INTRODUCTION

The term fragmented QRS (fQRS) represents the various RSR' patterns (≥1 R' or notching of S wave or R wave) in two contiguous leads corresponding to a major coronary artery territory.1 fQRS was found to be associated with lethal ventricular arrhythmias and sudden cardiac death.5,6 The reason for all the above-mentioned associations between fQRS and various cardiovascular diseases was found to be cardiac fibrosis.7 Additionally, heterogeneous activity of ischemic ventricle alters the ventricle depolarization and may be responsible for fQRS formation.8 It is reasonable to anticipate that these changes in the ventricle may influence the atrium and cause atrial arrhythmias. Indeed it was demonstrated that the fQRS was as predictor of the occurrence of post-operative atrial fibrillation (AF) in isolated coronary artery by-pass surgery.9

We hypothesized that presence of fQRS may be useful for predicting atrial arrhythmias, especially paroxysmal AF (PAF) which is the most common cardiac arrhythmia with important clinical implications.
METHODS

Study design: This was a prospective observational study. Study population: A total of 301 patients, who were referred for 24 h Holter ECG monitoring because of complaint of palpitation, at our institution between June 2012 and December 2012 were enrolled consecutively.

Pediatric Holters, pacemaker-dependent patients, patients with complete bundle branch block and patients with ongoing antiarrhythmic therapy, patients with thyroid disorders, patients with severe cardiac diseases including valvular disease, heart failure and cardiomyopathies were excluded. We also excluded the Holters which were performed to hospitalized patients. The study was carried out in accordance with Declaration of Helsinki principles and was approved by the Local Ethics Committee. Study protocol: The patients referred for 24 h Holter ECG monitoring were evaluated by a cardiologist before Holter evaluation. Each patient’s history and examination was collected by a cardiologist. We recorded the baseline characteristics, which included hypertension (HT), smoking status, diabetes mellitus (DM), family history of CAD, height and weight and medication.

Routine laboratory measurement, which were obtained after at least 8 h fasting, including glucose, creatinine, lipid profile, thyroid stimulating hormone (TSH) and hemogram were recorded. Basic echocardiography measurements including chamber diameters, wall thicknesses an ejection fraction (EF) obtained with Vivid 7 (GE Vingmed Ultrasound AS, Horten, Norway) according to the guidelines of the American Society of Echocardiography and recorded on echopacs. Electrocardiography: A 12 lead surface ECG was obtained from all patients before connecting the Holter device to the patient. This 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 cardiologist who were blinded to Holter data. fQRS was defined as presence of different RSR’ patterns (QRS duration <120 ms) which include 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. The inter-observer concordance rate for determining fQRS was 98.2% between two readers. In case of disagreement, the final decision was made mutually. We also evaluated the number of fQRS, because fragmentation in only one lead is not accepted as the presence of fQRS; we accepted as absence of fQRS if the number of fQRS was zero or one.

Holter monitoring and interpretation: Then two independent cardiologist evaluated the recordings for presence of any AF episodes. More than 3 consecutive QRS complexes without P wave and with irregular RR intervals was accepted as AF. The inter-observer concordance rate for determining AF episodes was 99.7% between two readers. If the device software defined AF or supraventricular arrhythmia these tracings were evaluated visually to confirm the presence of AF episodes.

Statistical analysis: All statistical studies were carried out with the program SPSS (version 15.0, SPSS, Chicago, Illinois, USA). Quantitative variables were expressed as the mean value ±SD or median (minimum-maximum), and qualitative variables were expressed as percentages (%). All measurements were evaluated with the Kolmogorov-Smirnov test. A comparison of parametric values between two groups, according to presence of fQRS, was performed using the Mann-Whitney U-test or student t test. The study population was divided into three groups based on fQRS number. Groups 1, 2 and 3 were defined as the presence of fQRS in 0 or 1 lead, in 2 or 3 leads, and in ≥4 leads in electrocardiogram, respectively. A comparison between these groups was performed using Kruskal-Wallis test and if there was significance, a Mann-Whitney U-test was used for post hoc analysis. Categorical variables were compared by the likelihood-ratio χ² test or Fisher’s exact test.

A backward stepwise multivariate logistic regression analysis which included variables with p < 0.1 was performed to identify independent predictors of AF episodes. Age ≥65, increase left atrium diameter (≥35 mm), increase interventricular septum diameter (≥11 mm), male gender, DM, HT, family history, beta-blocker treatment using and presence of fQRS were entered into the model. A p <0.05 (two-sided) was considered significant.

