Significance of Fragmented QRS Complex in Acute Coronary Syndrome and its Correlation with Coronary Angiography to Identify the Culprit Lesion

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INTRODUCTION

The diagnosis of ST-elevation myocardial infarction (STEMI) has evolved a lot from electrocardiogram (ECG) to two-dimensional echocardiogram (2D echo/echo) to coronary angiogram (CAG) to comment on the culprit vessel involved in the MI. But still, the data are lacking in the correlation of non STEMI (NSTEMI) and the culprit vessel involved. In NSTEMI, there are ECG changes that may suggest that there is some ischemic activity going on in the heart but all are not very specific as compared to the STEMI. The researchers observed some slurring in the ECG in 1960. Investigators tried to correlate the same with the left ventricle (LV) dysfunction. It was Flowers et al., who first discovered the presence of fragmented QRS (fQRS) complex in the
patients who already had an MI. It was thus reported as a high-frequency component.\(^1\) According to Friedman et al., there are persistent changes in the Purkinje fibers and myocardial fibrosis that will slow down the myocardial activation which he analyzed in the canine heart with induced MI.\(^2\)

Varriale and Chryssos suggested that RSR’ complex unrelated to right bundle branch block or left bundle branch block could be associated with impaired depolarization within tissue surrounding the myocardial scar.\(^3\) It was de Luna who suggested that abnormalities in the second half of the QRS complex (i.e., terminal slurring, sometimes with R’ in lead V1) during MI might represent necrosis in late depolarized basal zones.\(^4\) It was Das et al. who defined the fQRS in 2006, as presence of an additional R-wave (R’i) or notching in the nadir of the S wave, or the presence of >1 R’i in 2 contiguous leads, corresponding to a major coronary artery territory on the resting 12-lead ECG with filter range 0.16-100 Hz, AC filter 60 Hz, paper speed 25 mm/s, and 10 mm/mV.\(^5\) As very little is known about this fQRS in NSTEMI, we planned to do a prospective study.

**MATERIALS AND METHODS**

**Aim**
- To document the fQRS in the ECG of the acute coronary syndrome (ACS) patients and to correlate with the coronary artery involved by doing CAG.
- To determine the culprit artery from the fQRS leads.

**Objectives**
- To identify the incidence of fQRS in the ACS (NSTEMI/UA).
- To identify the sensitivity and specificity of the fQRS in determining the culprit artery in ACS.
- fQRS complex in ECG correlation with the CAG to identify the culprit lesion in ACS patients.

**Hypothesis**
The incidence of fQRS is around 60% which is due to the scarring of the myocardium.\(^6\) It has a strong correlation in determining the culprit artery lesion.

**Inclusion Criteria**
- All patients with ACS undergoing CAG.

**Exclusion Criteria**
- All patients with bundle branch block.
- Patients not willing for CAG.

**Study Population**
- All the patients who were admitted to our hospital with chest pain, effort angina (EA), dyspnea, palpitation, with ECG changes fulfilling the inclusion criteria within the period of March 2014-October 2015 were included in the study.
- We studied the mode of presentation, past history such as diabetes mellitus (DM), hypertension (HTN), dyslipidemia (DLP), and peripheral vascular disease (PVD), and the family history of DM, HTN, DLP, coronary artery disease (CAD), as well as the habits like smoking and alcohol consumption.

The ECG changes in the various leads, like fQRS, ST-T changes (depression and inversion) were also recorded. These ECG changes were correlated with CAG to find out any relation between the two.
- This study was approved by the institutional ethics committee, and an informed consent was obtained from all enrolled patients.

**Outcome**
We recorded the ECG of all the patients who were admitted to the hospital on admission for CAG which was done within 24 h of admission. The ECG correlation was done with the CAG findings. No follow-up was done for the patients thereafter.

**Electrocardiography**
About 12-lead ECG was done in all the patients on admission as well as when the patient complains of chest pain. The ECG criteria for fQRS were met according to the definition by Das et al.\(^5\) The resting 12-lead ECG filter range: 0.15-100 Hz; AC filter, 60 Hz, 25 mm/s, and 10 mm/mV.

**Coronary Angiography**
CAG were analyzed by two experienced interventional cardiologists. CAG was either done by radial or femoral route by standard technique. Coronary stenosis ≥70% was considered as significant.

