Fragmented QRS is associated with frequency of premature ventricular contractions in patients without overt cardiac disease

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ABSTRACT

Objective: In this study, we aimed to demonstrate whether the presence of fragmented QRS (fQRS) is associated with the frequency of premature ventricular contractions (PVCs).

Methods: We retrospectively analyzed 282 cases by 24-hour Holter monitorings (HMs) between August 2012 and February 2013. Firstly, the patients were divided into 2 groups with respect to presence of fQRS and then divided into 3 groups with respect to frequency of PVCs as Group 1: seldom PVC (<120 PVCs/day), Group 2: moderate-frequency PVC (120-720 PVCs/day), and Group 3: frequent PVC (>720 PVCs/day). We investigated the predictors of frequent PVCs by using multinomial logistic regression analysis.

Results: Ninety-eight patients had fQRS. There was no difference between the 2 groups with respect to body mass index, gender, hypertension, and diabetes mellitus. Patients with fQRS were older (54.9±15.6 vs. 47.0±16.3, p<0.001) and had more family history of coronary artery disease (25% vs. 13%, p=0.012). Patients with fQRS was more likely to be on aspirin therapy (28.6% vs. 10.4%, p<0.001) and have a larger left atrium diameter (33.5±5.7 vs. 30.4±5.8, p=0.001). Presence of fQRS was significantly associated with the frequency of PVCs (for frequent PVC 27.7% vs. 7.6%, p<0.001; for moderate-frequency PVC 18.4% vs. 11.4%, p=0.012); 26.2% of Group 1 (n=202) had fQRS, 46.2% of Group 2 (n=39) had fQRS, and 65.9% of Group 3 (n=41) had fQRS. In the multinomial regression analysis, only age (odds ratio: 4.24, 95% confidence interval 2.08-8.64, p=0.001) and fQRS (odds ratio: 2.11, 95% confidence interval 1.00-4.45, p=0.05) were predictors of frequent PVCs.

Conclusion: This study demonstrated that the presence of fQRS is associated with frequent PVCs in patients without overt structural heart disease. (Anatol J Cardiol 2015; 15: 456-62)

Keywords: fragmented QRS, premature ventricular contraction, Holter monitoring

Introduction

Premature ventricular contractions (PVCs) are common in the general population, and most of them are not clinically important in the absence of underlying structural heart disease, but it is well known that PVCs are associated with mortality and morbidity when there is an underlying structural heart disease (1-3). It is shown that frequent PVCs have a good prognosis in the absence of structural heart disease (4). On the contrary, some studies demonstrated an increased risk of sudden cardiac death, myocardial infarction, and all-cause mortality in patients with frequent PVCs but without structural heart disease (5, 6). Some investigators found that frequent PVCs may cause cardiomyopathy by itself and may be responsible for increased cardiac risk (7, 8). Additionally, PVCs without underlying heart disease may be associated with ventricular tachycardia (VT), and elimination of these PVCs with catheter ablation prevents further occurrence of VT (9-11).

Fragmented QRS (fQRS) is a finding on the surface electrocardiogram (ECG), and it is associated with cardiac mortality and morbidity in various cardiac conditions (12, 13). Furthermore, fQRS was found to be associated with ventricular arrhythmias in patients with various cardiac disorders, such as chronic heart failure, hypertrophic cardiomyopathy, Brugada syndrome, and idiopathic ventricular fibrillation (14-17), but the association between fQRS and PVCs is not well studied.