RESULTS

A total of 301 patients included in the study. fQRS was present in 103 patients. PAF episodes were seen in 31 patients. Baseline clinical characteristics are presented in Table-I. Patients with fQRS were older (p=0.001), with larger left atrium (LA) (p=0.001), with thicker interventricular septum (IVS) (p=0.032), more had DM and AF episodes (p<0.001) in comparison with patients without
fQRS. Differences with respect to number of fQRS lead are detailed in Table-II, while group 1 describing patient with 0 or 1 lead, group 2 with 2 or 3 leads and group 3 with > 3 leads with fQRS. Presence of AF episodes (p<0.001), age (p=0.001), beta-blocker use (p=0.016), fasting blood glucose levels (p=0.015), TSH levels (p=0.049) were found to be increased with raised numbers of fQRS. Table-III presents the dependent parameters for predicting AF episodes and Table-IV shows the independent predictors of AF episodes. Presence of fQRS, HT and DM were independent predictors of AF episodes in 24 h HM.

The area under the receiver operating characteristics (ROC) curve values for the presence of fQRS and number of fQRS to detect PAF on HM were 0.704 and 0.797 (Fig.1). Presence of fQRS had 74% sensitivity and 71% specificity for detecting PAF, the specificity was increased with the increased number of fQRS leads (91% for 3 leads and 98% for 4 leads) while the sensitivity was decreased (54% for 3 leads, 32% for 4 leads).

![ROC Curve](image)

**Fig.1:** The sensitivity and specificity of fQRS and number of fQRS for detecting PAF episodes in HM.

### Table-I: Baseline characteristics of the study population.

|                     | fQRS (-) (n=198) | fQRS (+) (n=103) | p      |
|---------------------|------------------|------------------|--------|
| Gender (male) (%)   | 36.9 (73)        | 48.5 (50)        | 0.051  |
| Age (years)         | 45.3±17.2        | 53.5±16.8        | <0.001 |
| BMI (kg/m²)         | 27.4±5.1         | 26.8±6.1         | 0.382  |
| Hypertension (%)    | 28.3 (36)        | 37.3 (38)        | 0.113  |
| Diabetes mellitus (%) | 10.6 (21)  | 19.8 (20)        | 0.029  |
| Smoking (%)         | 25.3 (50)        | 22.5 (23)        | 0.605  |
| Family history of CAD (%) | 12.1 (24)  | 23.8 (24)        | 0.010  |
| Previous MI (%)     | 2 (4)            | 2.9 (3)          | 0.693  |
| Ejection fraction (%) | 63.4±4.1     | 61.9±6.5         | 0.056  |
| LVEDD (mm)          | 42.6±4.6         | 43.9±4.9         | 0.082  |
| LVESD (mm)          | 28.1±4.9         | 28.5±4.2         | 0.499  |
| PWd (mm)            | 9.7±1.9          | 10.2±2.4         | 0.096  |
| IVSd (mm)           | 9.5±2.3          | 10.2±1.9         | 0.032  |
| LA (mm)             | 30.1±5.9         | 33.2±5.9         | 0.001  |
| BB (%)              | 15.7 (31)        | 29.1 (30)        | 0.006  |
| ND-CCB (%)          | 8.7 (17)         | 14.6 (15)        | 0.117  |
| FPG (mg/dL)         | 91 (70-196)      | 96.5 (73-359)    | 0.007  |
| Creatinin (mg/dL)   | 0.70(0.47-4.15)  | 0.75 (0.48-2.69) | 0.665  |
| Total cholesterol(mg/dL) | 200±37.3     | 223.6±91.8       | 0.078  |
| Triglyceride (mg/dL) | 92 (28-283)     | 113.5 (11-368)   | 0.063  |
| LDL-C (mg/dL)       | 126±37.0         | 127.7±31.9       | 0.831  |
| HDL-C (mg/dL)       | 51±12.5          | 51.8±11.8        | 0.965  |
| Hemoglobin (g/dL)   | 12.8±1.5         | 13.0±1.4         | 0.425  |
| Leukocytes (10³/mm³) | 7.5±2.1         | 7.5±2.3          | 0.928  |
| TSH                  | 1.50 (0.23-8.3)  | 1.89 (0.4-8.5)   | 0.101  |
| PAF episode (%)     | 4.1 (8)          | 22.3 (23)        | <0.001 |

BMI: Body mass index, MI: Myocardial infarction, LVEDD: Left ventricle end-diastolic diameter, LVESD: Left ventricle end-systolic diameter, PWd: Posterior wall end-diastolic thickness, ISDd: Interventricular septum end-diastolic diameter, LA: left atrium, BB: Beta blocking agent, ND-CCB: Non dihydropyridin calcium channel blocking agent, FPG: fasting plasma glucose, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TSH: thyroid stimulating hormone, PAF: Paroxysmal atrial fibrillation.
DISCUSSION