**Statistical Analysis**
The quantitative variables in the baseline data were expressed in mean ± standard deviation. Presenting complaints, past history, family history, ECG, 2D echo, and CAG findings were all divided into 2 groups, one group with fQRS and the other without fQRS. We used two-tailed Students t-test for comparing the continuous variables. Chi-square and fisher exact tests were done to compare the dichotomous data. Sensitivity, specificity,
likelihood ratio, and positive and negative predictive values (NPV) were recorded to evaluate the diagnostic value of fQRS complexes in each patient. To examine the influence of various clinical factors, logistic regression analysis was used by estimating the probability of fQRS occurrence on an ECG. Receiver operating characteristic curves were used to assess the relationship between fQRS complexes and ischemic T-wave inversion and ST segment depression for the diagnosis of NSTEMI. To identify the independent predictors of fQRS in various risk factors, CAG findings, step-wise multivariate logistic regression analyses were performed.

RESULTS

Study Patients
A total of 450 patients with NSTEMI were evaluated. Among them, 68.4% (308) were male and 31.6% (142) were females. fQRS complexes were identified in 230 patients (51.11%). The baseline characteristics of the patients were divided into fQRS (Group 1) and non-fQRS (Group 2) group. It was found that the EF and blood sugar levels (BSL) were found to be significant. Furthermore, patients with a history of chest pain, EA, dizziness, smokers and those with family history of systemic HTN were more likely to have fQRS. All other characteristics were insignificant.

Most of the patients presented with EA, i.e., 284, among which 156 were in fQRS group and 128 were in non-fQRS group. Chest pain was the next presenting complaint with 118 patients in fQRS group as compared to 80 patients in non-fQRS group. Rest of the patients presented with dyspnea (34 in fQRS vs. 28 in non-fQRS group), dyspnea on exertion (DOE) (58 in fQRS vs. 62 in non-fQRS group), and palpitation (28 in fQRS vs. 26 in non-fQRS group). The mode of the presentation was also studied according to the two groups. In which it was found that chest pain, EA, dizziness was found to be significant.

A total of 196 patients had HTN among which 96 were in fQRS group, whereas 100 were in non-fQRS group. Out of 188 patients who had DM, 106 were in fQRS whereas 82 were in non-fQRS group. DLP and PVD were equal in both the groups with 52 patients and 2 patients each, respectively. Among the past history nothing was statistically significant ($P = 0.427$). Family history of HTN, DM, DLP, and CAD was a more common in the fQRS group than non-fQRS group (16 vs. 6, 20 vs. 10, 4 vs. 2, and 48 vs. 32, respectively). Family history of HTN was found to be significant ($P = 0.038$) in the fQRS group. Smoking and alcohol intake was also more common in the fQRS group. Among personal history smoking and alcohol intake was also more common in the fQRS group, but smoking was found to be significant ($P = 0.0001$).

Cardiac biomarkers like troponin I and CKMB were not only elevated in the fQRS group than non-fQRS group (44 vs. 22 and 16 vs. 0, respectively) but was also found to be significant ($P = 0.001/0.0001$). Mitral regurgitation (MR) was found to be more in non-fQRS group and was also found to be significant ($P = 0.029$). LV hypertrophy though more in non-fQRS group but was non-significant. Among the 450 patients, 4 patients were found to have elevated JVP and presence of S3 which was also statistically insignificant ($P = 0.438$).

Regional wall motion abnormality (RWMA) was more in the fQRS group than in the non-fQRS group and was found to be significant in the anterior ($P = 0.007$) as well as inferior group ($P = 0.023$).

ECG correlation was done. In this ST depression in the anterior leads was found to be significant ($P = 0.003$), T-wave inversion in the lateral lead was found significant ($P = 0.0001$) in the fQRS group.

CAG was done in all the patients who were also found to be significant in all the coronaries except for left main coronary artery. Right coronary artery (RCA) was the most commonly involved artery (176) followed by left anterior descending (LAD) artery (172), followed by left circumflex artery (LCX) (130). And which was seen to be quite significant in the fQRS versus non-fQRS group.

In addition, non-fQRS group was more commonly associated with ectatic coronaries, normal coronaries, and minor CAD. Whereas fQRS group was more commonly associated with single vessel disease, double vessel disease (DVD) and triple vessel disease (TVD).

Similarly, the sensitivity, specificity, positive predictive value (PPV), NPV, likelihood ratio was calculated. The sensitivity of fQRS with CAG was 63.24 as compared to fQRS with ST status (52.23%) and fQRS with T status (58.87). The specificity of fQRS with CAG was again higher (83.05) as compared to the both.

