Fragmented QRS complex is an independent predictor of plaque burden in patients at intermediate risk of coronary artery disease

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**Abstract**

**Objective:** We aimed to evaluate the relationship between fragmented QRS complex and plaque burden in patients presented with typical chest pain and deemed to have intermediate pretest probability of CAD using coronary computed tomography angiography (CCTA).

**Methods:** We studied electrocardiograms (ECGs) obtained from 172 subjects (47.5 ± 9.5 years, 125 were men) presented with chest pain and had intermediate pretest probability for CAD. The presence was found and evaluation of CAD was performed with CCTA.

**Results:** Seventy four (43%) of the study cohort had CCTA-documented CAD. Meanwhile the frequency of fQRS in our cohort was (57%). 70 (71.4%) patients with fQRS had CAD compared with only 4 (5.4%) patients without fQRS (p < 0.001). The number of leads with fQRs was correlated with the calcium score (p < 0.005), segment stenosis score, segment involvement score, total plaque score (TPS), and E/e ratio (p < 0.001, for all). Multivariate analysis demonstrated that fQRS was a strong independent predictor for CAD (β = 2.15, p < 0.001). ROC analysis showed that the number of leads with fQRS was the optimal number for predicting CAD (AUC = 0.89, sensitivity 88%, and specificity 83%, p < 0.001).

**Conclusion:** Fragmented QRS was seen more often in patients with high plaque burden. We suggest that fQRS might provide a useful noninvasive prognosticator for subjects with intermediate pretest probability of CAD for further investigation.

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1. Introduction

Usually, it is accepted to recommend noninvasive testing in evaluation of subjects, who are complaining of chest and have intermediate pretest probability of coronary artery disease (CAD). Yet, a considerable percentage of those patients had a normal or equivocal results. Furthermore, more than 95% of them have a favorable outcome along 2 years of follow-up, in spite of them having intermediate pretest probability of CAD.

Das et al. reported that the presence of fQRS complex in subjects with CAD was attributed to myocardial scaring, which resulted in delayed ventricular conduction, and they reported that fQRS has emerged as an independent predictor for major adverse cardiovascular events in individuals with CAD.

Coronary computed tomography angiography (CCTA) is a noninvasive test, which has a good image quality with high specificity and negative predictive significance in detecting coronary artery stenosis.

However, the significance of fQRS in patients with chest pain, who have intermediate pretest probability of CAD, is not clearly evaluated. We hypothesize that the presence of fQRS could be associated with coronary plaque burden in patients with chest pain and have intermediate pretest probability for CAD. Herein, we aimed to investigate the presence of fQRS and its relation to plaque burden in patients presented with chest pain and had intermediate pretest probability of CAD using CCTA.

2. Subjects and methods

About 172 subjects who presented with chest pain and had intermediate pretest probability for CAD were included in a prospective study.

2.1. Evaluation of the pretest probability of CAD

We categorized chest pain based on the following: Substernal or not; relation to exertion; duration of chest pain; relief within...
10 min with rest or with nitroglycerin). Then, chest pain was classified into: a) typical angina = the three described criteria, b) atypical angina = any two criteria of the three, and c) nonanginal pain = chest pain with one or none of the three criteria. The pretest probability of CAD was categorized with respect to age, sex, and character of chest pain into three categories: low pretest probability (10–20%), moderate (20%–50%), and high pretest probability (50%–90%). Exclusion criteria included previous myocardial infarction, coronary artery bypass grafting, resting or exercise electrocardiographic CAD, previous coronary stenting, extensive coronary artery calcification, significant arrhythmias, chronic liver disease, congenital/valvular heart disease. Patients with ejection fraction <50%, wall motion abnormalities, asthma allergy to contrast material, and those with serum creatinine ≥2.0 mg/dl were also excluded.

Morphological assessment was performed for coronary artery plaque distribution, a segment involvement score was assigned a score of 1, 26% extent. Each individual coronary segment was graded as having no vessel lumen, which was clearly distinguished from the lumen and adjacent pericardial fat tissue.

We acknowledged the following subsets of coronary artery stenosis for each segment: 1) no obstruction, 2) mild CAD (<25% stenosis), 3) moderate (25%–<50% luminal stenosis), 4) moderately severe stenosis (50–70%), and 5) severe stenosis (luminal obstruction >70%). For each segment, plaque was described as calcified plaque (>130 HU), noncalcified plaque (<130 HU), or mixed plaque.

