number of ECG leads showing fQRS. There were 35 (68.6%) patients with fQRS (fQRS group) and 16 (31.4%) patients without fQRS (non-fQRS group). fQRS was observed more frequently in the inferior (n=26) and precordial (n=25) leads versus the lateral leads (n=5). The patients in the fQRS group had a worse functional class, greater cardiothoracic ratios, more severe tricuspid regurgitation, larger atrialized right ventricular areas, higher EA severity scores, and more frequent arrhythmic events compared with those in the non-fQRS group. The atrialized right ventricular area showed a positive correlation with the fQRS extent (r=0.51; P<0.001). In multivariable Cox regression models, the presence of fQRS was independently associated with arrhythmic events (P=0.036).

Conclusions—Fragmented QRS on 12-lead ECG was associated with larger atrialized right ventricular area and an increased risk of arrhythmic events in adult patients with EA. **(*Circ Arrhythm Electrophysiol*. 2013;6:1148-1155.)**

Key Words: arrhythmias, cardiac ■ Ebstein anomaly ■ electrocardiography

Ebstein anomaly (EA) is a congenital malformation of the tricuspid valve (TV) and the right ventricle (RV). The most prominent morphological feature of EA is the varying degree of apical displacement of the TV into the RV, dividing the RV into a proximal chamber of atrialized RV (aRV) and distal portion of functional RV. This abnormality often causes tricuspid regurgitation (TR), progressive dilatation, and dysfunction of the right atrium (RA) and RV.[1] Therefore, the most common clinical presentations in adolescents and adults with this malformation are arrhythmic events and right-sided heart failure.[2–5] Moreover, these complications are expected to become more frequent with the improvement in long-term survival of patients.[5,6] However, there have been few studies investigating the risk factors for arrhythmic complications, especially in adults with EA.

Clinical Perspective on p 1155

Fragmented QRS complexes (fQRS) on 12-lead ECG, which represent conduction delay caused by myocardial scar, have been identified as a predictor of arrhythmic events in patients with ischemic or nonischemic heart disease[7,8] Recently, the fQRS found in adults with repaired tetralogy of Fallot was reported to represent more extensive RV scarring and dilatation.[9]

In this study, we evaluated whether the presence of fQRS reflects a greater risk of arrhythmic events and more severe abnormalities of the right-sided chambers in adult patients with EA.

Methods

Patient Population

Fifty-one adult patients (aged >18 years) diagnosed consecutively with EA at the Samsung Medical Center from November 1994 to April 2011 were enrolled for the present study. EA was diagnosed by echocardiography when the apical displacement of the septal leaflet of the TV relative to the insertion of the anterior leaflet of the mitral valve was measured at least 20 mm or 8 mm/m^2 body surface area. Patients with failed ablation of accessory pathways (APs), paced ventricular rhythms, and a previous cardiac surgery were excluded because these conditions could affect the QRS morphology. Demographic, electrocardiographic, and echocardiographic data were analyzed retrospectively. The study protocol was approved by

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our institutional review board, and the requirement for written informed consent was waived.

Definition of fQRS and Measurement of ECG Parameters

Standard 12-lead ECGs were obtained with an optimal low-pass filter setting (filter range, 0.15–100 Hz; alternating current filter, 60 Hz, 25 mm/s, 10 mm/mV; GE Marquette, Milwaukee, WI). To assess the correlation between fQRS and the severity of the structural abnormality in EA, we analyzed the index ECG recorded closest in time to the echocardiographic examination performed during the first visit to our institute. The time interval between electrocardiographic and echocardiographic study ranged from 0 to 105 days (median, 1 day). QRS complexes were defined to be fragmented when ≥1 additional R wave (R′) or notch on the R/S waves was present in narrow QRS complexes (<120 ms), or when >2 notches on the R/S waves were noted in wide QRS complexes (≥120 ms).[7–9] This fragmentation should be observed in ≥2 contiguous leads representing anterior (V1–V5), inferior (II, III, aVF), or lateral (I, aVL, V6) myocardial segments (Figure 1). The extent of the fQRS in each patient was estimated by counting the number of ECG leads showing fQRS.[9] In the presence of delta waves in the QRS complex, ECGs obtained after AP ablation were used because pre-excitation of the ventricle through the AP could alter the QRS morphology, mimicking fQRS. All ECG tracings were analyzed by 2 independent cardiologists who were blinded to clinical outcome data. There was a 97% and 95% intra- and interobserver agreement for the presence of fQRS, respectively. Electrocardiographic parameters such as PR/QRS/corrected QT/corrected JT intervals and QRS/QT/JT dispersion were also measured manually.

Echocardiographic Parameters and Severity Grading of EA

Comprehensive transthoracic echocardiography was performed using 2.5 to 4 MHz transducers (Vivid 7, GE Medical System, Milwaukee, WI or Acuson 512, Siemens Medical Solution, Mountain View, CA). Maximal apical displacement of the TV was measured from the hinge point of TV septal leaflet to the insertion point of the mitral valve anterior leaflet. The severity index of EA was estimated using the Great Ormond Street Score, an echocardiographic method described previously.[10] The Great Ormond Street Score was calculated as the ratio of the combined area of the RA and aRV divided by the combined area of the RV proper, left atrium, and left ventricle in a 4-chamber view at the end of diastole (Figure 2). Four grades of increasing severity were defined: grade 1, ratio <0.5; grade 2, 0.5 to 0.99; grade 3, 1 to 1.49; and grade 4, ≥1.5. The degree of TR was determined by a semiquantitative measurement depending on vena contracta width, proximal isovelocity surface area, hepatic vein flow reversal, RV or RA enlargement, and the plethora of the inferior vena cava.[11] The left ventricular ejection fraction was calculated using Simpson's biplane method.

Clinical Outcomes

Clinical arrhythmias were defined as spontaneous episodes associated with palpitation, dizziness, or syncope with ECG documentation. Occurrence of clinical arrhythmias has been investigated since the index ECGs were taken. The index ECGs were obtained during the first visit as mentioned above. Regular clinical and electrocardiographic follow-up (3- to 6-month interval) was performed in all patients. If a patient reported symptoms suggesting arrhythmia at any time, ECG and 24-hour Holter monitoring were repeated. Ventricular tachyarrhythmia included ventricular fibrillation, ventricular tachycardia, appropriate implantable cardioverter-defibrillator shock, and nonsustained ventricular tachycardia (≥3 consecutive ventricular beats at a rate of ≥100 beats/min with a duration of <30 s). Atrial tachyarrhythmia included atrial tachycardia, atrial fibrillation, atrial flutter, and atrioventricular re-entrant tachycardia (AVRT) using AP. For the present study, tachycardia episodes caused by AVRT using AP were not included when analyzing the relationship between fQRS and arrhythmic events. Because fQRS is a marker of myocardial fibrosis, we focused on specific relationships between fQRS and arrhythmias more directly related to myocardial dysplasia/degeneration. Therefore, the AVRT with a bypass tract was analyzed separately. Open heart surgery and cardiac death were also investigated.

