

Frequency of Fragmented QRS in Subjects without Cardiovascular Disease

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Introduction: Fragmented QRS (fQRS) is a marker of depolarization abnormality due to in homogenous electrical activation of the infarcted ventricular myocardium. However, it is a nonspecific finding and can be present in persons without the cardiovascular disease. In this study, we aimed to investigate the prevalence and characteristics of the fQRS in subjects without cardiovascular disease.

Materials and Methods: 417 patients were included in the study. All participants were evaluated with the history, physical examination and 12 lead electrocardiogram (ECG) along with 2-dimensional echocardiography. Criteria used in the diagnosis of fQRS include additional spikes within the QRS complex, the presence of additional R wave, notching in the S wave, the presence of R' more than two contiguous leads corresponding a major coronary artery on the resting 12-lead ECG.

Results: There was no statistically significant difference between two groups with respect to age, body mass index, smoking habits, cholesterol, LDL-C, HDL-C and triglyceride levels. Percentage of fQRS was statistically significantly higher in males compared to females ($p=0.03$). QRS duration and Glucose level were significantly higher in patients with fQRS than those of the control subjects ($p<0.001$ for both comparisons). fQRS showed strong positive correlation with QRS duration and plasma glucose levels ($r=0.437$; $p<0.001$ and $r=0.202$ and $p<0.001$, respectively).

Conclusions: fQRS is not an uncommon finding in subjects without cardiovascular disease. Increased glucose levels could be one of the mechanisms that cause the formation of fQRS in those subjects.

Keywords: Electrocardiogram, fragmented QRS, incidence

Introduction

Fragmented QRS (fQRS) is defined as the presence of R' wave or notching of R or S wave in two contiguous leads, corresponding to major coronary artery territory with normal QRS duration (1). In the presence of a wide QRS complex (QRS>120 ms), more than two notches in the R or S wave in two or more contiguous leads are required to confirm the

diagnosis of fQRS (1). Regional myocardial fibrosis, scar or ischemia which the cause depolarization heterogeneity across ventricular myocardium is being recognized as the underlying causative mechanism for fQRS (2). The location of fQRS in the electrocardiogram has also generally correlated well with the location of myocardial scar (3). It can be found in the patients with coronary artery disease,

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cardiomyopathy, congenital heart disease, arrhythmogenic right ventricular dysplasia, Brugada syndrome, hypertension, and connective tissue diseases (1, 4, 5). Its presence is associated with increased risk of death in patients with structural heart disease (6-8). It is a relatively common incidental finding in normal subjects. In this study we aimed to evaluate the incidence and characteristics of the fQRS in subjects without cardiovascular disease.

Materials and Methods

A total of 417 patients who had undergone a health check-up program between January 2015 and March 2016 were enrolled in this prospective study. Patients with ischemic heart disease, congestive heart failure, hypertension, valvular heart disease, arrhythmia, bundle branch block, hypo-or-hyperthyroidism, liver disease, renal failure, psychiatric disease were excluded. All patients were provided informed consent and the study was approved by a local ethics committee. All patients had their history records, and underwent a physical examination along with a 12-lead electrocardiogram (ECG) (Comen CM100B, China). Diagnosis of fQRS was made through a definition by Das et al. (6): presence of an additional R wave (R') or slurring in the nadir of the S wave, or the presence of >1 R' in 2 contiguous leads, corresponding to a major coronary artery territory on the resting 12-lead ECG. A complete echocardiographic examination was performed according to the recommendations of the American Society of Echocardiography (Vivid 3 pro, GE Vingmed Ultrasound AS, Horten, Norway) (9). After an overnight fast, blood samples drawn from the antecubital vein were analyzed for fasting glucose, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), total cholesterol (TC) levels and full

blood count test. Samples were assayed by the clinical laboratory in 3-5 hours after sampling. (COBAS c311, Roche Diagnostics, Germany).

Continuous variables and categorical variables were expressed as mean $\pm$ standard deviation (SD) and percentages, respectively. Nonparametric values were analyzed by Chi-Square Test and Mann Whitney-U Test; parametric values of the patients were analyzed by Independent Samples T-Test. The binary logistic regression analysis was used to evaluate significant associations between fQRS and clinical variables of the patients. ROC curve analysis was used to determine the cut-off values of QRS duration and glucose level to predict fQRS. All statistical analyzes were performed using SPSS 23 (SPSS, Inc., Chicago, Illinois, USA). P value <0.05 was considered significant.