The clinical coronary artery plaque scores were obtained. The SSS was calculated as a measure of overall coronary artery plaque extent. Each individual coronary segment was graded as having no to severe plaque (i.e., scores from 0 to 3) based on the extent of obstruction of coronary luminal diameter. The total plaque score was obtained by summation of the extent scores of all 16 individual segments (a total score ranging from 0 to 48). To assess the overall coronary artery plaque distribution, a segment involvement score (SIS) was considered. The SIS was calculated with the sum of the number of segments with coronary artery disease, ranging from 0 to 16. For severity classification, as regards the diameter stenosis: normal or no stenosis was assigned a score of 0, 1%–25% stenosis was assigned a score of 1, 26%–50% stenosis was assigned a score of 2, 51%–70% stenosis was assigned a score 3, 71%–99% stenosis was assigned a score of 4 and a score 5 for total occlusion.16–19

2.5. Statistical analysis

Study variables were continuous variables (mean ± standard deviation) and categorical variables (percentages). The analysis of covariance was used to compare groups adjusted for sex, age, and hypertension, with log-transformed variables for nonnormally distributed variables. The correlation analysis was performed with Spearman’s correlation methods. Multivariable logistic regression analysis was performed to assess independent variables that predict obstructive CAD. Receiver operating characteristic (ROC) curve analysis was used to investigate the optimal number of leads with fQRS to predict obstructive CAD in subjects with intermediate pretest probability for CAD. The SPSS 18.0 (Chicago, IL, USA) was utilized for statistical analysis.

3. Results

One hundred seventy two subjects (125 males and 47 females, mean age of 47.5 ± 9.5 years) were enrolled. CCTA evidence of any obstructive CAD was present in 74 (43%). The calcified or mixed coronary artery plaque was observed in 49 (66%), while the noncalcified plaques were found in 25 (34%). Among the vessels with coronary artery stenosis >50%, 42 (56.7%) had single vessel disease, 25 (33.8%) had two vessel disease, and 7 (9.5%) had three vessel disease. The total plaque score (TPS) was 8.2 ± 4.1, SSS was 79.7 ± 44, and the SIS was 5.6 ± 2.5, while, the CACS was 292 ± 261 (Table 1). Data analysis showed that out of the 172 subjects enrolled for the study, fQRS were detected in 98 (57%) patients. Table 2 shows a comparison between patients with fQRS and those without fQRS. All the demographic data were comparable among subjects with and without fQRS except smoking habit (p < 0.01), LDL-cholesterol (p < 0.05), and hs-CRP (p < 0.01), which were higher in those with fQRS. In addition, left ventricular filling pressure (E/e') was significantly increased in patients with positive fQRS (p < 0.001). Importantly, patients with fQRS had a higher prevalence of CAD than those without CAD (71.4% vs 5.4%, p < 0.001), Fig. 1. We found that the number of leads with fQRS was positively correlated with SSS (r = 0.581, p < 0.001) Fig. 2, SIS (r = 0.460, p = 0.001), and total plaque score (TPS) (r = 0.293, p = 0.01), Table 3. Furthermore, fQRS was significantly correlated with E/e' ratio.
showed that male gender (Fig. 3).

A comparison between patients with those without fragmented QRS.

Table 2

| Variable                                    | n (98)       | n (74)    | p value |
|---------------------------------------------|--------------|-----------|---------|
| Age (years)                                 | 47.9 ± 9.8   | 47.2 ± 8.3| 0.38    |
| Male n (%)                                  | 125 (73%)    | 47.2      | 0.005   |
| Body mass index (kg/m²)                     | 24.9 ± 4.7   | 24.3 ± 3.8| 0.25    |
| Hypertension                                | 59 (60%)     | 42 (57%)  | 0.47    |
| Diabetes mellitus n (%)                     | 26 (27.3%)   | 22 (21%)  | 0.13    |
| Family history of CAD n (%)                 | 20 (21%)     | 17 (23%)  | 0.21    |
| Smokers n (%)                               | 59 (60%)     | 27 (26%)  | <0.05   |
| Total cholesterol (mg/dL)                   | 199 ± 59     | 185 ± 36  | 0.35    |
| LDL-cholesterol (mg/dL)                     | 145 ± 28     | 99 ± 35   | <0.05   |
| HDL-cholesterol (mg/dL)                     | 42 ± 9       | 47 ± 11   | 0.19    |
| hs-CRP (mg/L)                               | 4.3 ± 1.1    | 1.4 ± 1.07| <0.01   |
| Triglycerides (mg/dL)                       | 155 ± 65     | 143 ± 52  | 0.09    |
| Ejection fraction%                          | 69 ± 8       | 66 ± 8    | >0.05   |
| E/e' value                                  | 9.8 ± 1.2    | 5.1 ± 0.6 | <0.01   |
| Myocardial ischemia on CTA: n (%)          | 70 (71.4%)   | 4 (5.4%)  | <0.001  |

CCTA: Coronary computed tomography angiography.