In the present study, we aimed to demonstrate whether the presence of fQRS is associated with frequent PVCs on 24-hour Holter monitorings (HMs) in patients without overt structural heart disease.
Methods

Study population

We retrospectively evaluated 412 patients who underwent 24 hour HM due to complaints of palpitation in our hospital between August 2012 and February 2013. To exclude possible coronary artery disease (CAD), we did not evaluate and include the patients with complaints of chest pain and dyspnea. Patients with positive noninvasive stress tests were also not done. Among the evaluated 412 patients, 62 patients with missing ECGs, 26 patients with ischemic cardiomyopathy, 18 patients with bundle branch block, 11 patients with moderate to severe valvular disease, 8 patients with nonischemic cardiomyopathy, 4 patients with pacemaker activity, and 1 patient with hypertrophic cardiomyopathy were excluded from study. Finally, 282 patients were included in the study. Firstly, the patients were divided into 2 groups with respect to the presence of fQRS, and then, patients were divided into 3 groups with respect to frequency of PVCs, with groups 1, 2, and 3 representing seldom PVCs (<120 PVCs/day), moderate-frequency PVCs (120-720 PVCs/day), and frequent PVCs (>720 PVCs/day), respectively (18).

Patients’ medical history and baseline characteristics were extracted from the medical recordings. Hypertension (HTN), diabetes mellitus (DM), smoking, and family history of coronary artery disease (CAD) were noted. Body mass index (BMI) was calculated by using the standard formula [weight (kilogram)/height (meters)]^2. Baseline laboratory findings, including fasting plasma glucose (FPG), creatinine, potassium, hemoglobin (Hgb), leukocytes, thyroid-stimulating hormone (TSH), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and total cholesterol levels, were noted from the laboratory recordings obtained prior to HM. Glomerular filtration rate (eGFR) was measured using the standard Cockcroft-Gault formula.

Echocardiographic recordings (all of them were done with a Vivid 7, General Electric Vingmed, Horten, Norway) were evaluated, and ejection fraction (EF) (by Simpson method), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum (IVS) thickness in diastole, posterior wall (PW) thickness in diastole, and left atrium (LA) diameter in apical for chamber dimensions were noted. All echocardiographies in our institution were performed according to previous guidelines of the American Society of Echocardiography (19).

Electrocardiography

A 12-lead surface ECG was obtained from all patients before connecting the Holter device to the patient. The 12-lead ECGs (Nihon-KohdenCardiofax ECG1350K, Tokyo, Japan, filter range 0.5 Hz to 150 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV) were analyzed by 2 independent cardiologists who were blinded to the Holter data. fQRS was defined as the presence of different RSR’ patterns (QRS duration <120 ms), which included an additional R wave (R’ prime) or notching of the R wave or S wave, or the presence of more than one R’ prime without typical bundle branch block in two contiguous leads corresponding to a major coronary artery territory (12-14). ECGs were evaluated with the naked eye by two cardiologists, who were blinded to the Holter results for the presence of fQRS without using any magnification. The inter-observer concordance rate for determining fQRS was 98.5% between the two readers. In cases of disagreement, the final decision was made mutually.

Holter monitoring and interpretation

Holter devices (Universal resting 12-lead Holter dms 300-4A, mtm multitechmed gmbh, Schwarzwaldstrasse, Germany) were applied to the patient by our clinic’s nurse; the patient came back after 24 hours, and the nurse took off the device and uploaded the recordings to the Holter archive. Two independent cardiologists evaluated the recordings for PVCs, and the number of PVCs was recorded.

Statistical analysis

All statistical studies were carried out with the SPSS program (version 15.0, SPSS, Chicago, Illinois, USA). Quantitative variables were expressed as the mean value±SD, and qualitative variables were expressed as percentages (%). All measurements were evaluated with the Kolmogorov-Smirnov test. A comparison between two groups, according to the presence of fQRS, was performed using the student-t test. A comparison between three groups, according to the number of PVCs, was performed using one-way ANOVA and Tukey test for post-hoc analysis. Categorical variables were compared by the likelihood ratio χ^2 test or Fisher’s exact test. Multinomial logistic regression analysis, which included variables with p<0.1, was performed to identify independent predictors of PVC frequency. Age ≤65, increased left atrium diameter (≥35 mm), increased interventricular septum diameter (≥11 mm), male gender, DM, HT, family history, beta-blocker usage, and presence of fQRS were entered into the model. A p value <0.05 was considered statistically significant.

