ORIGINAL ARTICLE

Fragmented QRS Can Predict Severity of Aortic Stenosis

Eser Açıkgoz, M.D.,* Belma Yaman, M.D.,* Sadık Kadri Açıkgoz, M.D.,†
Salih Topal, M.D.,* Yusuf Tavil, M.D.,* and Nuri Bulent Boyacı, M.D.*

From the *Cardiology Department, Gazi University Faculty of Medicine, Ankara, Turkey; and †Cardiology Clinic, Türkiye Yüksek İhtisas Education and Research Hospital, Ankara, Turkey

Background: Fragmented QRS (fQRS) is an indicator of nonhomogeneous ventricular activity caused by myocardial fibrosis. Aortic stenosis (AS) is known to be a cause of myocardial fibrosis. We aimed to investigate the relationship of fQRS with severity of AS, echocardiographic, and electrocardiographic findings, and development of atrial fibrillation and manifest heart failure in AS patients.

Methods: One hundred four patients with moderate and severe AS were recruited for the study. Patients with mitral or tricuspid stenosis, previous myocardial infarction, segmental wall motion abnormality or left ventricular ejection fraction (LVEF) below 50% and patients with complete-incomplete BBB and pacemaker rhythm were excluded.

Results: Mean age of the patients was 69 ± 14.8 and 73.1% had fQRS. Patients with fQRS had lower LVEF, higher mean QRS duration, intrinsic deflection, Cornell voltage, Romhilt-Estes Score, systolic pulmonary artery pressure, mean and peak systolic transaortic gradients and left atrium diameter. Manifest heart failure was more frequent in patients with fQRS. In stepwise multivariate logistic regression analyze, manifest heart failure, peak systolic transaortic gradient, LVEF, intrinsic deflection, strain pattern and Cornell voltage were independently associated with fQRS. Strain pattern and fQRS were found as independent predictors of severe AS.

Conclusions: fQRS is independently associated with the severity of AS while traditional LVH criteria, except strain pattern, are not. fQRS may be better than traditional ECG criteria of LVH and echocardiographic LVH as an indicator of myocardial fibrosis in AS. Thus, fQRS may have a role in determining the severity and prognosis of AS.

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Fragmented QRS (fQRS) is a relatively novel indicator of nonhomogeneous ventricular activity caused by myocardial scar.¹ Fragmented QRS is simply defined as additional spikes within QRS complexes, such as a RSR, without a typical bundle-branch block pattern.² Previous studies revealed that fQRS is related with depolarization anomalies and fibrosis in patients with ischemic cardiomyopathy.^{3–5} It was also associated with increased mortality and arrhythmic events in Brugada syndrome and arrhythmogenic right ventricular dysplasia.^{6–8}

Several studies have investigated the relationship of fQRS with valvular heart disease. It was shown that severity of mitral stenosis, myocardial

dysfunction, and pulmonary hypertension were associated with fQRS in mitral stenosis.⁹ Aortic stenosis (AS) is the most frequent type of valvular heart disease in Europe and North America.¹⁰ As a response to pressure overload, a marked remodeling process including fibrosis and myocyte degeneration occurs in AS.¹¹ However, there are not any studies investigating the relationship of echocardiographic and clinical findings of AS with the newly proposed fibrosis marker fQRS. Therefore, we aimed to investigate the relationship of fQRS with severity of AS, echocardiographic findings, electrocardiographic findings, and development of atrial fibrillation and manifest heart failure in AS patients.

METHODS

The study population included patients who were admitted to the cardiology outpatient clinics for any reasons and had moderate or severe AS. Patients who have mitral or tricuspid stenosis, previous myocardial infarction, documented coronary artery stenosis greater than 50%, nonischemic dilated cardiomyopathy, segmental wall motion abnormality or left ventricular ejection fraction (LVEF) below 50% in echocardiography and patients with complete or incomplete BBB and pacemaker rhythm on ECG were excluded from the study.

A transthoracic echocardiography was performed in all subjects (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). All patients underwent a comprehensive examination, including M-mode, two-dimensional and Doppler echocardiography.