(p < 0.001) as a marker of diastolic filling pressure and diastolic function of the left ventricle (Fig. 3).

Univariate Cox proportional hazards regression analyses showed that male gender (p < 0.01), smoking (p < 0.05), LDL-C (p < 0.03), hs-CRP (p < 0.01), E/e' ratio (<0.03), and number of leads with fQRS (p < 0.001) were significantly associated with CAD on CCTA. While, with multivariate Cox proportional hazards regression analysis, the number of leads with fQRS was the strongest independent predictor for coronary plaque burden in subjects with chest pain, who had intermediate pretest probability of CAD (Fig. 1). Interestingly, when the cut-off number of leads set at ≥ 3 leads, we might predict the presence of CAD. Furthermore, we observed that patients with fQRS had a higher values of hs-CRP and LDL-cholesterol, in spite of comparable others with cardiovascular risks factors among both groups. These findings suggest that systemic inflammatory changes, in association with high LDL-cholesterol, have a significant impact on the development of ischemic changes that initiate a process of fibrosis, scarring, and consequently ventricular electrical aberration conduction abnormalities, which resulted in QRS fragmentation.18

4. Discussion

We found a higher incidence of fQRS in subjects with any CCTA evidence of CAD, compared with those without CCTA evidence of CAD. We investigated the cut-off number of leads with fQRS for prediction of the presence of CAD in the setting of intermediate pretest probability for CAD. Interestingly, when the cut-off number of leads set at ≥ 3 leads, we might predict the presence of CAD. Furthermore, we observed that patients with fQRS had a higher values of hs-CRP and LDL-cholesterol, in spite of comparable others with cardiovascular risks factors among both groups. These findings suggest that systemic inflammatory changes, in association with high LDL-cholesterol, have a significant impact on the development of ischemic changes that initiate a process of fibrosis, scarring, and consequently ventricular electrical aberration conduction abnormalities, which resulted in QRS fragmentation.18
We found an obvious higher prevalence (57%) of fQRS in our cohort. Oner, et al.\textsuperscript{19} found that 26.1% of patients with metabolic syndrome had fQRS. Moreover, Terho, et al.\textsuperscript{20} demonstrated that 21.9% of patients with acute myocardial infarction had fQRS complexes, while, the prevalence was 60% in patients with chronic renal failure as reported by Adar, et al.\textsuperscript{21} The different percentages among different studies and ours might be attributed to ethnicity or due to small sample volume enrolled in our study.

Notably, the detection of any CAD in individuals without known CAD, who have an intermediate pretest probability of CAD, is of critical importance. Revealing and evaluation of high-risk atherosclerotic plaque by assessing coronary artery calcium score and coronary plaque burden with coronary computed tomographic angiography has a significant impact in clinical practice. This might increase the efficiency of diagnosis of significant coronary stenosis in the assessment of acute chest pain.\textsuperscript{22} Nonetheless, it is a costly test and not available universally. This gives a value for easily applicable and less costly tests, like fQRS complex on surface ECG for risk stratiﬁcation of subjects presented with chest pain and have an intermediate pretest probability for CAD and to avoid the need for more costly and invasive procedures. Hence, in our study we tried to ﬁnd any relation between the presence of fQRS complex and coronary CT angiography ﬁndings in subjects presented with chest pain and have an intermediate pretest probability of CAD.

A lot of studies had demonstrated that fQRS is an independent predictor of impaired myocardial perfusion, cardiac remodeling, and reduced left ventricular ejection fraction in patients with coronary heart disease and is strongly correlated with unfavorable events\textsuperscript{23-25}.

Another interesting aspect in the current study is that, patients with fQRS had impaired left ventricular diastolic function evidenced by increased E/e’ ratio, in spite of normal ejection fraction and mitral E/A ratio on conventional echo-Doppler assessment. The association between fQRS, atherosclerosis, and diastolic dysfunction may be explained by the presence of CAD in our cohort. A probable cause of the relationship between fQRS and diastolic function could be myocardial remodeling and ﬁbrosis due to CAD causing both diastolic dysfunction and inhomogeneous myocardial activation.\textsuperscript{26,27} Furthermore, previous investigators had found that\textsuperscript{19,28} the existence of fQRS was signiﬁcantly associated with subclinical LV dysfunction.