Results

In total, the study included 282 patients. Fragmented QRS was present in 98 (34.7%) of them. The baseline characteristics of the patients are shown in Table 1. There were no differences between the 2 groups (defined according to the presence of fQRS) with respect to gender, HTN, DM, BMI, and smoking status. Patients with fQRS were older (54.9±15.6 vs. 47.0±16.3, p<0.001) and more likely to be on aspirin therapy for primary prevention (28.6% vs. 10.4%, p<0.001) and β-blocker therapy (29.6% vs. 15.8%, p=0.007). The baseline laboratory findings, except TSH and FPG, were not different between the 2 groups. Patients with fQRS had higher TSH levels (2.3±1.6 vs. 1.8±1.3, p=0.016) and higher FPG levels (111.2±44.4 vs. 99.7±24.9, p=0.006) than patients without fQRS. Patients with fQRS had a larger left atrium (33.5±5.7 vs. 30.4±5.8, p=0.001) and thicker IVS (10.2±1.8 vs. 9.5±2.3, p=0.042) than patients without fQRS. Frequency of PVCs was significantly higher in patients with fQRS (27.6% vs.
7.6%, p<0.001). Moderate PVC was also higher in patients with fQRS (18.4% vs. 11.4%, p=0.012) when compared to the seldom PVC group.

In Table 2, we demonstrated the characteristics of the study population with respect to PVC frequency. There were no differences between the 3 groups with respect to gender, age, BMI, HTN, DM, smoking status, and family history of CAD. The EF was lower in groups 2 and 3 than in group 1 (p=0.007). Higher LVEDD measurements were present in group 3 than in groups 1 and 2 (p=0.003). The left atrium was larger in groups 2 and 3 than in group 1 (p=0.010). Creatinine was higher in group 3 than in group 1 (p=0.025), and eGFR was lower in group 3 than in group 1 (p=0.010). Creatinine was higher in group 3 than in group 1 (p=0.025), and eGFR was lower in group 3 than in group 1 (p=0.010). The percentage of patients with fQRS was significantly different between all 3 groups. While 65.9% of group 3 patients had fQRS, 46.2% and 26.2% of group 2 and group 1 patients had fQRS, respectively (p=0.001).

| Table 1. Baseline characteristics of study patients according to the presence of fragmented QRS |
|-----------------------------------------------|
| **Age, years** | **fQRS- (n=184)** | **fQRS+ (n=98)** | **P** |
| Gender, female, n (%) | 114 (62) | 50 (49) | 0.053 |
| BMI, kg/m² | 27.1±6.1 | 27.6±5.0 | 0.491 |
| Hypertension, n (%) | 53 (28.8) | 38 (39.2) | 0.077 |
| Diabetes mellitus, n (%) | 11.4 (21) | 19 (19) | 0.057 |
| Family CAD history, n (%) | 24 (13) | 24 (25) | 0.012* |
| Smoking, n (%) | 47 (25.5) | 22 (22.7) | 0.596 |
| Ejection fraction, % | 63.3±4.1 | 61.6±8.6 | 0.086 |
| LVEDD, mm | 42.7±4.7 | 44.1±4.7 | 0.067 |
| LVESD, mm | 28.0±5.0 | 28.6±4.1 | 0.495 |
| LAD, mm | 30.4±5.8 | 33.5±5.7 | 0.001* |
| IVSD, mm | 9.5±2.3 | 10.2±1.8 | 0.042 |
| LVPWD, mm | 9.7±1.8 | 10.2±2.4 | 0.131 |
| Potassium, mmol/L | 4.4±0.3 | 4.5±0.5 | 0.551 |
| FPG, mg/dL | 101.4±24.8 | 110.4±57.6 | 0.624 |
| Creatinine, mg/dL | 0.7±0.2 | 0.8±0.3 | 0.360 |
| eGFR, mL/min/1.73 m² | 102.4±27.2 | 93.8±29.0 | 0.013* |