On comparing individually fQRS in the various leads with the CAG corresponding vessels, it was found that the sensitivity of fQRS in the inferior leads in ECG with RCA lesion in CAG was highest with 59.69. Moreover, the specificity was the highest in fQRS in the anterior leads with LAD in CAG group (96.74) followed by fQRS in lateral leads in ECG with LCX in CAG (94.35).

The sensitivity and specificity of ST depression and T-wave inversion in various leads corresponding to their
CAG vessels were very low as compared to the fQRS group.

DISCUSSION

Ventricular depolarization (QRS complex) and ventricular repolarization (ST-T wave) changes are easily, quickly and less expensively detected on the ECG. Therefore, any changes in the ECG can be easily dealt with. Among the 450 patients who had NSTEMI, 68% were male whereas 32% were females. The patients in fQRS group in the present study had a higher mean age as compared to non-fQRS, but this was not statically significant (0.475). However, Cetin et al. Guo et al., and Dabbagh Kakhki et al. found the association of age with fQRS as significant. Probably because of this contradiction age may not be playing a significant role. The fQRS was found in 51% patients. In other studies, like Guo et al. fQRS was 60% whereas in another study by Li et al. fQRS was 56% which is almost comparable to our study. The most common mode of presentation in fQRS group was EA, followed by chest pain as compared to the non-fQRS group, which was very significant. Rest all the modes such as dyspnea (P = 0.57), DOE (P = 0.477), and palpitations (P = 0.0908) were not statistically significant. As we know that the fQRS complex is normally formed when there is scarring of the myocardium, but having angina is an indication of ongoing ischemia or still viable myocardium which should be dealt with more aggressively in order to prevent the further LV dysfunction. Past history of HTN, DM, and DLP was insignificant in both the groups. Although we know that the presence of these risk factors leads to CAD, here these risk factors are insignificant in both the groups, similar to the study by Li et al. The findings by Guo et al. and Dabbagh Kakhki et al. contrary to ours have significant DM patients in the fQRS group. In our study, the family history of HTN was insignificant which was not sought out in the studies like Li et al. and Guo et al. In our study, smoking was found to be significant in the fQRS group. Dabbagh Kakhki et al. also report increased incidence of smoking in their positive fQRS group. As we all know that smoking itself leads to atherosclerosis, this might be one of the reasons that the more smokers have more fQRS as well as more severe CAD. In Guo et al. study, it was tobacco they have compared, rather than smoking. According to Guo et al., tobacco was not significant in their findings. According to our study, alcohol consumption was not found to be significant (P = 0.052).

Very few patients presented in our study with raised JVP and S3, which was again clinically insignificant (P = 0.70). On comparing the fQRS and the non-fQRS groups, it was found that differences in EF and BSL were statistically significant. The patients in the fQRS group had a wide variation in the EF, i.e., 58.67 ± 12.92 as compared to the non-fQRS group. The patients in fQRS group had low EF as compared to the non fQRS group. The reduced EF is due to more severe disease in the fQRS group as seen by CAG. This may need further evaluation. Dabbagh Kakhki et al. also report a reduction of resting ejection fraction using the myocardial perfusion imaging studies. Abdelrehman, Cheema et al., Korhonen et al., Li et al., and Yan et al. have also reported reduced LV function in patients with fQRS.

Similarly, BSL variation was more in the fQRS group. Probably a better regulation of glucose levels may lead to improved outcomes. The association of fQRS with elevated BSL was also seen in the study by Çetin et al. The association of elevated BSL was significant (P = 0.006) in our study, but it was not significant in the study by Cetin et al. Rest of the other baseline characteristics were similar in both the group.

The cardiac enzymes were raised in the fQRS group which suggests the ongoing ischemia and was significant, similar to the Çetin et al. In Guo et al. study, troponin T-value is not very significant (P = 0.049), which was contrary to our results. This could be explained by the ongoing ischemia or chest pain in the patients in our study, which has not been mentioned in the other studies.

The percentage of MR was seen to be less in the fQRS group as compared to non-fQRS group which could not be explained. Abdelrehman has also reported a higher incidence of MR. We thought that the EF in the fQRS group was more variable and low as compared to the non-fQRS group, so the MR, if its ischemic should be more in the fQRS group, which was opposite to our prediction. As we had taken into account even the mild MR, we do not know who were the patients who previously had MR, so could be explained on that basis only.