Septal and posterior walls' thicknesses and systolic and end diastolic dimensions are measured from parasternal long-axis view. Ejection fraction was calculated by modified Simpson's single plane method using left ventricular end systolic and end diastolic volumes from apical four-chamber view. Aortic jet velocity was calculated by Doppler echocardiography. Valve anatomy was evaluated by two-dimensional echocardiography. Aortic stenosis was accepted as mild if mean systolic transaortic gradient is less than 20 mmHg or jet velocity is less than 3.0 m/s, moderate if mean systolic transaortic gradient is between 20 mmHg and 40 mmHg or jet velocity is between 3.0 and 4.0 m/s, and severe if mean systolic transaortic gradient is more than 40 mmHg or jet velocity greater than 4.0 m/s. All examinations were performed by an experienced cardiologist who had no knowledge of the patients' clinical information.

A 12-lead electrocardiogram with standard chest and limb leads was used to evaluate the presence of fQRS. The paper speed and amplitude were set to 25 mm/s and 10 mm/mV, respectively. The low-frequency cutoff (high-pass filter) was set at 0.16 Hz and high-frequency cut off (low-pass filters) was set at 100 Hz. All ECGs were interpreted by two cardiologists who had no knowledge of the patients' clinical information. Fragmented QRS was defined as the QRS complexes with the presence of an additional R wave (R') or notching in the nadir of the R wave or the S wave, or the presence of >1 R' in two contiguous

leads, corresponding to a major coronary territory (Fig. 1). Some electrocardiographic criteria, namely QRS voltage, intrinsic deflection, LV strain pattern, Cornell voltage and Romhilt-Estes score were used and compared with fQRS to evaluate severity of aortic stenosis. Intrinsic deflection was measured from the beginning of the QRS complex to the peak of the R wave. LV strain pattern was defined as the presence of down-sloping convex ST segment with at least 0.5 mm ST depression and concomitant inverted asymmetrical T wave opposite to QRS axis in any of the leads V₄₋₆, DI, or aVL. Cornell voltage was defined as summation of R-wave voltage on aVL and S-wave voltage on V₃. Romhilt-Estes Score was calculated as described elsewhere.¹²

Demographic information, comorbidities, medications, symptoms, and medical histories of the patients were obtained from patients and hospital archives. Manifest heart failure is defined as current NYHA III and IV heart failure or history of hospitalization with a diagnosis of decompensated heart failure due to the AS, and includes both low output and congestive states.

The SPSS statistical software (SPSS 17.0 for Windows, Inc., Chicago, IL, USA) was used for data analysis. Quantitative data were presented as mean $\pm$ standard deviation or median and interquartile range, and categorical variables presented as percentages. After testing data for normal distribution by using Shapiro-Wilk test, Student's t-test or Mann-Whitney U test were used to compare continuous variables. Chi-square test or Fisher's exact test, as appropriate, were used to identify statistically significant differences for categorical variables. Logistic regression analysis was used to examine an association between fragmented QRS, aortic stenosis, and other variables. Variables with a P value of <0.05 in univariate logistic regression analysis were included in a multivariate logistic regression model. Statistical significance was defined as P < 0.05.

RESULTS

Of 104 consecutive patients, 54 (51.9%) were male and 50 (48.1%) were female, with moderate and severe AS were recruited for the study. Mean age of the patients was 69 ± 14.8 . Among the participants, 70 (67.3%) had hypertension, 32 (30.8%) had diabetes mellitus, and 30 (28.8%) had hyperlipidemia.

Figure 1. Examples of fragmented QRS.

Table 1. Clinical and Echocardiographic Characteristics of Patients with and without Fragmented QRS