Statistical Analysis

Continuous variables were expressed as medians (25th–75th percentiles) and were compared using the Mann–Whitney test. The results for categorical variables were described as percentages, and the Fisher

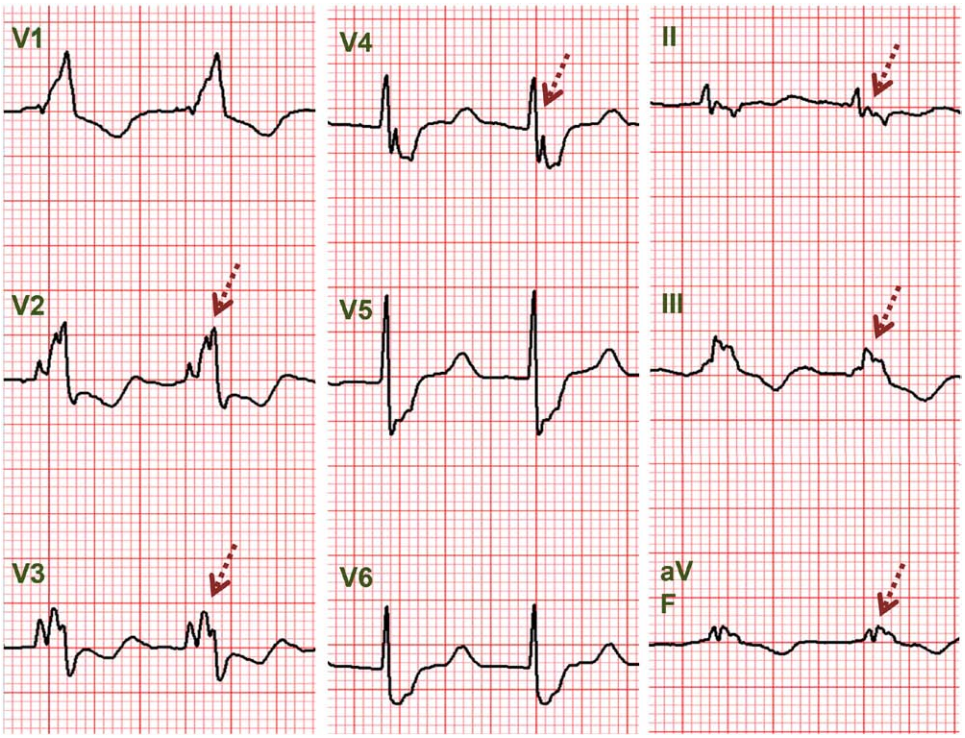

Figure 1. Fragmented QRS complexes observed in adult patients with Ebstein anomaly. Dashed arrows indicate fragmentation of QRS complexes in precordial and inferior leads.

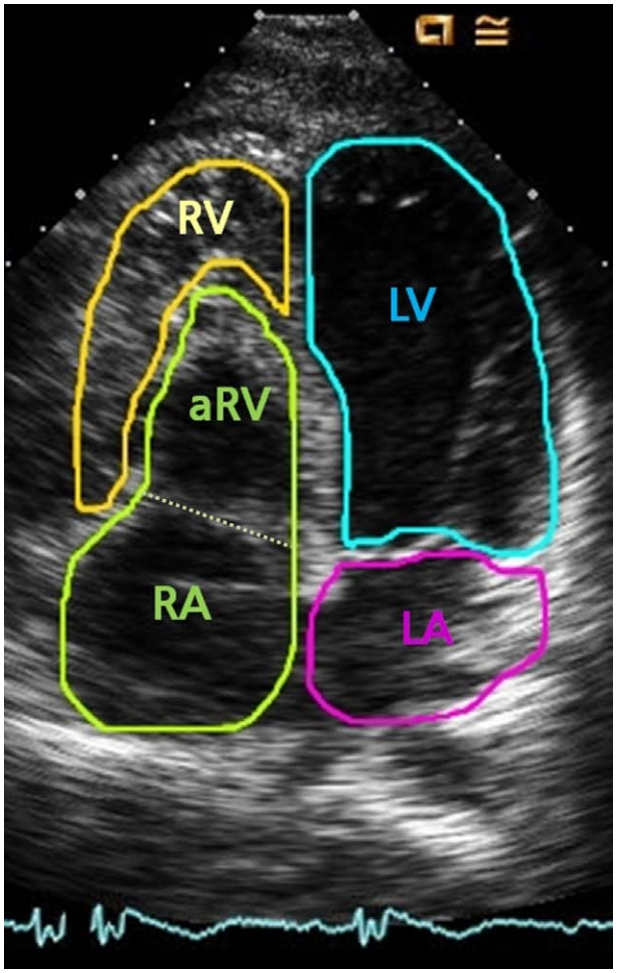

Figure 2. Measurement of the severity of Ebstein anomaly. Planimetry was performed in the apical 4-chamber view at end diastole. In this case, the ratio of the combined area of the right atrium (RA) and atrialized right ventricle (aRV) divided by the combined area of the functional RV proper, left atrium (LA), and left ventricle (LV) was 0.82, which falls under severity grade 2.

exact test was performed to compare these results. Correlations between QRS duration or fragmentation and the severity of disease were assessed by the Spearman rank correlation coefficient. Crude survival in each group was assessed using the Kaplan–Meier method, and the log-rank test was applied. Hazard ratios with 95% confidence intervals were computed using Cox regression models after the proportional hazards assumption was tested based on correlations between survival rankings and Schoenfeld residuals. The overall C-index was calculated using Cox survival methods to evaluate the discriminatory accuracy of several electrocardiographic variables (see Table in the online-only Data Supplement) for the occurrence of arrhythmic events.[12] All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC). All *P* values were 2 sided, and results with a *P* value <0.05 were considered statistically significant.

Results

Patient Demographics

Baseline characteristics of the 51 patients are summarized in Table 1. Median (25th–75th percentiles) age was 37 (31–45) years, and the median (25th–75th percentiles) cardiothoracic ratio was 0.55 (0.50–0.62). About half of the patients (27/51; 52.9%) were in New York Heart Association functional class III and IV. Atrial septal defects were the most common associated cardiac defect (n=19; 37.3%). In most of the patients (48/51; 94.1%), the right-sided chamber was much larger than the left, with a combined RA and RV area of 53 (43–75) cm^2 compared with a combined left atrial and left ventricular area of 37 (32–44) cm^2 (*P*<0.001). The median (25th–75th percentiles) value of the EA severity index was 0.79 (0.63–0.94).