| Table 2. Patient characteristics according to PVC frequency |
|-----------------------------------------------|
| **Group 1 (n=202)** | **Group 2 (n=39)** | **Group 3 (n=41)** | **P** |
| **PVC< (PVC  (PVC≥** |
| **Age, years** | 48.7±16.2 | 51±17.1 | 53.9±17.1 | 0.168 |
| **BMI, kg/m²** | 27.1±6.1 | 27.1±5.1 | 28.2±5.5 | 0.596 |
| **Fragmented QRS, n (%)** | 53 (26.2) | 18 (46.2) | 27 (65.9) | 0.001* |
| **Hypertension, n (%)** | 62 (30.7) | 13 (34.2) | 16 (39.0) | 0.563 |
| **Diabetes mellitus, n (%)** | 29 (%14.4) | 6 (15.8) | 5 (12.2) | 0.896 |
| **Smoking, n (%)** | 49 (24.3) | 12 (31.6) | 8 (19.5) | 0.453 |
| **Family history of CAD, n (%)** | 32 (15.8) | 7 (18.4) | 9 (22.5) | 0.579 |
| **Ejection fraction, %** | 63.5±4 | 60.6±6.3 | 60.8±7.3 | 0.007* |
| **LVEDD, mm** | 42.7±4.7 | 42.6±4.3 | 46.2±4.3 | 0.003* |
| **LVESD, mm** | 27.6±4.8 | 29.3±4.1 | 30±4.2 | 0.039* |
| **LVPWD, mm** | 9.8±1.8 | 9.5±2.9 | 10.7±2.2 | 0.089 |
| **IVSd, mm** | 9.7±2.1 | 9.7±2.3 | 10.3±1.9 | 0.475 |
| **LAD, mm** | 30.8±6 | 32.5±5.2 | 31.6±6 | 0.010* |
| **BB, n (%)** | 35 (17.4) | 10 (25.6) | 13 (31.7) | 0.085 |
| **ND-CCB, n (%)** | 14 (7.0) | 8 (20.5) | 8 (19.5) | 0.006* |
| **FPG, mg/dL** | 104.2±49.6 | 110.4±57.6 | 106.1±31.3 | 0.624 |
| **Creatinine, mg/dL** | 0.7±0.2 | 0.8±0.3 | 0.9±0.4 | 0.025* |
| **eGFR, mL/min/1.73 m²** | 102.4±27.2 | 93.8±29.0 | 86.2±25.0 | 0.013* |
| **Total cholesterol, mg/dL** | 204.2±39.6 | 240.2±122.4 | 215±29.2 | 0.079 |
| **Triglyceride, mg/dL** | 115.9±57.4 | 140.1±63.3 | 113.5±58 | 0.197 |
| **LDL-C, mg/dL** | 128.8±36.4 | 134.3±32.4 | 117.5±27.6 | 0.267 |
| **HDL-C, mg/dL** | 51±12 | 52±12 | 72±12 | 0.748 |
| **LDL-C, mg/dL** | 120/day) | 120-720/day) | 720/day) | 0.748 |
| **Triglyceride, mg/dL** | 115.9±57.4 | 140.1±63.3 | 113.5±58 | 0.197 |
| **LDL-C, mg/dL** | 128.8±36.4 | 134.3±32.4 | 117.5±27.6 | 0.267 |
| **HDL-C, mg/dL** | 52±12 | 47.2±8.4 | 53.7±11.5 | 0.262 |
| **Hemoglobin, g/dL** | 12.9±1.6 | 12.9±1.5 | 12.8±1.2 | 0.963 |
| **Leukocytes,10³/mm³** | 7.8±2.3 | 7.1±1.3 | 7.1±2.3 | 0.355 |
| **TSH, UI/mL** | 1.9±1.4 | 1.7±1.1 | 2.6±2.2 | 0.334 |
| **Potassium, mmol/L** | 4.4±0.3 | 4.5±0.5 | 4.4±0.4 | 0.551 |

