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Increased Frequency of Fragmented QRS in Patients with Severe Aortic Valve Stenosis

Mustafa Tarık Ağaç[a] Levent Korkmaz[a] Hüseyin Bektas[a] Zeydin Acar[a]
Hakan Erkan[a] Ibrahim Halil Kurt[b] Adem Adar[a] Şükrü Çelik[a]

[a]Department of Cardiology, Ahi Evren Cardiovascular and Thoracic Surgery Training and Research Hospital, Trabzon, and [b]Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey

Key Words
Aortic valve stenosis · Fragmented QRS · Myocardial fibrosis

Abstract
Objective: To investigate the presence of myocardial fibrosis determined by fragmented QRS in patients with severe aortic valve stenosis. ***Subjects and Methods:*** Eighty-seven consecutive patients with severe aortic valve stenosis and 83 age- and gender-matched control subjects were enrolled into this study. Severe aortic valve stenosis was defined as an aortic valve area <1 cm^2, a V_{max} >4 m/s, or a mean gradient ≥40 mm Hg. Fragmented QRS was assessed using a 12-lead electrocardiogram. ***Results:*** Fragmented QRS was detected in 40 (46%) patients in the aortic valve stenosis group and in 15 (18%) control subjects ($p < 0.001$). In multivariate binary logistic regression analysis, the presence of aortic valve stenosis was the only independent factor associated with fragmented QRS (OR = 3.69; 95% CI 1.81–7.55, $p < 0.001$). ***Conclusion:*** A higher frequency of fragmented QRS was detected in patients with severe aortic valve stenosis compared to controls.

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Introduction

Fragmentation of QRS complexes (fQRS) includes various RSR' patterns with different morphologies of QRS complexes with or without the Q wave on a resting 12-lead electrocardiogram (ECG) [1]. Various RSR' patterns include an additional R wave (R') or notching in the nadir of the S wave, or the presence of >1 R' (fragmentation) in 2 contiguous leads, corresponding to a major coronary artery territory. Several investigators have demonstrated that fQRS on a routine 12-lead ECG signifies a myocardial scar in different clinical situations [2, 3]. Also, fQRS reflects myocardial conduction abnormalities likely due to myocardial fibrosis which is considered a prognostic marker for lethal cardiac arrhythmias [4].

Myocardial fibrosis starts in the subendocardial layers and progresses toward replacement fibrosis of the left ventricle in patients with aortic stenosis [5]. The amount of myocardial fibrosis is a predictor of long-term survival after aortic valve surgery [6]. It has a negative impact on regional and global myocardial function and does not regress even a long time after aortic valve surgery [7, 8]. Since myocardial fibrosis has a prognostic impact on patients with aortic stenosis, the detection of

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Mustafa Tarık Ağaç, MD
Ahi Evren Cardiovascular and Thoracic Surgery Training and Research Hospital
Çamlık Street, TR–61187 Trabzon (Turkey)
E-Mail tarikagac@gmail.com