Comparison Between the fQRS and Non-fQRS Groups

Approximately two thirds of the patients (35/51; 68.6%) showed fQRS in ≥2 contiguous leads (fQRS group). fQRS occurred primarily in the inferior (26 patients) and precordial (25 patients) leads. fQRS in the lateral leads was observed in only 5 patients. The detailed distribution of fQRS complexes is presented in Figure 3.

The fQRS group had a worse functional class, a greater cardiothoracic ratio, a longer PR interval, a longer QRS duration, more frequent right bundle branch blocks, and more frequent right axis deviations compared with the non-fQRS group (Table 1 and 2). On echocardiographic examination, apical displacement and regurgitation of the TV were more severe in patients with fQRS versus those without (Table 2). Functional RV, left ventricular, and left atrial areas indexed to body surface area showed no significant differences between the 2 groups. However, aRV and RA enlargements were more prominent in the fQRS group; therefore, the fQRS group showed a greater severity index compared with the non-fQRS group (*P*<0.001). The indexed aRV area (Spearman *r*=0.51; *P*<0.001), indexed RA areas (Spearman *r*=0.60; *P*<0.001), and Ebstein severity index (Spearman *r*=0.58; *P*<0.001) were positively correlated with the extent of the fQRS (see Figure I in the online-only Data Supplement).

Associations Between fQRS Complexes and Arrhythmic Complications

Table 3 summarizes clinical outcomes. Median follow-up duration (25th–75th percentiles) was 49 (25–116) months with no significant difference between the fQRS and non-fQRS groups (49 [29–112] versus 51 [1–126] months, *P*=0.699). Compared with the non-fQRS group, a greater proportion of patients in the fQRS group underwent TV replacement/repair or a Fontan operation because of severe TR and right heart failure. The incidence of AVRT with AP was not significantly different between the 2 groups (fQRS versus non-fQRS group, 5/35 versus 4/16; *P*=0.436). However, ventricular tachyarrhythmia (9/35; 25.7%), unexplained syncope (4/35; 11.4%), and cardiac death attributable to right heart failure (1/35; 2.9%) were only found in patients with fQRS. Sustained ventricular tachycardia, appropriate shock for ventricular fibrillation, and nonsustained ventricular tachycardia episodes occurred in 5, 1, and 3 patients with fQRS, respectively. The atrial tachyarrhythmic event (atrial fibrillation, atrial flutter, and atrial tachycardia) rate was also higher in the fQRS group (48.6% versus 18.8%; *P*=0.064). In addition, permanent pacemaker implantation was performed only in patients with fQRS because of complete (n=2) or advanced (n=1) AV block. Overall, total arrhythmic events occurred more frequently in the fQRS group compared with the non-fQRS group during the follow-up

Table 1. Comparison of Clinical Characteristics Between the fQRS Group and the Non-fQRS Group

	Total (N=51)	fQRS (+) (n=35)	fQRS (–) (n=16)	*P* Value*
Demographics				
Age,† y	37 (31–45)	36 (31–45)	41 (27–45)	0.604
Male sex, n (%)	18 (35.3)	11 (31.4)	7 (43.8)	0.529
Diabetes mellitus, n (%)	2 (3.9)	2 (5.7)	0 (0.0)	1.000
Hypertension, n (%)	6 (11.8)	6 (17.1)	0 (0.0)	0.159
NYHA class III–IV, n (%)	27 (52.9)	23 (65.7)	4 (25.0)	0.014
CT ratio†	0.55 (0.50–0.62)	0.58 (0.53–0.66)	0.49 (0.45–0.52)	<0.001
CT ratio ≥0.65, n (%)	8 (15.7)	8 (22.9)	0 (0.0)	0.045
Associated anomaly				
Atrial septal defect, n (%)	19 (37.3)	16 (44.4)	3 (20.0)	0.123
Patent foramen ovale, n (%)	5 (9.8)	5 (13.9)	0 (0.0)	0.305
Mitral valve prolapse, n (%)	1 (2.0)	0 (0.0)	1 (6.7)	0.294
Ventricular septal defect, n (%)	1 (2.0)	1 (2.8)	0 (0.0)	1.000

CT ratio indicates cardiothoracic ratio; fQRS, fragmented QRS complex; and NYHA, New York Heart Association.
*The *P* value is based on the Mann–Whitney test for continuous variables and the Fisher exact test for categorical variables.
†Data are represented as the median (25th–75th percentiles).

(Figure 4). The presence of fQRS in Cox regression analysis was independently associated with total arrhythmic events, even after adjusting for relevant clinical, radiographic, echocardiographic, and electrocardiographic parameters (Table 4).

Discussion

New Findings

The present study is the first to reveal a significant relationship between the presence of fQRS and an increased risk of ventricular or atrial arrhythmic events. We also found fQRS to be associated with poorer functional class, more severe TR, a larger right-sided chamber, and greater severity of EA in adult patients with this cardiac defect.

Recently published data suggests that the fQRS detected in patients with EA reflects the presence of RV dysfunction with greater aRV volume.[13] However, arrhythmic risk was not evaluated in that study. In addition, adult patients (aged >18 years) accounted for only 60% of their study population. Although there have been some studies dealing with arrhythmic complications in adult patient groups, they only described the prevalence of a few types of arrhythmias in a limited number of patients.[2–5] Most of the previous data focused primarily on the characteristics or management of AVRT with a bypass tract.[14–16]

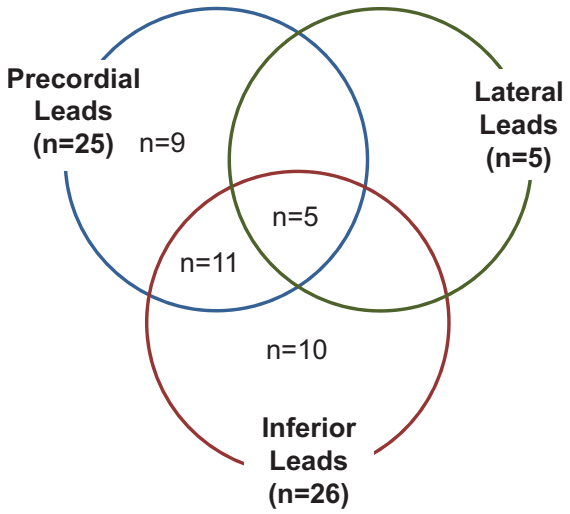

Figure 3. Detailed distribution of fragmented QRS (fQRS) complexes. fQRS complexes occurred primarily in inferior and precordial leads.