*significant differences
†significant difference between groups
BB - beta-blocking agent; BMI - body mass index; eGFR - estimated glomerular filtration rate; FPG - fasting plasma glucose; HDL-C - high-density lipoprotein cholesterol; IVSd - interventricular septum end-diastolic diameter; LAD - left atrium diameter; LDL-C - low-density lipoprotein cholesterol; LVEDD - left ventricle end-diastolic diameter; LVEDD - left ventricle end-systolic diameter; LVFSd - left ventricular posterior wall end-diastolic thickness; ND-CCB - non-dihydropyridine calcium channel-blocking agent; PVC - premature ventricular contraction; TSH - thyroid-stimulating hormone
Table 3. Univariate and multivariate analyses for predictors of frequent premature ventricular contraction

| Variable                          | Univariate | Multivariate |
|-----------------------------------|------------|--------------|
|                                  | OR (95% CI) | P            | OR (95% CI) | P            |
| Age ≥65 years                     | 2.47 (1.21-5.05) | 0.013 | 4.24 (2.08-8.64) | 0.001 |
| GFR < 60 mL/min/1.73m²            | 1.98 (0.50-7.86) | 0.328 |          |          |
| Diabetes mellitus                 | 0.81 (0.29-2.21) | 0.679 |          |          |
| Family history                    | 1.49 (0.66-3.38) | 0.334 |          |          |
| Male gender                       | 1.36 (0.70-2.65) | 0.357 |          |          |
| CCB                               | 2.39 (0.98-5.81) | 0.054 |          |          |
| fQRS                              | 4.61 (2.28-9.32) | <0.001 | 2.11 (1.00-4.45) | 0.05 |

CCB - calcium channel blocker; CI - confidence interval; fQRS - fragmented QRS; GFR - glomerular filtration rate; OR - odds ratio

In the multinomial regression analysis, only age (odds ratio: 4.24, 95% confidence interval 2.08-8.64, p=0.001) and fQRS (odds ratio: 2.11, 95% confidence interval 1.00-4.45, p=0.05) were found as predictors of frequent PVCs on the HMs in this study (Table 3).

Table 4. Patient characteristics according to presence of fragmented QRS when hypertension, diabetes mellitus, and left ventricular hypertrophy are excluded

|                      | fQRS (-) (n=122) | fQRS (+) (n=49) | P      |
|----------------------|-------------------|-----------------|--------|
| Gender, male, n (%)  | 37 (30.3)         | 21 (42.9)       | 0.118  |
| Age, years           | 39.1±15.6         | 44.7±17.5       | 0.045* |
| BMI, kg/m²           | 25.1±5.8          | 25.4±4.8        | 0.757  |
| Smoking, n (%)       | 34 (27.9)         | 13 (27.1)       | 0.918  |
| Family history of CAD, n (%) | 14 (11.5) | 6 (12.5) | 0.852 |
| Ejection fraction, % | 63.7±3.0          | 63.2±4.8        | 0.588  |
| LVEDD, mm            | 41.7±4.1          | 43.0±4.9        | 0.133  |
| LVESD, mm            | 27.1±3.4          | 28.0±3.5        | 0.324  |
| LVPW, mm             | 8.8±1.4           | 8.9±1.0         | 0.720  |
| IVSd, mm             | 8.3±1.1           | 8.8±1.0         | 0.100  |
| FPG, mg/dL           | 89.9±11.2         | 92.6±10.1       | 0.318  |
| Creatinine, mg/dL    | 0.77±0.45         | 0.81±0.41       | 0.288  |
| Total cholesterol, mg/dL | 190.1±32.1     | 243.9±138.2     | 0.028* |
| Triglyceride, mg/dL  | 105.8±53.3        | 127.6±87.8      | 0.517* |
| LDL-C, mg/dL         | 120.9±33.1        | 126.8±21.6      | 0.480  |
| HDL-C, mg/dL         | 54.8±12.3         | 54.7±13.1       | 0.976  |
| Hemoglobin, g/dL     | 13.0±1.5          | 13.1±1.5        | 0.715  |
| TSH, UI/mL           | 1.77±1.04         | 2.08±0.96       | 0.073**|
| Frequent PVCs, n (%)  | 7 (5.7)           | 14 (28.6)       | <0.001*|