Results

A total of 417 patients were studied, 29 of them had fQRS and 388 of them had normal ECG. There was no statistically significant difference between the two groups with respect to body mass index, smoking habits. Statistical analysis revealed a significantly higher percentage of males in the study group compared to the control group ($p=0.03$). Moreover the mean age of the patients with fQRS was older than those of the controls. QRS duration of the study group was significantly longer than that of the control group. Table-1 shows the baseline characteristics of the two groups. There were no significant differences in respect to total cholesterol, LDL-C, HDL-C triglyceride, hemoglobin, creatinine levels, neutrophil, lymphocyte count, neutrophil lymphocyte ratio between two groups. The glucose level was significantly higher in the patients with fQRS than those of control ($p=0.006$). Table 2 shows the biochemical characteristics of the study population.

Table-1. Baseline characteristics of the subjects

Parameters	Normal ECG (N:388)	fQRS (N:29)	p
Age, Mean±SD	39.9±10.9	42.9±8.12	0.018
Gender, n (%)			0.031
Female	197 (50.8)	9 (31)	
Male	191 (49.2)	20 (69)	
Smoking, n (%)			0.644
No	186 (47.9)	15 (51.7)	
Using	164 (42.3)	10 (34.5)	
Gave up	38 (9.8)	4 (13.8)	0.956
BMI, Mean±SD	28±4.88	28.07±5.14	
QRS Type, n (%)			<0.001
Anterior		7 (24.2)	
Inferior		22 (75.8)	
QRS Duration	82.6±4.15	90.5±4.28	

ECG: electrocardiogram; BMI: body mass index.

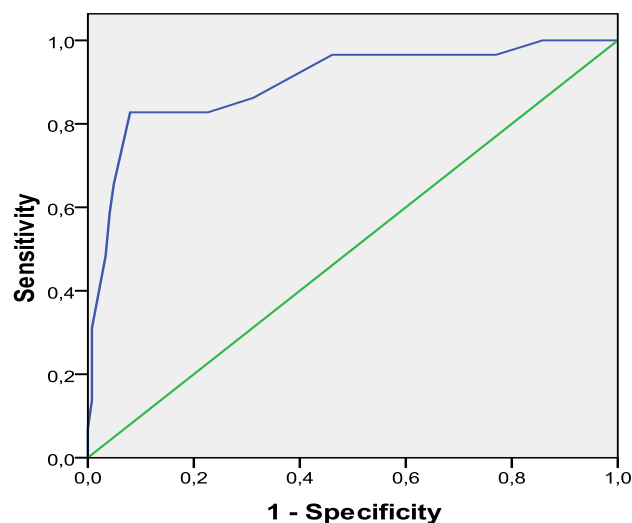
We observed a strong positive correlation between fQRS and QRS duration as well as plasma glucose levels ($r=0.437$; $p<0.001$ and $r=0.202$ and $p<0.001$, respectively) (Table-2).

Table-2. Biochemical parameters of the groups

Tests	Normal ECG (N:388)	FQRS (N:29)	p
TKOL (mg/dl)	184.8±30.8	182.1±26.8	0.641
TG (mg/dl)	135.8±72.8	139.2±52.4	0.544
HDL-C (mg/dl)	46.3±11.2	43.3±10.58	0.172
LDL-C (mg/dl)	121±31.02	118.2±20.2	0.486
GLU (mg/dl)	96.5±9.23	104.5±16.9	0.006
RDW (%)	13.6±1.52	13.5±0.79	0.739
HGB (g/l)	14.05±1.6	14.5±0.72	0.367
MPV (fL)	9.13±1.69	9.46±1.67	0.301
NEU (K/uL)	4.24±2.17	3.89±1.59	0.552
LYM (K/uL)	2.19±0.83	1.91±0.79	0.034
NLR	2.11±1.32	2.34±1.27	0.066
Creatinin(mg/dl)	1.01±0.14	1±0.16	0.423

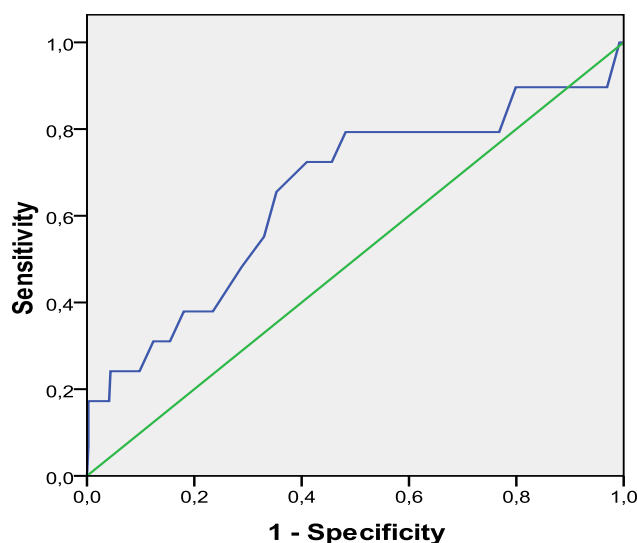
TC: Total Cholesterol; TG: Triglycerides; HDL-C: High Density Cholesterol; LDL-C: Low Density Cholesterol; GLU: Glucose; HGB: Hemoglobin; RDW: Red Cell Distribution Width; MPV: Mean Platelet Volume; NEU: Neutrophil; LYM: Lymphocyte; NLR: Neutrophil Lymphocyte Ratio.