In contrast, we evaluated the association between fQRS and arrhythmic risk as well as the severity of the structural abnormality. Moreover, we tried to identify predictors for arrhythmic events more directly associated with dysplasia/degenerative changes in the atrial/ventricular myocardium; these arrhythmic complications will pose greater challenges to clinicians than AVRT using bypass tracts especially in adult patients with EA because of recent advances in their long-term survival and in ablation technology. Our data show that ≈50% of adult patients with EA experienced arrhythmic complications, which is consistent with previous studies.[2,4,5,16] In addition, we found the presence of fQRS to be independently associated with overall arrhythmic events, even after adjusting for relevant clinical and echocardiographic parameters.

fQRS Complexes and Risk of Ventricular Tachyarrhythmias

Fragmentation of QRS morphology on surface ECG reflects inhomogeneous ventricular activation caused by myocardial scar in patients with a prior myocardial infarction.[7,17] Because the myocardium is replaced by scar tissue after an infarction, myocardial conduction slows or becomes blocked around the infarcted zone, resulting in a zigzag course of activation.[18] fQRS was also associated with an increased risk of arrhythmic events in patients with nonischemic dilated cardiomyopathy.[8]

Several histopathologic studies on EA demonstrated that the atrialized portion of the RV becomes disproportionately

Table 2. Comparison of Electrocardiographic and Echocardiographic Variables

Variable	Total (N=51)	fQRS (+) (n=35)	fQRS (–) (n=16)	*P* Value*
Electrocardiographic variables				
PR interval,† ms	176 (162–193)	182 (163–200)	166 (138–182)	0.030
RBBB, n (%)	15 (29.4)	15 (42.9)	0 (0.0)	0.002
Right axis deviation, n (%)	26 (51.0)	23 (65.7)	3 (18.8)	0.003
QRS duration,† ms	119 (107–148)	135 (118–156)	99 (94–112)	<0.001
Corrected QT,† ms	441 (416–486)	472 (428–498)	414 (406–444)	0.003
Corrected JT,† ms	314 (297–330)	311 (285–330)	299 (282–326)	0.422
QRS dispersion,† ms	26 (20–40)	40 (22–40)	20 (15–36)	0.006
QT dispersion,† ms	40 (28–80)	55 (40–80)	35 (20–74)	0.106
JT dispersion,† ms	60 (28–80)	60 (46–100)	33 (20–60)	0.011
QRS pre-excitation, n (%)	9 (17.6)	5 (14.3)	4 (25.0)	0.436
Echocardiographic variables				
RA area,†‡ cm^2/m^2	14.5 (10.9–21.5)	17.1 (12.3–24.3)	11.6 (8.7–14.1)	0.004
Atrialized RV area,†‡ cm^2/m^2	9.04 (7.4–13.1)	9.7 (8.0–14.5)	7.4 (6.1–9.3)	0.013
Functional RV area,†‡ cm^2/m^2	8.2 (6.3–12.8)	9.1 (6.2–13.8)	6.9 (6.3–10.2)	0.204
LV area,†‡ cm^2/m^2	15.0 (12.3–18.6)	14.8 (12.1–17.6)	17.7 (12.4–19.2)	0.369
LA area,†‡ cm^2/m^2	7.5 (6.1–9.2)	7.4 (6.1–9.5)	7.6 (6.3–8.8)	0.958
LV ejection fraction,† %	60 (54–65)	59 (54–66)	60 (53–64)	0.911
TV displacement,† mm/m^2	1.9 (1.3–2.6)	1.9 (1.4–2.8)	1.5 (1.1–2.1)	0.072
Severe TR, n (%)	25 (49.0)	22 (62.9)	3 (18.8)	0.006
Ebstein severity index†	0.79 (0.63–0.94)	0.87 (0.67–1.07)	0.63 (0.44–0.74)	0.001
Ebstein severity grade, n (%)				0.030
1	5 (12.5)	1 (3.6)	4 (33.3)	
2	28 (70.0)	20 (71.4)	8 (66.7)	
3	4 (10.0)	4 (14.3)	0 (0.0)	
4	3 (7.5)	3 (10.7)	0 (0.0)	

fQRS indicates fragmented QRS complex; LA, left atrium; LV, left ventricle; RA, right atrium; RBBB, right bundle branch block; RV, right ventricle; TR, tricuspid regurgitation; and TV, tricuspid valve.

*The *P* value is based on the Mann–Whitney test for continuous variables and the Fisher exact test for categorical variables.

†Data represented as the median (25th–75th percentiles).

‡Each value is indexed to body surface area.

dilated and has extensive fibrosis with reduced numbers of myocytes.[19,20] In addition, the abnormal signal observed during endocardial mapping of the aRV was related to the bizarre configuration of the widened QRS complexes on surface ECG.[21,22] They also showed that the aRV was particularly irritable and, therefore, could serve as a substrate for ventricular fibrillation.[21,23] Indeed, in our study, patients in the fQRS group had significantly larger aRV area and more frequent ventricular arrhythmic complications compared with the non-fQRS group. Moreover, the extent

Table 3. Comparison of Clinical Outcomes

	Total (N=51)	fQRS (+) (n =35)	fQRS (–) (n =16)	*P* Value*
Total arrhythmic events, n (%)	26 (51.0)	23 (65.7)	3 (18.8)	0.003
Bradyarrhythmia requiring PPM, n (%)	3 (5.9)	3 (8.6)	0 (0.0)	0.227
Tachyarrhythmia, n (%)	26 (51.0)	23 (65.7)	3 (18.8)	0.003
Atrial tachyarrhythmia, n (%)	20 (39.2)	17 (48.6)	3 (18.8)	0.064
Ventricular tachyarrhythmia, n (%)	9 (17.6)	9 (25.7)	0 (0.0)	0.043
Unexplained syncope, n (%)	4 (7.8)	4 (11.4)	0 (0.0)	0.295
Tricuspid valve repair/replacement, n (%)	27 (52.9)	22 (62.9)	5 (31.3)	0.036
Fontan operation, n (%)	1 (2.0)	1 (2.9)	0 (0.0)	1.000
Cardiac death, n (%)	1 (2.0)	1 (2.9)	0 (0.0)	1.000

fQRS indicates fragmented QRS complex; and PPM, permanent pacemaker.

*The *P* value is based on the Fisher exact test.