*significant differences

In Table 4, we show the baseline characteristics of the patients without hypertension, diabetes, and left ventricular hypertrophy. Fragmented QRS was also more prevalent in patients with frequent PVCs in these groups. While 7 (5.7%) of the 112 patients without fQRS had frequent PVCs, 14 (28.6%) of the 49 patients with fQRS had frequent PVCs. In this group, only fQRS was associated with frequent PVCs, as shown by univariate analysis (Table 5).

Table 5. Univariate analyses for risk factors of frequent premature ventricular contractions in patients without hypertension, diabetes, and left ventricular hypertrophy

| Variable                          | OR (95% CI) | P      |
|-----------------------------------|------------|--------|
| Age ≥45 years                     | 1.93 (0.77-4.85) | 0.159  |
| Male gender                       | 1.03 (0.39-2.71) | 0.952  |
| fQRS                              | 6.57 (2.45-17.56) | <0.001 |
| Smoking                           | 0.58 (0.18-1.82) | 0.351  |
| Family history                    | 1.95 (0.58-6.53) | 0.276  |
| Total cholesterol ≥200 mg/dL      | 1.31 (0.23-7.25) | 0.753  |

CI - confidence interval; fQRS - fragmented QRS; OR - odds ratio

In Table 4, we show the baseline characteristics of the patients without hypertension, diabetes, and left ventricular hypertrophy. Fragmented QRS was also more prevalent in patients with frequent PVCs in these groups. While 7 (5.7%) of the 112 patients without fQRS had frequent PVCs, 14 (28.6%) of the 49 patients with fQRS had frequent PVCs. In this group, only fQRS was associated with frequent PVCs, as shown by univariate analysis (Table 5).

**Discussion**

The main finding of the present study is that the presence of fQRS on surface ECG is related to frequent PVCs in patients without overt structural heart disease. We also found that patients with frequent PVCs have lower EF values and higher LV and LA dimensions. To our knowledge, this is the first study demonstrating the association between fQRS and PVC frequency.

Fragmentation of QRS complex can easily be detected by the naked eye, and growing evidence corroborates its role in various areas of cardiac manifestations. First of all, it was found to be associated with increased cardiac mortality and morbidity in patients with CAD (20), acute coronary syndromes (13, 21), and ischemic and nonischemic cardiomyopathy (22, 23). Secondly, fQRS was found to be associated with ventricular arrhythmias in various conditions, such as ischemic and nonischemic cardiomyopathy (23), hypertrophic cardiomyopathy (15), Brugada syndrome (24), acquired long QT syndrome (25), and arrhythmogenic right ventricular dysplasia (26, 27). Additionally, fQRS was found to be associated with the response to cardiac resynchronization therapy (28) and shock delivery from implanted devices (29).

Although the main causative mechanism of fQRS formation is not fully understood yet, myocardial fibrosis and/or ischemia is generally accepted as being responsible for fQRS formation through the altered homogeneity of myocardial electrical activity (30, 31). Really, studies with cardiac magnetic resonance imaging (MRI) (31, 32) and myocardial single-photon emission tomography (SPECT) (33) showed that fQRS was associated with myocardial scars and had higher sensitivity and specificity for detecting myocardial scars than Q wave. Myocardial scarring or fibrosis is not only developed by myocardial infarction or isch-
Hypertension and DM are major risk factors for CVD, and markers of early atherosclerosis (like carotid intima-media thickness), which may strengthen our findings.

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