Area under curve for QRS duration ROC curve analysis was 0.899 indicating 89.9% predictive value. Sensitivity was 82.8% and specificity was 92.0% for 88.50ms QRS Duration level (Fig 1).

**Figure 1.** ROC of QRS duration for predicting fQRS

Area under curve for glucose ROC curve analysis was 0.653 indicating a 65.3% predictive value. Sensitivity was 72.4% and specificity was 59.0% for 97.5 mg/dl glucose level (Fig 2).

On binary logistic regression analysis sex and glucose level were the factors found significantly associated with fQRS (OR=1.162, $p=0.009$ and OR=1.09, $p<0.001$, respectively).

**Figure 2.** ROC of Glucose level for predicting fQRS

Discussion

Our study showed that 6.95% of the subjects without cardiovascular disease had fQRS. It was more common in males than females and older individuals. Subjects with fQRS had longer QRS durations and higher glucose levels compared to the subjects with normal QRS. Moreover, fQRS was positively correlated with male sex and fasting glucose levels.

The fQRS is an electrocardiographic sign of delayed myocardial depolarization due to the myocardial ischemia, fibrosis, scar or inflammation (10, 11). Garder et al, demonstrated that fQRS resulted from inhomogeneous and slow depolarization of the ventricles due to the myocardial scar in infarcted canine heart (12). Beyond its diagnostic value, it has prognostic value in patients with coronary artery disease (4), cardiomyopathy (13), Brugada syndrome (5), and hypertrophic cardiomyopathy (14). A poor survival has been reported among fQRS compared to those (4, 5, 13, 14).

Although fQRS has been considered as a pathological finding for a long time, it is relatively common among healthy subjects as well. Tian et al., investigated the prevalence of fQRS in healthy persons (15). Of 1500 individuals who were screened on admission to hospital, findings showed that fQRS was present in 76 (5.1%) of subjects, 66/76 (86.8%) of which occurred in the inferior leads and 10/76 (13.2%) in anterior leads. Subjects with fQRS abnormalities tended to be older, male and have longer QRS duration. In that study, 16 subjects with the fQRS underwent late gadolinium enhancement-cardiac resonance scanning which showed no structural abnormalities. Terho et al (16), with a mean follow-up of 30 ± 11 months, observed inferior fQRS in 15.6%, anterior in 2.9% and lateral in 0.5% of

the subjects without known cardiac disease in a general population sample of 10,904 middle aged subjects. In their study fragmentation was not associated with increased mortality in subjects without known heart disease.

Our numerical results range between the values of the studies mentioned above. We found a strong male preponderance with common localization of fQRS in inferior leads similar to Tian et al's results. Furthermore, fQRS was independently associated with QRS duration. The unique finding of our study was that the blood glucose levels of the subjects with fQRS were higher than those of the subjects without.

Some general ECG changes reported in diabetic patients, irrespective of whether they had autonomic nervous system abnormalities or not. It is well known that microangiopathy of the heart including arteriosclerosis, dilatation of venules, thickening of capillary walls and endothelial proliferation impair the cardiac microcirculation in the diabetic patients (17). Accumulating evidences reveals that insulin resistance strongly related to inflammation, vasoconstriction and vascular smooth muscle proliferation (18). Patients with diabetes mellitus frequently have intraventricular conduction disturbances even if they are asymptomatic including those with no detectable cardiac abnormalities on physical examination (19). Howarth et al. investigated the long term effects of type 2 diabetes mellitus on heart rhythm in rats, their ECG displayed prolonged QRS duration and QT interval (20). Although the subjects included in our study were not diagnosed with diabetes mellitus, the blood glucose level of the subjects with fQRS was significantly higher than that of the subjects without fQRS. Upon further analysis we found

strong positive correlation between fQRS and blood glucose levels indicating that higher glucose levels could predispose an inhomogeneous activation of the ventricles. fQRS reflecting minor intraventricular conduction defect is a common finding, especially in the inferior leads. Our results suggest that the observed association between blood glucose levels and fQRS warrants further investigation.

Main limitation of our study was the relatively low number of included subjects. Long term follow-up of participants is missing. Although all subjects had echocardiographic examination, coronary angiography was not performed to exclude coronary artery disease.

Conflict of Interests

The authors declare that they have no conflict of interest in the current study.

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