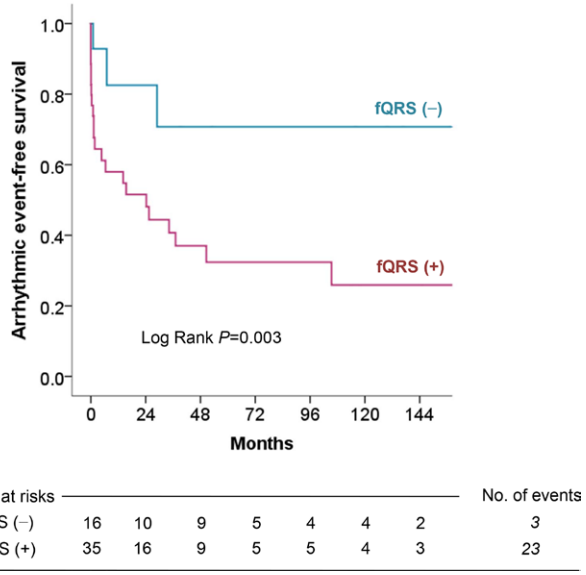

Figure 4. Arrhythmic event-free survival curves depending on the presence of fragmented QRS complexes (fQRS).

of fQRS complexes was positively correlated with the aRV area (Spearman r=0.51; P<0.001). Therefore, fQRS in adults with EA might signify a higher burden of arrhythmogenic substrate. We previously reported that in adults with repaired tetralogy of Fallot, myocardial fibrosis was predominant in the RV outflow tract, and that fQRS was found at least twice as frequently in the right to mid precordial leads than in the inferior lead showing a good spatial concordance between the fQRS and RV scarring.[9] In the present study, however, the most common locations of fQRS were the inferior and precordial leads, and fQRS were negligible in the lateral leads. In EA, the aRV, or the inlet component, is the main site of congenital dysplasia and subsequent degeneration. With further enlargement, the aRV could occupy a greater proportion of the inferior wall of the heart, making fQRS complexes in the inferior leads as frequent as that in precordial leads. Repolarization parameters such as QTc and QRS/QT dispersions were measured worse in the fQRS group compared with the non-fQRS group. Repolarization parameters therefore might also be associated with an increased susceptibility to ventricular arrhythmia.

fQRS Complexes and Risk of Atrial Tachyarrhythmias

The degree of apical displacement, regurgitation of the TV, and RA enlargement were more severe in the fQRS group than the non-fQRS group. The indexed RA areas were positively correlated with the extent of the fQRS. These abnormalities could make patients with fQRS more vulnerable to atrial tachyarrhythmias related to degenerative changes in the atria, such as atrial fibrillation, atrial flutter, and atrial tachycardia. As mentioned above, atrial tachyarrhythmias including atrial fibrillation, atrial flutter, and atrial tachycardia tended to occur more frequently in the fQRS group than in the non-fQRS group (48.6% versus 18.8%; P=0.064).

fQRS Complexes and Risk of Bradyarrhythmias

The AV conduction system in EA, especially the right bundle branch traveling over the dysplastic aRV portion, is abnormally formed and shows marked fibrosis. The AV node is also compressed because of enlargement of the right-sided chambers.[1,24,25] In addition, chronic hemodynamic stress in adult patients with EA can aggravate right-sided chamber dilatation, dysfunction, and fibrosis.[1,2] All of these factors could predispose the development of bradyarrhythmia. The longer PR intervals and more frequent right bundle branch block observed in the fQRS group might suggest more fibrosis within the right-sided chambers and in the right bundle branch and more adverse hemodynamic impact on these structures. Although not statistically significant, first-degree AV block (24% versus 13%; P=0.464) was more prevalent in the fQRS group, and permanent pacemakers were implanted only in patients showing fQRS because of advanced or complete AV block.

Clinical Implications

In our study, lower functional class at the time of presentation, a greater cardiothoracic ratio, more advanced grade

Table 4. Predictors for Arrhythmic Events in Univariate and Multivariable Cox Regression Analyses

	Univariate Analysis		Multivariable Analysis Model 1		Multivariable Analysis Model 2*	
Characteristics	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
NYHA class III–IV	1.72 (0.76–3.90)	0.194	1.53 (0.54–4.34)	0.421	…	…
CT ratio ≥0.65	2.13 (0.85–5.34)	0.108	1.04 (0.35–3.10)	0.951	…	…
LV ejection fraction	1.01 (0.96–1.05)	0.876	1.01 (0.95–1.07)	0.815	…	…
Severe tricuspid regurgitation	1.48 (0.67–3.25)	0.335	1.46 (0.56–3.82)	0.446	…	…
Atrialized RV area index	1.05 (0.97–1.14)	0.200	1.02 (0.92–1.13)	0.751	…	…
Ebstein anomaly severity index	1.45 (0.41–5.07)	0.565	0.25 (0.03–1.84)	0.809	…	…
QRS duration	1.01 (1.01–1.03)	0.015	1.00 (0.98–1.02)	0.844	1.01 (0.99–1.02)	0.444
Corrected QT interval	1.01 (0.99–1.01)	0.254	1.01 (0.99–1.02)	0.527	…	…
fQRS	5.05 (1.50–16.9)	0.009	5.91 (1.07–32.6)	0.041	4.13 (1.09–15.6)	0.036

CI indicates confidence interval; CT, cardiothoracic ratio; fQRS, fragmented QRS complex; HR, hazard ratio; LV, left ventricle; NYHA, New York Heart Association; and RV, right ventricle.

*Multivariable analysis model 2 incorporated parameters attaining a *P* value<0.05 in univariate analysis.

of EA, and a higher rate of corrective surgery were found in the fQRS group, which had a larger average aRV area. These results are in agreement with previous studies that showed aRV volume to be independently related to aerobic capacity and that the volume of the aRV is a novel cardiac magnetic resonance measure which may describe the severity of disease in adults with unrepaired EA.[13,26] On the other hand, QRS duration is considered a good surrogate marker for severity of disease. The wider the QRS complex and the greater the degree of TR and RV enlargement, the worse the clinical course.[13,27] Our data also showed that QRS duration was as good as QRS fragmentation in predicting RV structural remodeling (see Figure II in the online-only Data Supplement) and arrhythmic risks (see Figure III in the online-only Data Supplement).

Therefore, further investigation might be worthwhile to ascertain whether fQRS, independently or in combination with QRS duration, could be a potential marker of worsening right-sided heart dysplasia/dysfunction (see Figure IV and Table in the online-only Data Supplement). Also, it would be useful to further investigate the association between fQRS and increased vulnerability to atrial and ventricular tachyarrhythmia as well as bradyarrhythmia in larger adult cohorts with this anomaly.