Few previous studies tried to introduce a set of ﬁndings that help in risk stratiﬁcation of patients with chest pain and have an

| Variable                        | $r$     | $p$ value |
|--------------------------------|---------|-----------|
| Low-density lipoprotein-C       | 0.249   | <0.03     |
| High-sensitivity C-reactive protein | 0.315  | <0.005    |
| E/e’                           | 0.425   | <0.001    |
| Calcium score                  | 0.328   | $p < 0.005$ |
| Segment stenosis score         | 0.374   | <0.001    |
| Segment involvement score      | 0.460   | <0.001    |
| The total plaque score         | 0.293   | <0.01     |

**Table 3**
Correlation analysis of fQRS complex and other variable in patients with CAD in the study cohort.

![Fig. 3. Correlation between number of fQRS and left ventricular filling [E/e’] in patients with coronary artery disease.](image)

**Table 4**
Univariate and multivariate logistic regression analysis to determine the independent predictor for plaque burden.

| Variable                        | OR      | 95% CI        | $p$     | OR      | 95% CI        | $p$     |
|--------------------------------|---------|---------------|---------|---------|---------------|---------|
| Male gender                     | 0.71    | 0.33–1.25     | <0.01   | 0.99    | 0.51–1.85     | <0.05   |
| Smoking                         | 1.59    | 0.83–3.14     | <0.05   |         |               |         |
| LDL-C                           | 1.65    | 1.13–2.48     | <0.03   |         |               |         |
| hs-CRP (mg/L)                   | 1.41    | 1.09–1.85     | <0.01   |         |               |         |
| E/e’                            | 1.63    | 0.83–2.79     | <0.03   |         |               |         |
| Number of leads with fQRS      | 7.92    | 2.15–18.13    | <0.001  | 2.15    | 1.27–3.99     | <0.001  |

LDL-C: Low-density lipoprotein cholesterol, hs-CRP: High-sensitivity C-reactive protein; E/e’: ratio of early diastolic mitral flow velocity to the early mitral annulus velocity.

![Fig. 4. Receiver operating characteristic (ROC) curve analysis to identify positive coronary artery disease with CCTA. The cut-off value of number of leads with fQRS was set at ≥3.](image)
intermediate pretest probability for CAD, who are probable to get slight or no advantage from noninvasive testing. This conception of not testing subjects with intermediate pretest probability for CAD goes in line with guideline recommendations to not test unless the pretest probability of obstructive CAD is greater than 10%.29,30

With multivariate logistic regression analysis, we found an independent association between the number of leads with FQRS and plaque burden in our cohort. The following two reasons may explain the relationship between them: first, studies showed that FQRS was related to increased hs-C reactive protein level, so the development of FQRS may be associated with systemic inflammation in patients with CAD.31,32 Inflammatory response mediated by oxygen free radical usually results in microvascular dysfunction. Second, coronary lesion with more plaque burden and calcium score may increase the risk of plaque from falling down and embolizing microvasculature to some extent.

Myocardial ischemia has been found to cause heterogeneous fibrosis,31,33,34 and it was thought that this could result in QRS fragmentation on surface ECG. Pietraski, et al.35 suggested that FQRS might be a useful marker to identify myocardial ischemia and higher risk for unfavorable outcomes.

Chest pain is a fuzzy complaint that has several causes related to either cardiovascular or noncardiovascular source. Chest pain related to CAD is the commonest type of cardiovascular pain in subjects presented to emergency departments. Besides, it constitutes nearly one-fifth of all mortalities attributed to CAD. The socioeconomic import, unfavorable outcomes of CAD are critical considerations for risk stratification and make judicious, early precise diagnosis and cost-effectively managing CAD of the extreme value.36

ROC curve analysis revealed that the number of leads ≥3 was the optimal number to coronary plaques with a sensitivity of 88% and a specificity of 83%. These findings demonstrate the usefulness of FQRS to predict higher fibrotic burden in myocardium in subjects with intermediate pretest probability for CAD. Therefore, FQRS might be of prognostic importance and may be of value in the monitoring of patients with chest pain, who have intermediate pretest probability for CAD.

Yet, Terho et al. reported that, in spite of the prognostic significance of FQRS in different CV diseases, it may not be related with adverse outcomes in subjects without a known cardiac disease.30

The ability to identify a subset of subjects with intermediate pretest probability of CAD, who might safely defer noninvasive testing, is appealing of given concerns about the low yield of testing in current practice and the associated costs.