	Patients without fQRS (n = 28)	Patients with fQRS (n = 76)	P Value
Age (years) ^a	68.1 ± 11.4	69.3 ± 15.9	0.71
Male gender	18 (64.3%)	32 (42.1%)	0.045
Hypertension	1 (57.1%)	54 (71.1%)	0.18
Diabetes mellitus	10 (35.7%)	22 (28.9%)	0.507
Hyperlipidemia	10 (35.7%)	20 (26.3%)	0.348
Smoking	2 (7.1%)	14 (18.4%)	0.225
QRS duration ^a	83.9 ± 8.7	89.3 ± 10.9	0.021
Intrinsic deflection ^a	37.1 ± 4.6	43.4 ± 9.5	0.001
Cornell voltage ^a	1.48 ± 0.40	1.98 ± 0.64	<0.001
Romhilt-Estes score ^a	2.14 ± 1.91	4.55 ± 2.08	<0.001
LV strain pattern	6 (21.4%)	42 (55.2%)	0.002
Left axis deviation	8 (28.5%)	32 (42.1%)	0.208
LVEF% ^a	65.1 ± 3.6	63.3 ± 4.5	0.037
Septum (mm) ^a	13.6 ± 1.4	14.3 ± 2.6	0.15
Posterior wall (mm) ^a	12.5 ± 1.2	12.9 ± 1.9	0.30
sPAP (mmHg) ^a	30.7 ± 5.3	43.2 ± 19.8	<0.001
Mean gradient (mmHg) ^b	24.5 (11)	38.0 (17)	<0.001
Peak gradient (mmHg) ^b	45.0 (17)	61.5 (25)	<0.001
Left atrium (mm) ^b	40.5 (5)	44.0 (9)	0.01
Heart failure	2 (7.1%)	28 (36.8%)	0.003
Atrial fibrillation	4 (14.3%)	20 (26.3%)	0.20

LV = left ventricle; LVEF = left ventricular ejection fraction; sPAP = systolic pulmonary artery pressure.

^aPresented as mean ± standard deviation, ^bPresented as median and interquartile range.

Seventy six (73.1%) patients had fQRS on their ECGs. Compared to patients without fQRS, patients with fQRS had lower LVEF, higher mean QRS duration, intrinsic deflection, Cornell voltage, Romhilt-Estes Score, systolic pulmonary artery pressure, mean systolic transaortic gradient, peak systolic transaortic gradient, and left atrium diameter. Left ventricular strain pattern was more frequent in fQRS group. Septal and posterior left ventricular wall thicknesses of the groups were similar. While manifest heart failure was more frequent in patients with fQRS, frequency of atrial fibrillation did not differ significantly between groups (Table 1).

In stepwise multivariate logistic regression analyze, peak systolic transaortic gradient and

LVEF were independently associated with fQRS. Furthermore, the presence of fQRS was independently predictive of manifest heart failure (Table 2). Strain pattern and fQRS were independent predictors of severe aortic stenosis in another stepwise multivariate logistic regression model that evaluates association of severe aortic stenosis with electrocardiographic parameters. (Table 3).

DISCUSSION

In this study, we aimed to investigate the relationship of fQRS with electrocardiographic, echocardiographic, and clinical features of AS,

Table 2. Association of Fragmented QRS with Clinical and Echocardiographic Characteristics

Variables	Univariable		Multivariable	
	OR (95% CI)	P Value	OR (95% CI)	P Value
LVEF	0.898 (0.800–1.008)	0.067	-	
Septum	1.162 (0.945–1.429)	0.156	-	
Posterior wall	1.142 (0.889–1.468)	0.299	-	
Left atrium	1.142 (1.053–1.238)	0.001	-	
Mean gradient	1.095 (1.040–1.153)	0.001	- ^a	
Peak gradient	1.083 (1.040–1.127)	<0.001	1.123 (1.057–1.192)	<0.001
sPAP	1.069 (1.020–1.121)	0.005	1.101 (1.017–1.193)	0.018
QRS duration	1.059 (1.007–1.113)	0.027	-	
Intrinsic deflection	1.121 (1.038–1.210)	0.003	1.222 (1.085–1.377)	0.001
Romhilt-Estes score	1.672 (1.325–2.109)	<0.001	-	
Cornell voltage	4.906 (1.958–12.296)	0.001	4.964 (1.106–22.277)	0.036
Strain pattern	4.529 (1.650–12.431)	0.003	5.536 (1.111–27.592)	0.037
Left axis deviation	1.818 (0.712–4.645)	0.212	-	
Hypertension	1.842 (0.750–4.518)	0.183	-	
Diabetes mellitus	0.733 (0.293–1.837)	0.508	-	
Heart failure	7.583 (1.672–34.391)	0.009	1.876 (1.010–4.983)	0.042
Atrial fibrillation	2.222 (0.685–7.205)	0.183	-	

HR = hazard ratio; CI = confidence interval; LVEF = left ventricular ejection fraction; sPAP = systolic pulmonary artery pressure.