Study Limitations

This study has several limitations. First, comparisons from this analysis are limited by their retrospective design, in which unmeasured confounders may preclude any definite conclusion. Therefore, prospective studies on a larger scale are needed to validate our findings and to show the clinical implications of fQRS complexes more definitely. Second, although our cohort is one of the largest adult-only groups, the study population was relatively small and the follow-up duration was short. Third, the extent of the cardiac fibrosis and the volumetric measurements were not confirmed by biopsy or cardiac magnetic resonance imaging. However, we adopted a grading system to quantify the severity of EA, and our data correspond well to those acquired from cardiac magnetic resonance examination.[13]

Conclusions

fQRS on 12-lead ECG were found in approximately two thirds of adult patients with EA. fQRS complexes were associated with larger aRV, a more severe anomaly, and an increased risk of arrhythmic events in this patient group.

Disclosures

None.

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CLINICAL PERSPECTIVE

Arrhythmias are the most common complications seen in adult patients with Ebstein anomaly, a congenital malformation of the tricuspid valve and the right ventricle. The present retrospective study is the first to show that fragmented QRS complexes on 12-lead ECG, which reflect the presence of myocardial scar and risk of arrhythmic events in patients with ischemic or nonischemic cardiomyopathy, were associated with severity of Ebstein anomaly and increased risk of ventricular or atrial arrhythmic events in this patient group. Evaluating the fragmented QRS complexes is inexpensive and easy to repeat for serial follow-up of the patients. It might be reasonable to pay more attention to those who show new-onset fragmented QRS complexes or an increase in its extent during the follow-up. In addition, further prospective investigation might be worthwhile to ascertain whether fragmented QRS complexes could be a potential marker of worsening right-sided heart dysplasia/dysfunction and increased vulnerability to atrial/ventricular arrhythmia in larger cohorts with this anomaly.

Fragmented QRS Complex in Adult Patients With Ebstein Anomaly and Its Association With Arrhythmic Risk and the Severity of the Anomaly

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SUPPLEMENTAL MATERIAL

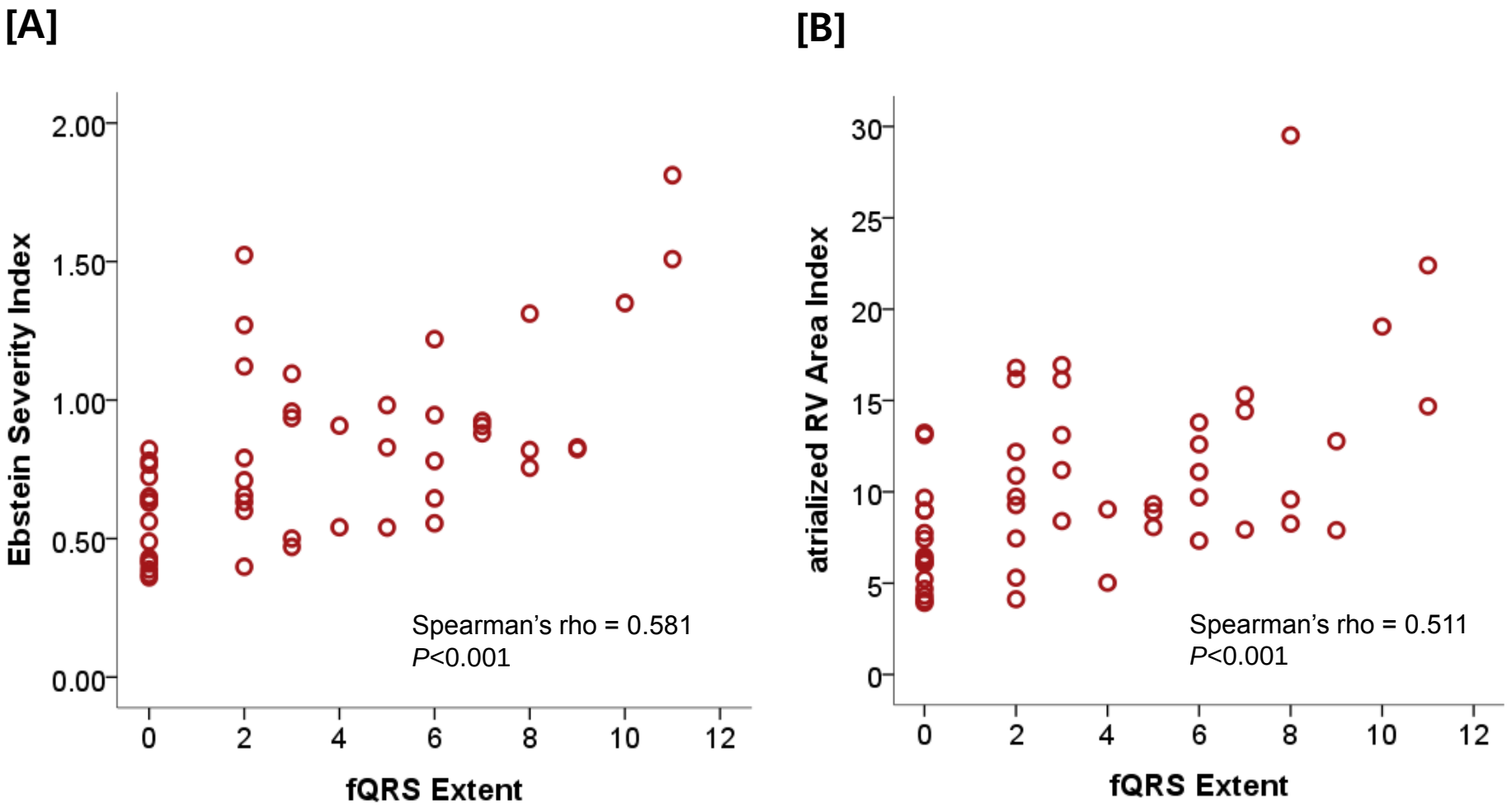
Supplemental Table. C-index calculated using Cox survival methods

	C-index	*Lower 95% CI*	*Upper 95% CI*
QRS duration	0.784	0.387	0.999
Wide QRS	0.814	0.422	0.999
fQRS	0.841	0.455	0.999
Combined parameter*	0.751	0.348	0.999