Coming to ECG findings, patients with fQRS had associated findings like ST flattening, depression and T inversion in the anterior, inferior as well as lateral leads. ST depression in anterior leads (P = 0.003) and T inversion in lateral leads (P = 0.0001) in fQRS group was found to be significant. However, ST depression in inferior and lateral leads and T inversion in anterior and inferior leads were not significant. Guo et al. reported that specificity of fQRS complexes in identifying lesions in the left circumflex and RCA was lower for the inferior and lateral leads. These ECG findings had sensitivity of 52.23% for ST depression and 58.87% for T inversion. Das et al. report a sensitivity of 50% for fQRS in NSTEMI patients.
The patients with fQRS also had significant elevations of cardiac biomarkers like troponin and CKMB, and these elevations were highly significant indicating ongoing cardiac injury needing appropriate cardiac intervention.

Echocardiography findings of patients with fQRS showed significant association of RWMA of the anterior and inferior wall, whereas the RWMA involving posterior and lateral wall did not reach significance in the current study. Overall, 74% of patients in the current study showed RWMA ($P = 0.0001$) and this finding was significant. The patients with fQRS had reduction in basal EF as discussed before. The incidence of MR was less in our study. As echocardiography is easily available in most of the hospitals, this association of fQRS with RWMA is useful for evaluating patients non-invasively.

All patients in the current study underwent CAG. Patients with fQRS positivity had significant associations with lesions involving LAD, LCX, RAMUS, and RCA. Out of 230 patients with positive fQRS, 210 (91.3%) patients showed significant CAG lesions ($P = 0.0001$) with an OR of 8.43 (4.96-14.33). Whereas in the negative fQRS group of 220 patients, 122 (73.7%) patients showed significant CAG findings which is consistent with the Abdelrahman study.

Patients with normal coronaries or minor CAD had lower incidence of fQRS ($P = 0.0001$) which was also significant. In our study, patients with fQRS had higher incidence of DVD ($P = 0.0001$) and TVD ($P = 0.0001$) which was consistent with the findings in the study by Guo et al. and Li et al.

In fQRS group, the most common artery involved was RCA with 76.5% followed by LAD with 74.4% and then LCX with 56.5% which is comparable to study by Abdelrahman. The association of positive fQRS with significant CAG lesions had higher sensitivity of 63.24%, as compared to the association of fQRS with ST depression (52.63%) and T-wave inversion (58.87%). Furthermore, the association of positive fQRS with significant CAG lesions had more specificity (83.05%) with a PPV of 91.30 as compared to fQRS with ST depression and T inversion. Dabbagh Kakhki et al. report a sensitivity of 78% and specificity of 65% using myocardial perfusion scan imaging. On comparing fQRS in each ECG leads territory with corresponding CAG lesions, it was found that the association of fQRS in anterior leads was highly specific for LAD lesion with a specificity of 96.74% whereas fQRS in inferior leads was associated RCA lesions with a high sensitivity of 59.69% along with a specificity of 84.38%. Similarly, the association of fQRS in lateral ECG leads was associated LCX lesions in CAG with a high specificity of 94.35%. Dabbagh Kakhki et al. report a sensitivity and specificity of 52% and 87% for LAD lesions, 51% and 77% for RCA lesions and 15% and 96% for LCX lesions, respectively, with the myocardial perfusion imaging studies (Tables 1-7).

Table 1: Baseline clinical data

<table>
<thead>
<tr>
<th>Variable</th>
<th>fQRS +ve (230)</th>
<th>fQRS –ve (220)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.22±8.80</td>
<td>58.56±10.56</td>
<td>0.475</td>
</tr>
<tr>
<td>SBP</td>
<td>133.50±26.37</td>
<td>134.77±22.34</td>
<td>0.583</td>
</tr>
<tr>
<td>DBP</td>
<td>79.14±12.81</td>
<td>80.15±9.30</td>
<td>0.343</td>
</tr>
<tr>
<td>Pulse</td>
<td>76.28±12.99</td>
<td>75.25±13.66</td>
<td>0.416</td>
</tr>
<tr>
<td>EF</td>
<td>58.67±12.92</td>
<td>63.00±9.66</td>
<td>0.000</td>
</tr>
<tr>
<td>HB</td>
<td>11.91±3.39</td>
<td>12.23±3.54</td>
<td>0.321</td>
</tr>
<tr>
<td>BSL</td>
<td>101.41±89.85</td>
<td>79.53±77.15</td>
<td>0.006*</td>
</tr>
<tr>
<td>Total CHS</td>
<td>155.43±78.42</td>
<td>166.61±29.26</td>
<td>0.517</td>
</tr>
<tr>
<td>HDL</td>
<td>33.30±15.70</td>
<td>38.0±14.22</td>
<td>0.117</td>
</tr>
<tr>
<td>LDL</td>
<td>106.03±61.26</td>
<td>107.4±59.70</td>
<td>0.978*</td>
</tr>
<tr>
<td>TGL</td>
<td>95.39±51.96</td>
<td>101.52±71.33</td>
<td>0.967*</td>
</tr>
</tbody>
</table>