^aNot included in multivariable analyze in order to prevent multicollinearity.

Table 3. Association of Severe Aortic Stenosis with Electrocardiographic Parameters

Variables	Univariable		Multivariable	
	OR (95% CI)	P Value	OR (95% CI)	P Value
fQRS	2.968 (1.082–13.547)	0.035	3.895 (1.120–13.547)	0.033
QRS duration	0.976 (0.939–1.014)	0.218	-	
Intrinsic deflection	0.995 (0.952–1.041)	0.835	-	
Romhilt-Estes score	1.134 (0.949–1.356)	0.166	-	
Cornell voltage	0.778 (0.410–1.476)	0.442	-	
Strain pattern	3.545 (1.547–8.127)	0.003	3.291 (1.048–10.329)	0.041
Left axis deviation	1.815 (0.786–4.193)	0.163	-	

HR = hazard ratio; CI = confidence interval; fQRS = fragmented QRS.

and demonstrated for the first time that fQRS is independently associated with manifest heart failure, higher peak systolic transaortic gradient, and lower LVEF in patients with moderate and severe AS.

Determining the severity and progression of AS has critical importance in daily clinical practice. Although echocardiography is a more specific technique and gives quantitative information, ECG is more readily available and generally obtained before an echocardiography.¹³ Left ventricular hypertrophy (LVH), often with secondary ST-T changes, is typical ECG finding of AS.¹⁴ Despite having good specificity, conventional ECG criteria have poor sensitivity in detecting LVH.¹⁵ Thus, absence of LVH on ECG does not preclude severe AS. In one study, Romhilt-Estes score was shown

to have 86% sensitivity and 81% specificity for LVH in aortic valve disease and it may be the ECG score of choice to detect LVH in AS patients.¹⁶ Left atrial enlargement, left or right axis deviation, atrial fibrillation and conduction anomalies such as right and left bundle block are other common ECG findings of AS.¹⁴ QRS duration is also important in AS. In SEAS study, it was shown that longer QRS duration is independently associated with poor prognosis, particularly the risk of sudden cardiac death.¹⁷ Significance of fQRS in AS has not been studied extensively so far. In a study comparing 87 severe AS patients with age- and gender-matched healthy controls, higher frequency of fQRS was detected in severe AS group.¹⁸

Fragmented QRS is a sign of myocardial scar and fibrosis.^{3,4} Nonhomogenous ventricular activity

caused by myocardial scar results in fQRS.¹⁹ Furthermore, in patients with left ventricular hypertrophy, fQRS has been suggested to be a result of an intraventricular conduction defect.²⁰ Fibrosis is an early morphological change in patients with AS and it is a determinant of both diastolic and systolic dysfunction. Fibrosis and myocyte enlargement starts in early stages of AS with normal LVEF and elevated left ventricular end diastolic pressure (LVEDP).²¹ With worsening of fibrosis and myocyte degeneration, LVEDP increases more and later EF decreases.¹¹ Fibrosis is also one of the structural substrates for arrhythmogenicity, thus playing a major role for sudden death and the progression to heart failure.^{22,23} The amount of myocardial fibrosis has significant effect on long-term survival in severe AS even after aortic valve replacement.²⁴

The results of the present study suggest that fragmented QRS indicates the severity of AS, independent from echocardiographic left ventricular wall thicknesses and electrocardiographic indicators of left ventricular hypertrophy. Furthermore, while fQRS predicts severity of AS, traditional LVH criteria such as Cornell voltage and Romhilt-Estes Score cannot. These results may be considered as a sign of that fQRS is better than electrocardiographic and echocardiographic LVH as an indicator of myocardial fibrosis caused by AS. Thus, we believe fQRS may have a role in determining the severity of AS. Larger trials that assess long-term prognosis are needed to establish the exact role of fQRS in AS.

The present study has several limitations that should be taken into account when interpreting its results. First, it has a relatively low number of patients from only one center. Second, patients with other severe valvular heart diseases and patients with an LVEF lower than 50% were excluded from the study in order to avoid any possible confounding effect. As a consequence, the results of the study cannot be generalized to all AS patients.

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