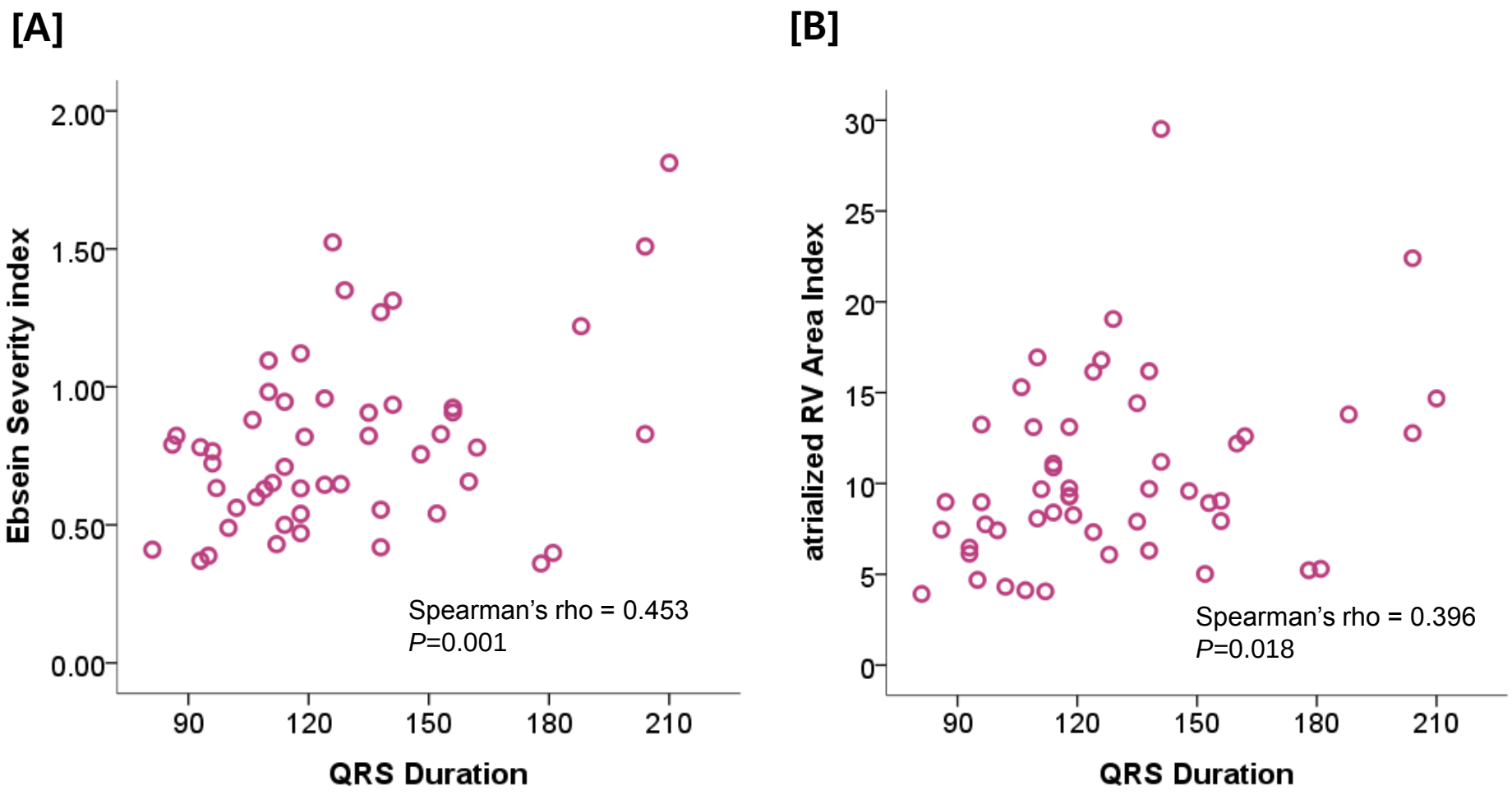
C-index was computed to evaluate the discriminatory accuracy of several electrocardiographic variables (QRS duration, wide QRS, fQRS, and combination of QRS duration and fragmentation) for predicting the occurrence of arrhythmic events.

* Combined parameter refers to categorized electrocardiographic variable determined by QRS duration and fragmentation; narrow non-fragmented (normal), narrow fragmented, wide non-fragmented, and wide fragmented.

