

Contribution of fragmented QRS on myocardial perfusion imaging in the assessment of functionally significant coronary artery stenoses

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Abstract. – OBJECTIVE: The evaluation of the functional significance of coronary artery stenosis is of great clinical importance in patient management or for decisions concerning coronary intervention. Recently, fragmented QRS (fQRS) on electrocardiography (ECG) has been introduced as a predictor of myocardial scarring as well as myocardial ischaemia in coronary artery disease. We aimed to investigate any additive value of fQRS to myocardial perfusion SPECT in evaluating the functional significance of the intermediate degree of coronary stenosis.

PATIENTS AND METHODS: Patients who were referred for myocardial perfusion imaging (MPI) to evaluate the functional significance of intermediate (40-70%) coronary artery stenosis were analyzed retrospectively; 102 patients were included in the study. ECG records were evaluated to detect fQRS. MPI was interpreted visually and semiquantitatively by two nuclear medicine physicians blinded to the electrocardiographic findings. Summed stress scores (SSS), summed rest scores and summed difference scores (SDS) were calculated according to the 17-segment model.

RESULTS: The mean age of the patients was 62.56 ± 9.5 years, and 64 were males (62.7%). Ischaemia was detected in 30 patients, and the frequency of fQRS was significantly higher in patients with ischaemia than in patients with normal perfusion (54.8% vs. 23.8%, respectively; $p < 0.001$). Myocardial scarring was detected in 15 patients, 7 of whom had coexistent myocardial ischaemia. fQRS was positively correlated with the SSS ($r=0.374$, $p=0.001$), SDS ($r=0.460$, $p=0.001$) and summed motion score ($r=0.228$, $p=0.024$). fQRS was an independent predictor of myocardial ischemia in multivariate analyses (OR=11.181; CI=3.900-32.057; $p < 0.001$).

CONCLUSIONS: The presence of fQRS on ECG is associated with myocardial ischaemia in patients who had an intermediate degree of coronary stenosis.

Key Words:

Fragmented QRS, Myocardial perfusion SPECT, Ischaemia, Functional significance, Coronary artery stenosis.

Introduction

Coronary angiography has been used for the diagnosis of coronary stenosis and decision-making concerning coronary interventions. However, intermediate coronary stenosis or the functional significance of lesion severity cannot be estimated by coronary angiography. Quantitative intravascular ultrasound or myocardial fractional flow reserve (FFR) measurements are well-established methods for evaluation of the functional significance of coronary stenosis^{1,2}. These modalities are not commonly used because of their relatively high cost and invasiveness. Myocardial perfusion imaging (MPI) provides diagnostic and prognostic information in patients with coronary artery disease (CAD) or suspected CAD³. There is a consensus on the usage of stress MPI in patients with angiographically intermediate coronary stenosis⁴. Myocardial SPECT imaging can reflect the haemodynamic significance of coronary stenosis and the site and extent of ischaemia and scarring. The concordance between MPI and FFR ranges from 60% to 90% in the previous studies⁵. Sahiner et al⁶ suggested that quantitative evaluation of MPI increases the concordance of FFR and scintigraphy in detecting the functional significance of coronary stenosis. Fragmented QRS (fQRS) was defined by Das et al⁷ and is reported to be useful for the prediction of prognosis of patients with CAD. The presence of fQRS on electrocardiography

(ECG) was defined as the presence of a wave-like RSR' pattern in the QRS complex or notched R or S waves without a typical bundle branch block. A possible explanation for the fragmentation of the QRS complex may be an interruption of the ventricular conduction system due to myocardial scarring and/or ischaemia. fQRS was shown to be related to myocardial scarring and ischaemia as assessed by MPI in many studies⁷⁻¹⁰. The aim of the present study was to investigate any additive value of fQRS to MPI in evaluating the functional significance of the intermediate degree of coronary stenosis.

Patients and Methods

Study Design

The study group was selected from the patients who were referred for MPI to evaluate the functional significance of coronary stenosis between June 2013 and December 2015 to our university hospital. All of the patients underwent coronary angiography before MPI. Patients with a pace rhythm (n=2), left bundle branch block (n=8), right bundle branch block (n=1), left ventricular hypertrophic voltage criteria (n=4), ischaemic cardiomyopathy (n=4) and hypertrophic cardiomyopathy (n=1) were excluded from the study. Patients with a history of coronary artery by-pass grafts, digoxin use, left main coronary artery lesions were also excluded. One hundred two patients with of 40-70% stenosis of any coronary artery were included in the current study.