The main finding of our study is that presence of fQRS on 12 lead surfaces ECG is related with presence of PAF episodes in 24 h ambulatory HM. Additionally, increasing number of fQRS leads were also associated with increased presence of PAF episodes. To our knowledge this is the first study that demonstrates the relationship between fQRS and presence of PAF episodes in 24 h ECG monitoring. AF is most common cardiac rhythm disorder and it significantly increases mortality and morbidity.11 Mean catastrophic consequences of AF is stroke; the risk of stroke is 5 times higher in patient with non valvular AF than the general population.12 Because of these important clinical implications of AF,

| Variable                  | OR  | (% 95 CI) | P    |
|---------------------------|-----|-----------|------|
| Age ≥65 years             | 3.62 | (1.64-7.87) | 0.001 |
| LA ≥ 35 mm                | 3.55 | (1.39-9.04) | 0.008 |
| IVS ≥ 11 mm               | 4.75 | (1.83-12.3) | 0.001 |
| Hypertension              | 3.80 | (1.75-8.28) | 0.001 |
| Diabetes Mellitus         | 5.49 | (2.40-12.54) | 0.001 |
| Family history            | 3.61 | (1.59-8.20) | 0.002 |
| Male gender               | 0.52 | (0.24-1.11) | 0.094 |
| fQRS                      | 6.79 | (2.91-15.82) | 0.001 |

OR: Odds ratio, CI: Confidence Interval, LA: left atrium, IVS: interventricular septum, fQRS: fragmented QRS.

Table-II: Patient characteristics according to the number of leads with fragmented QRS.

| Number of leads with FQRS | 0-1 (n=198) | 2-3 (n=87) | >3 (n=16) | p    |
|---------------------------|-------------|-----------|----------|------|
| Gender (male) (%)         | 36.9        | 47.1      | 56.9     | 0.117|
| Age (years)               | 45.3±17.2*β | 53.2±17.0* | 55.2±15.8*β | 0.001|
| BMI (kg/m2)               | 26.7±6.1    | 27.2±4.9  | 28.4±    | 0.511|
| Hypertension (%)          | 28.3        | 37.2      | 37.5     | 0.284|
| Diabetes mellitus (%)     | 10.6        | 18.8      | 25       | 0.074|
| Smoking (%)               | 25.3 (50)   | 23.3 (20) | 18.8 (3) | 0.812|
| Family history of CAD (%) | 12.1 (24)*β | 22.4 (19)* | 31.3 (5) β | 0.023|
| Previs UMI (%)            | 2 (4)       | 2.3 (2)   | 6.3 (1)  | 0.559|
| Ejection fraction (%)     | 63.4±4.1    | 62.1±5.6  | 60.7±10.9| 0.127|
| LVESD (mm)                | 42.6±4.6    | 44.0±4.6  | 43.3±6.3 | 0.204|
| PWd (mm)                  | 28.0±4.9    | 28.3±3.7  | 29.6±6.4 | 0.586|
| IVSd (mm)                 | 9.6±1.8     | 10.0±2.4  | 11.3±2.1 | 0.053|
| LA (mm)                   | 30.1±5.9*   | 33.1±6.1* | 33.4±5.4 | 0.006|
| FPG (mg/dL)               | 8.7         | 13.8      | 18.8     | 0.247|
| Creatinin (mg/dL)         | 92 (70-205)* | 97 (73-221)* | 97 (81-359) | 0.015|
| Total cholesterol (mg/dL) | 95 (28-283) | 119 (11-368) | 92 (49-221) | 0.248|
| LDL-C (mg/dL)             | 126.3±37.0  | 129.7±31.3| 114.5±35.2| 0.560|
| HDL-C (mg/dL)             | 51.7±12.4   | 51.2±11.8 | 57.5±10.4 | 0.624|
| Hemoglobin (g/dL)         | 12.8±1.5    | 13.0±1.4  | 13.4±1.5 | 0.477|
| Leukocytes (10^3/mm3)     | 7.5±2.1     | 7.6±2.3   | 7.1±2.8  | 0.780|
| TSH                       | 1.50 (0.23-8.30)* | 2.05 (0.4-8.5)* | 1.94 (1.02-2.36) | 0.049|
| PAF episode (%)           | 4.1 (8)*    | 14.9(13)* β | 62.5 (10)* β | <0.001|