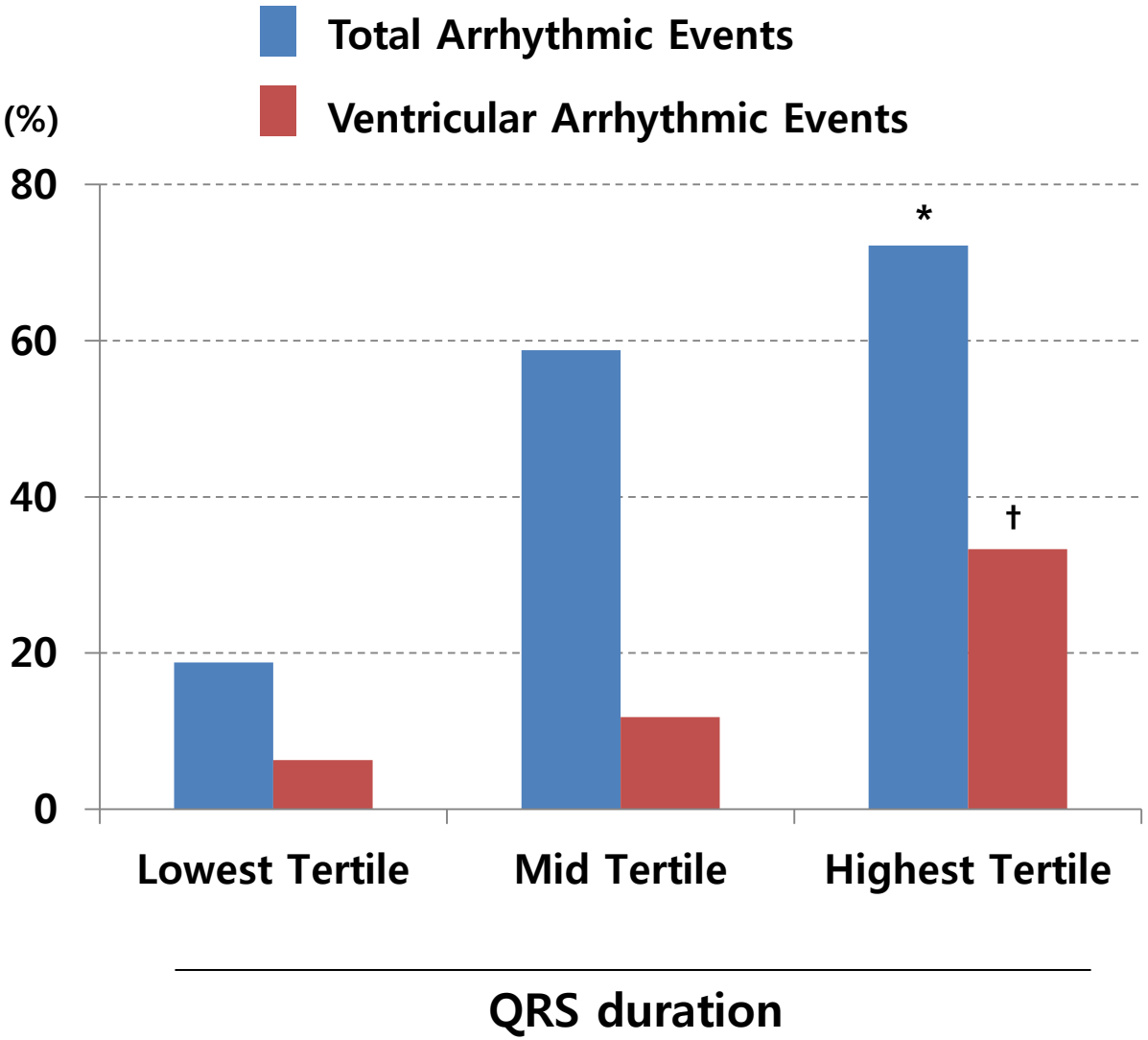
Supplemental Figure 1



Supplemental Figure 2

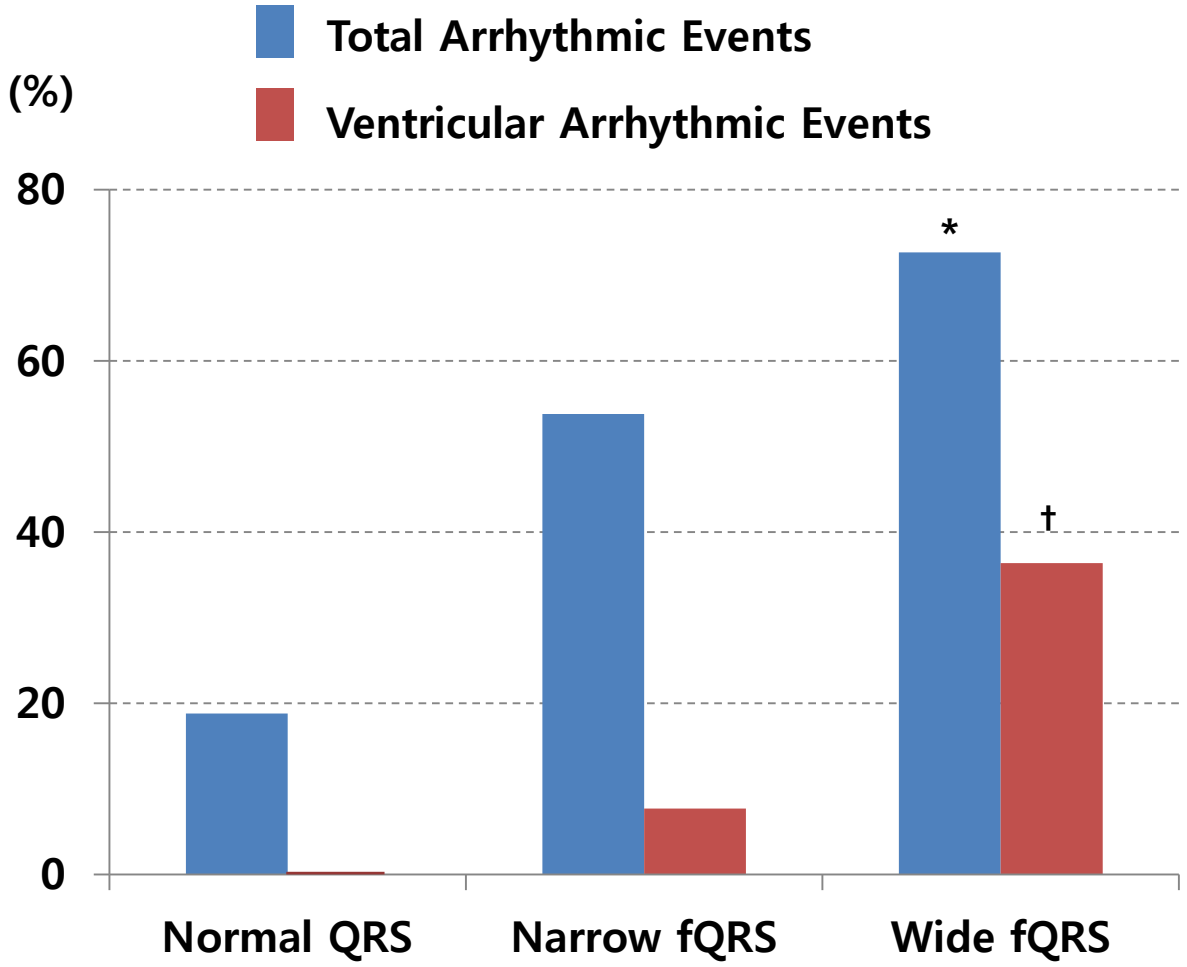


Supplemental Figure 3



* ***P for trend*** (total arrhythmic events)**=0.004**
† ***P for trend*** (ventricular arrhythmic events)**=0.050**

Supplemental Figure 4



* ***P for trend*** (total arrhythmic events)=**0.002**
† ***P for trend*** (ventricular arrhythmic events)=**0.025**

Supplemental Figure Legends

Supplemental Figure 1. The extent of fQRS and the severity of Ebstein's Anomaly

QRS fragmentation shows a significant positive correlation with the severity of Ebstein's anomaly.

Supplemental Figure 2. QRS duration and the severity of Ebstein's Anomaly

QRS duration seems to represent quite well the severity of Ebstein's anomaly. The degree of QRS widening showed a significant positive correlation with the aRVAi (A) as well as with the Ebstein severity index (B). The Ebstein severity index was calculated as described in the method section.

Supplemental Figure 3. QRS duration and arrhythmic burden

When our patients were divided into 3 groups depending on the degree of QRS widening, a clear trend toward more frequent arrhythmic events (total and ventricular tachyarrhythmias) was noted in patients with longer QRS duration.

Supplemental Figure 4. Combined QRS morphologic markers (duration & fragmentation) and arrhythmic burden.

The risk of arrhythmic events tended to rise as the abnormal features of QRS morphology (prolongation and fragmentation) were added (*P* for trend = 0.002 and 0.025 in total and ventricular arrhythmic events, respectively).