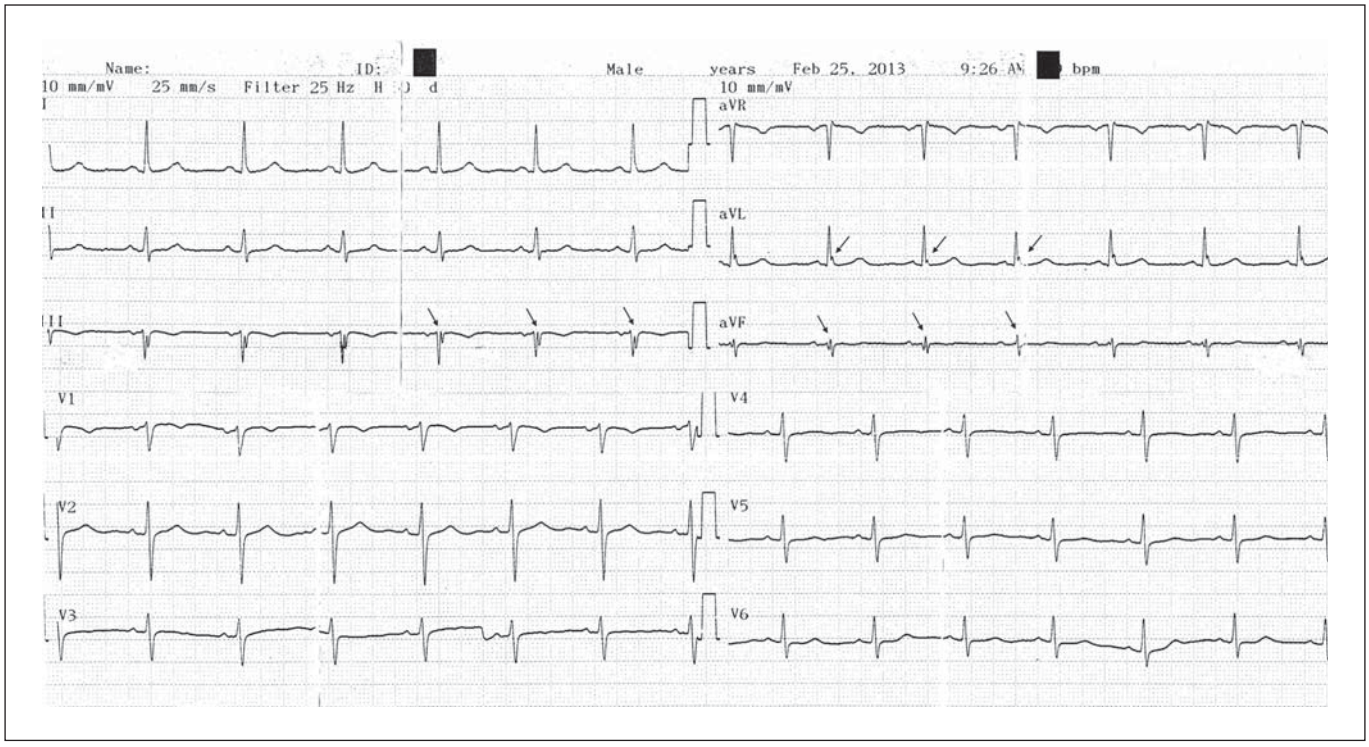

Fig. 1. Examples of various fQRS patterns. The arrows show fQRS in lead III, AVF and AVL in a patient with severe aortic stenosis. Note that QRS morphology is not compatible with the typical bundle branch block pattern and the duration is <120 ms.

those high-risk patients via simple methods may have clinical significance in daily routine clinical practice. Thus, the main purpose of the present study was to investigate the presence and frequency of fQRS in patients with severe aortic stenosis.

Materials and Methods

Study Population

Between January 2010 and July 2012, after exclusion, 87 patients with severe aortic stenosis (aortic valve area <1 cm^2, V_{max} >4 m/s, or mean gradient ≥40 mm Hg) and preserved left ventricular ejection fraction (≥50%) were enrolled into this single-center study. Exclusion criteria were: patients with significant concomitant valvular disease, coronary artery disease established by the history or angiography at index hospitalization, wall motion abnormalities, and severe pulmonary disease. Patients underwent comprehensive 2-D and Doppler transthoracic echocardiography. During the same period, 83 normal subjects matched for age and gender, without any history of cardiovascular disease, served as a control group. Informed consent was obtained from all participants and the study protocol was approved by the Ethics Committee of the Trabzon Numune Training and Research Hospital.

ECG Acquisition and Analysis

A 12-lead surface ECG was obtained from all patients in the supine position. fQRS was defined as the presence of various RSR' patterns with different morphologies of QRS complexes with or without the Q wave. Various RSR' patterns included an additional R wave (R'), notching of the R wave or the S wave, or the presence of >1 R' (fragmentation) without a typical bundle branch block in 2 contiguous leads corresponding to a major lead set for major coronary artery territory (fig. 1). Any QRS morphology with a QRS duration >120 ms, including bundle branch block or intraventricular conduction delay, was excluded. Analysis of the standard 12-lead ECG was performed without using any magnification, and fragmentations were considered to be present if a visually identifiable signal was demonstrated in all complexes of a particular lead. Thus, for statistical analysis, fQRS was defined to be present if found in ≥2 contiguous anterior leads, lateral leads, or inferior leads. QRS duration was determined by the longest QRS in any lead. All ECG were assessed by a single operator who was blinded to the patients' clinical and laboratory characteristics.

Assessment of Cardiovascular Risk Factors

A history (or symptoms) of diabetes mellitus and arterial hypertension, and smoking habits, were considered. Patients were considered to be hypertensive if they had a systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mm Hg or were using antihypertensive drugs. Subjects with fasting glucose

Table 1. Clinical and laboratory characteristics of the patients and control subjects

Variables	Control group (n = 83)	Patient group (n = 87)	p
Age, years	75±9	76±7	n.s.
Male gender	36 (43)	30 (35)	n.s.
Hypertension	33 (40)	51 (59)	0.02
Diabetes	5 (6)	12 (14)	n.s.
Smoking	17 (20)	11 (13)	n.s.
Hypercholesterolemia	9 (11)	13 (15)	n.s.
fQRS	15 (18)	40 (46)	<0.001
Cardiovascular medications			
ASA	3 (4)	6 (7)	n.s.
β-Blockers	10 (12)	13 (15)	n.s.
Cholesterol-lowering drugs	7 (8)	8 (9)	n.s.
ACEI or ARB	14 (17)	29 (33)	0.01

Values are presented as numbers (%) unless otherwise stated. ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; n.s. = not significant.