Myocardial Perfusion Imaging

The patients were recommended to discontinue any calcium channel blockers, beta blockers, or long-acting nitrates 48 h prior to the stress test. Myocardial perfusion SPECT images were provided using a standard 1-day stress-rest protocol. The standard 12-lead ECG and blood pressure were monitored during the symptom-limited treadmill test (Bruce protocol). Approximately 1 min before termination of the stress test, technetium-99m (Tc-99m) sestamibi (Mon.MIBI, Eczacibasi-Monrol, Turkey) was injected intravenously (8-10 mCi). The patients who failed to achieve their age-predicted heart rate or those who were unable to exercise underwent a pharmacologic stress test using a 6-min adenosine infusion protocol. SPECT images were acquired 40-60 min after injection of Tc-99m sestamibi using a dual-headed detector gamma camera (Sie-

mens e-cam signature; Siemens Medical Solutions, Malvern, PA, USA), fitted with a low-energy, high-resolution collimator and setting the energy photopeak at 140 keV with a 20% window. Sixty-four projections were obtained in a 64×64 matrix. The acquisition time per projection was 25 s for the stress SPECT studies. Routine prone imaging was obtained from all patients. The acquisition time per projection was 10 s for the prone imaging. Rest images were obtained using the same protocol 45-60 min after injection of 24-30 mCi of Tc-99m sestamibi. Images were filtered by back projection using a Butterworth filter (order of 5; cut-off frequency, 0.5 cycles per pixel).

Two independent physicians blinded to the patients' ECG data interpreted the images visually and semiquantitatively. Myocardial perfusion was interpreted using a 17-segment model and perfusion scoring system (0=normal perfusion, 1=equivocal hypoperfusion, 2=moderate hypoperfusion, 3=severe hypoperfusion, and 4=absent perfusion). Summed stress scores (SSS), summed rest scores (SRS), and summed difference scores (SDS) were calculated. An SDS of 2 or more below the at-rest imaging results and a SSS ≥ 4 were considered to indicate a reversible defect (ischaemia). Scans that had perfusion defects under both stress and rest were considered to have a fixed defect (scar). Perfusion defects with and without reversibility were considered to indicate the coexistence of ischaemia and scarring.

Functional parameters of the left ventricle were measured using QGS software (Cedars-Sinai Medical Center, Los Angeles, CA, USA). The summed motion score (SMS), summed thickening score (STS) and left ventricular ejection fraction (EF) were calculated using an automated QGS program.

Fragmented QRS

Standard 12-lead surface electrograms (filter range: 0.16-100 Hz; AC filter: 50 Hz, 25 mm/s; 10 mm/mV) were recorded at rest. A cardiologist who was blind to the MPI results interpreted the ECGs. The fQRS complex included the presence of an additional R wave (R') or notching of the R or S wave or the presence of fragmentation (more than one R') in two contiguous leads corresponding to a major coronary artery territory. Complete or incomplete bundle branch blocks were excluded from the definition of fQRS⁷.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v20 (SPSS Inc.,

Chicago, IL, USA). Normal distribution of the quantitative data was assessed using the Kolmogorov-Smirnov test. The independent samples *t*-test and the Mann-Whitney U-test were used to compare independent groups for continuous variables. Data are expressed as mean±SD or median (interquartile range), as appropriate. Spearman's correlation coefficient was used for correlation analysis. Logistic regression analyses were used to assess the prediction of myocardial perfusion abnormality. The concordance between fQRS and myocardial perfusion abnormality was assessed using the κ index. All of the differences associated with a probability of 0.05 or less were considered to be statistically significant.