4.1. Limitation

Several limitations were encountered. First, all the coronary artery lesions on CCTA were not confirmed by invasive coronary angiography. Second, we did not set a control group for the CAD screening. Third, myocardial fibrosis was not documented by imaging methods or biochemical or pathological markers. No follow-up study for our cohort was performed. Hence, we recommend that further studies are needed to clarify the significance of FQRS in predicting plaque burden.

5. Conclusion

We found that fragmented QRS was seen more often in patients with high plaque burden. FQRS might provide a useful noninvasive tool for selection of subjects with chest pain, who have intermediate pretest probability of CAD for further investigation.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflict of interest

All authors declare that they have no conflict of interest.

References

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American college of cardiology foundation/American heart association task force on practice guidelines, and the American college of physicians, American association for thoracic surgery, preventive cardiovascular nurses association, society for cardiovascular angiography and interventions, and society of thoracic surgeons. Circulation. 2012 Dec 18;126(25):3097–3137. https://doi.org/10.1161/CIRCULATIONAHA.112.160692.

2. Hachamovitch R, Berman DS, Kitai H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation. 1996;93(5):905–914. https://doi.org/10.1161/01.cir.93.5.905.

3. Bangalore S, Gopinath D, Yao S-S, Chaudhry FA. Risk stratification using stress echocardiography: incremental prognostic value over historic, clinical, and stress electrocardiographic variables across a wide spectrum of Bayesian pretest probabilities for coronary artery disease. J Am Soc Echocardiogr. 2007;20(3):244–252. https://doi.org/10.1016/j.echo.2006.08.014.

4. Mudrick DW, Cowper PA, Shah BR, et al. Downstream procedures and outcomes after stress testing for chest pain without known coronary artery disease in the United States. Am Heart J. 2012 Mar;163(3):454–461. https://doi.org/10.1016/j.ahj.2011.11.022.

5. Rozanski A, Gransar H, Hayes SW, et al. Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. J Am Coll Cardiol. 2013 Mar 12;61(10):1054–1065. https://doi.org/10.1016/j.jacc.2012.11.056.

6. Das MK, Saha C, E Masry H, et al. Fragmented QRS on a 12-lead ecg: a predictor of mortality and cardiac events in patients with coronary artery disease. Heart Rhythm. 2007 Nov;4(11):1385–1392. Epub 2007 Aug 1.

7. Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation. 2006 May 30;113(21):2495–2501. Epub 2006 May 22.

8. Hoffmann U, Nagueyot JT, Moselewski F, et al. Coronary multidector computed tomography in the assessment of patients with acute chest pain. Circulation. 2006 Nov 21;114(21):2251–2260. https://doi.org/10.1161/CIRCULATIONAHA.106.634808. Epub 2006 Oct 30.

9. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. A report of the American college of cardiology/American heart association task force on practice guidelines (committee on management of patients with chronic stable angina). Circulation. 1999 Jun 1;99(21):2829–2848. https://doi.org/10.1161/01.cir.99.21.2829.

10. Chopra S, Peter S. Screening for coronary artery disease in patients with type 2 diabetes mellitus: an evidence-based review. Indian J Endocrinol Metab. 2012 Jan;16(1):94–101. https://doi.org/10.4103/2230-8210.91202.

11. Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. Heart Rhythm. 2009 Mar;6(3 Suppl):S8–S14. https://doi.org/10.1542/hrtm.2008.0193. Epub 2008 Oct 17.

12. Gao D, Ning N, Guo Y, et al. Computed tomography for detecting coronary artery plaques: a meta-analysis. Atherosclerosis. 2011 Dec;219(2):603–609. https://doi.org/10.1016/j.atherosclerosis.2011.08.022. Epub 2011 Aug 22.

13. Arad Y, Spadaro LA, Roth M, et al. Correlations between vascular calcification and atherosclerosis: a comparative electron beam CT study of the coronary and carotid arteries. J Comput Assist Tomogr. 1998 Mar–Apr;22(2):207–211.

14. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990 Mar 15;15(4):827–832. https://doi.org/10.1016/0735-1097(90)90282-4.

15. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol. 2007 Sep 18;50(12):1161–1170. https://doi.org/10.1016/j.jacc.2007.03.067. Epub 2007 Sep 4.

16. Johnson KM, Dowle DA, Brink JA. Traditional clinical risk assessment tools do not accurately predict coronary atherosclerotic plaque burden: a CT