β: significantly difference between into groups BMI: Body mass index, MI: Myocardial infarction, LVEDD: Left ventricle end-diastolic diameter, LVESD: Left ventricle end-systolic diameter, PWd: Posterior wall end-diastolic thickness, ISDd: Interventricular septum end-diastolic diameter, LA: left atrium, BB: Beta blocking agent, ND-CCB: Non dihidropyridin calcium channel blocking agent, FPG: fasting plasma glucose, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TSH: thyroid situmulating hormone, PAF: Paroxysmal atrial fibrillation.
timely diagnosis and management is mandatory. The problem for diagnosing AF is that, it is not always symptomatic and not always detectable during examination or surface ECG due to its transient episodic nature. To detect PAF extended ECG monitoring is usually needed. Thirty seconds cut off for duration of PAF is used generally since it was first mentioned in the 2006 American Heart Association atrial fibrillation guidelines but this has been questioned nowadays, because it has been suggested that PAF episodes shorter than 30 sec may be indicator of longer episodes. These short episodes may become longer and finally may persist over time. Additionally, premature atrial contractions (PACs) detected by HM were found to be associated with recurrence of AF. In addition to PACs, other silent brief atrial tachyarrhythmias may result in increased stroke risk and finally may convert to clinically certain AF. As a consequence, it will not be wrong if we suggest that any brief atrial arrhythmia may predict future AF occurrences. Indeed longer rhythm monitoring showed that substantial proportion of patients, who were initially diagnosed as cryptogenic stroke, have AF episodes.

There are many causes of AF and it is beyond the scope in this paper to discuss all of them but there are some changes in atrium that cause AF, regardless of the cause. Initially electrical remodeling of atrium occurs and then anatomic remodeling occurs which include; patchy fibrosis, excessive collagen deposition, fatty infiltration and apoptosis, finally resulting in an enlarged atrium. In our study we found that fQRS, HT, and DM were independently associated with the presence of PAF. Male predominance was observed in our study but it was not statistically significant. Age is also important for developing AF, although our study included relatively young patients, patient with fQRS were significantly older: LA diameter was found to be associated with AF development. In our study, although they were in normal range, LA diameter was significantly higher in patients with fQRS. This finding suggests that fQRS is not only associated with ventricular abnormalities, but it may also be associated with atrial structural abnormalities that need further investigation. Interestingly, others found that fQRS was associated with left ventricular mass index in patients with HT, which may also be associated with LA enlargement and AF development. In accordance with this finding IVS diameter was significantly greater in patients with fQRS. Thyroid disorders were also associated with AF, although we excluded the patients with thyroid diseases, TSH levels were higher in patients with fQRS, but this was not significant.

Many studies have demonstrated a relationship between various cardiovascular diseases and fQRS. The presence of fQRS was found to be associated with adverse cardiac events including; mortality, lethal arrhythmia, sudden cardiac death in these studies. Main causative mechanisms were explained by myocardial fibrosis that is expressed on the ECG as fQRS. Magnetic resonance imaging and myocardial perfusion studies showed the value of fQRS for detecting myocardial fibrosis. Except for fibrosis, myocardial ischemia may also cause fQRS due to altered myocardial depolarization of the myocardium. Thirdly, some recent studies have demonstrated the role of inflammation for fQRS formation. So explaining the association between ventricular structural abnormalities, ventricular arrhythmias and fQRS is relatively easy. We could explain the association between fQRS and PAF as follows: fibrosis, ischemia, and/or inflammation alters both ventricular systolic and diastolic functions that results in elevated left ventricular end diastolic pressure (LVEDP) and this elevation in LVEDP reflects to the atrium and the atrium tries to adapt new condition and becomes vulnerable to arrhythmias.

Study limitations: Firstly, this study involves a relatively small number of patients. Secondly, we didn’t evaluate the patients with magnetic resonance imaging (MRI) or myocardial perfusion scintigraphy to detect the myocardial abnormalities attributable to fQRS. Thirdly, this is an observational study, further studies are needed to clarify whether the presence of fQRS is associated with clinical consequences of AF.

CONCLUSION

In conclusion, fQRS is a sign of structural (fibrosis) and functional (ischemia, inflammation) myocardial abnormality and independently associated with presence of PAF in HM. Presence of fQRS seems to be a useful marker to help decision making for extended rhythm monitoring and managing patients to reduce the AF-related complications.

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AT, EG, ÖG: Conceived, designed and did statistical analysis & editing of manuscript. AT, BA, AB, YZT, SO: Did data collection and manuscript writing. AÜY, TK, AB: Did review and final approval of manuscript. AT: Takes the responsibility and is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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