*Fisher exact test, Chi-square test is used for find out the association between two categorical variables. HTN: Hypertension, DM: Diabetes mellitus, DLP: Dyslipidemia, PVD: Peripheral vascular disease, CHS: Complete heart syndrome, BSL: Blood sugar level, EF: Ejection fraction, BSL: Blood sugar level, HDL: High density lipoprotein, LDL: Low-density lipoprotein, TGL: Triglyceride, fQRS: Fragmented QRS

Table 2: Presenting symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>fQRS +ve (230)</th>
<th>fQRS –ve (220)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>118 (51.3)</td>
<td>80 (36.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>34 (14.7)</td>
<td>28 (12.7)</td>
<td>0.527</td>
</tr>
<tr>
<td>AOE</td>
<td>156 (67.8)</td>
<td>128 (58.2)</td>
<td>0.034</td>
</tr>
<tr>
<td>DOE</td>
<td>58 (25.2)</td>
<td>62 (28.2)</td>
<td>0.477</td>
</tr>
<tr>
<td>Palpitation</td>
<td>28 (12.1)</td>
<td>26 (11.8)</td>
<td>0.908</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (2.6)</td>
<td>0 (0)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Other</td>
<td>6 (2.6)</td>
<td>0 (0)</td>
<td>0.016*</td>
</tr>
</tbody>
</table>

*Fisher exact test used, AOE: Angina on exertion, DOE: Dyspnea on exertion, fQRS: Fragmented QRS

Table 3: Past/family/personal history

<table>
<thead>
<tr>
<th>History</th>
<th>fQRS +ve (230)</th>
<th>fQRS –ve (220)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>96 (41.7)</td>
<td>100 (45.4)</td>
<td>0.427</td>
</tr>
<tr>
<td>DM</td>
<td>106 (46.1)</td>
<td>82 (37.2)</td>
<td>0.058</td>
</tr>
<tr>
<td>DLP</td>
<td>52 (22.6)</td>
<td>52 (23.6)</td>
<td>0.769</td>
</tr>
<tr>
<td>PVD</td>
<td>2 (0.86)</td>
<td>2 (0.90)</td>
<td>0.864*</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>16 (7.9)</td>
<td>6 (2.7)</td>
<td>0.038</td>
</tr>
<tr>
<td>DM</td>
<td>20 (8.6)</td>
<td>10 (4.5)</td>
<td>0.078</td>
</tr>
<tr>
<td>DLP</td>
<td>4 (1.7)</td>
<td>2 (0.90)</td>
<td>0.438*</td>
</tr>
<tr>
<td>CAD</td>
<td>48 (20.8)</td>
<td>32 (14.5)</td>
<td>0.079</td>
</tr>
<tr>
<td>Personal history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>smoking</td>
<td>66 (28.6)</td>
<td>32 (14.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Alcohol</td>
<td>12 (5.2)</td>
<td>4 (1.8)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

*Fisher exact test, Chi-square test is used for find out the association between two categorical variables. HTN: Hypertension, DM: Diabetes mellitus, DLP: Dyslipidemia, CAD: Coronary artery disease, PVD: Peripheral vascular disease, fQRS: Fragmented QRS
CONCLUSION

fQRS in NSTEMI has not been well established in day to day practice. In our study, we tried to establish the relationship between fQRS and the culprit vessel by CAG. We found that fQRS is seen in patients with significant lesions (DVD, TVD) on CAG as compared to patients with negative fQRS. The presence of fQRS is a predictor of coronary lesions with high sensitivity and specificity. We also found that patients with fQRS had higher BSL which were statistically significant. It was also found that Smokers had more fQRS as compared with the nonsmokers. Thus, we conclude that fQRS analysis can help in better evaluation of patients with NSTEMI.

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