Table 2. Clinical and laboratory characteristics of subjects with or without fQRS

Variables	fQRS (–) (n = 115)	fQRS (+) (n = 55)	p
Age, years	75±8	76±7	n.s.
Male gender	48 (42)	18 (33)	n.s.
Hypertension	52 (45)	32 (58)	n.s.
Diabetes	9 (8)	8 (15)	n.s.
Smoking	22 (19)	6 (11)	n.s.
Hypercholesterolemia	15 (13)	7 (13)	n.s.
Aortic stenosis	47 (41)	40 (73)	<0.001
Cardiovascular medications			
ASA	7 (6)	2 (4)	n.s.
β-Blockers	16 (14)	7 (13)	n.s.
Cholesterol-lowering drugs	10 (9)	5 (9)	n.s.
ACEI or ARB	26 (23)	17 (31)	n.s.

Values are presented as numbers (%) unless otherwise stated. ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; n.s. = not significant.

≥126 mg/dl and/or use of antidiabetic medications were considered to have diabetes. Smoking status was defined as 'current smoker' or 'nonsmoker'. Hypercholesterolemia was defined as total cholesterol >200 mg/dl or taking medications.

Statistical Analysis

Continuous variables were expressed as means ± SD and categorical variables were expressed as percentages. Analysis of the normality of continuous variables was performed with the Kolmogorov-Smirnov test. A comparison of the categorical variables between the groups was performed using a χ^2 test. Continuous variables were compared using an unpaired t test and a Mann-Whitney U test. Logistic regression analysis was performed to determine the independent factors associated with fQRS. For multivariate analysis, parameters having associations with fQRS with $p < 0.10$ were entered into the analysis. $p < 0.05$ was considered statistically significant. Statistical analysis was done using SPSS 14.0 statistical software.

Results

The baseline clinical and laboratory characteristics of the patient and control groups are given in table 1. There were no significant differences between the patient and control groups with regard to age, sex, smoking status, presence of diabetes mellitus and hypercholesterolemia, and use of cholesterol-lowering drugs, acetylsalicylic acid, and β-blockers. However, the presence of hypertension or fQRS and the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were statistically higher in patients with aortic stenosis. fQRS was detected in 40 (46%) patients in the aortic stenosis group and in 15 (18%) control subjects ($p < 0.001$).

The clinical and laboratory characteristics of subjects with or without fQRS are summarized in table 2. In binary logistic regression analysis, the presence of aortic stenosis was found to be the only independent factor associated with fQRS (OR = 3.69; 95% CI 1.81–7.55, $p < 0.001$).

Discussion

A higher frequency of fQRS was detected in patients with significant aortic stenosis compared to the age- and gender-matched subjects without aortic stenosis. Aortic valve stenosis was characterized by progressive accumulation of interstitial myocardial fibrosis and impairment of the myocyte ultrastructure. In patients with severe aortic stenosis, the amount of myocardial fibrosis appeared to have a significant effect on the clinical status and long-term survival after aortic valve replacement as previously reported [6]. Also, several studies indicate that quantitative assessment of myocardial fibrosis has the potential to

provide additional prognostic information in the evaluation of patients with severe aortic stenosis [9–11]. However, it may not be easy to assess myocardial fibrosis in routine clinical practice. Myocardial fibrosis cannot be detected by standard echocardiographic examination until the terminal stage of the disease. It has been shown that the amount of myocardial fibrosis detected on contrast-enhanced magnetic resonance imaging (MRI) is closely correlated to quantitative histopathology [9]. Even though it has a high sensitivity and specificity, the applicability of MRI to all aortic stenosis patients is limited due to technical and financial issues.

fQRS on a standard 12-lead ECG is a sensitive and highly specific sign of myocardial fibrosis in patients with known or suspected coronary artery disease and congenital heart disease [12–14]. The clinical significance of fQRS is related to its association not only with myocardial fibrosis but also with heterogeneity in myocardial conduction [15]. It has been shown that patients with fQRS might have a greater heterogeneity of myocardial conduction and an increased risk of ventricular tachycardia compared to those without fQRS [16].

The limitations of this study included a lack of clinical follow-up; therefore, we could not determine whether or not the presence of fQRS has a clinical significance in this patient population. Also, we did not perform cardiac MRI, which is considered a gold standard in myocardial fibrosis.

Conclusion

A higher prevalence of fQRS was detected in patients with significant aortic stenosis compared to controls. Further studies are required to determine the clinical significance of this association.

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