Results

Of the 102 patients (38 females and 64 males) included in the study, fQRS were detected in 42 (41%) patients. There were no statistically significant differences between patients with or without fQRS regarding coronary artery disease risk factors, sex or age (Table I). Myocardial scarring was detected in 15 patients, 7 of whom had coexistent myocardial ischaemia. Myocardial perfusion findings were normal in 57 (55%) patients. Ischaemia was detect-

ed in 30 (29%) patients and frequency of fQRS was significantly higher in patients with ischaemia than in patients with normal perfusion (54.8% vs. 23.8%, respectively; $p<0.001$; Table II, Figure 1).

fQRS was positively correlated with SSS ($r=0.374$, $p=0.001$), SDS ($r=0.460$, $p=0.001$), SMS ($r=0.228$, $p=0.024$). fQRS had no correlation with SRS ($r=0.043$, $p=0.670$) or STS ($r=0.190$, $p=0.062$). Ejection fraction was lower in patients with fQRS than in patients without fQRS (58.18 ± 14.26 vs. 63.15 ± 9.54 , respectively; $p=0.067$) but this was not statistically significant. Additionally, the SMS was significantly higher in patients with fQRS than in patients without fQRS ($p=0.025$). The comparison of the functional parameters of left ventricle and fQRS were shown in Table III.

The concordance between fQRS and MPI regarding myocardial perfusion abnormalities was moderate ($\kappa=0.539$, $p<0.001$). The MPI was normal in 82.5% of patients who did not have fQRS on ECG; it was abnormal in 71.1% of patients who did have fQRS on ECG.

In univariate analysis, fQRS, EF, EDV and ESV were found to be related to myocardial perfusion abnormalities. Multivariate logistic regression analyses demonstrated that fQRS was the only independent predictor of myocardial ischaemia (OR=11.181; CI=3.900-32.057; $p<0.001$, Table IV).

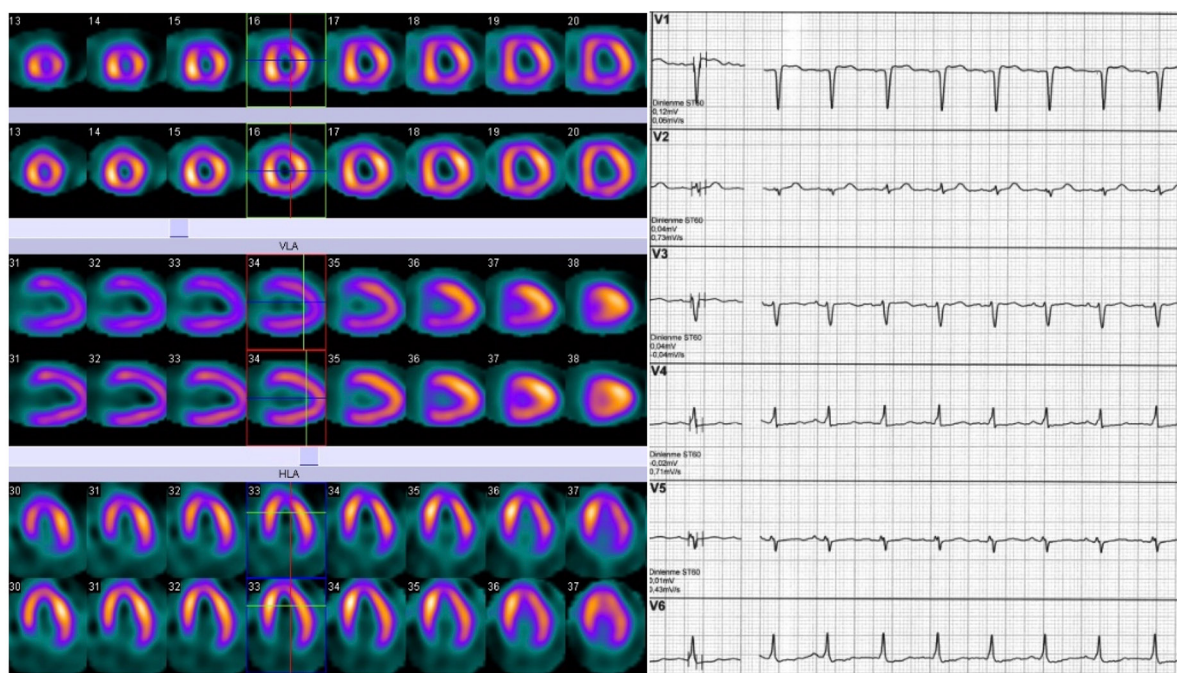


Figure 1. The short axis slice images of stress-rest myocardial perfusion imaging showed anterior wall ischaemia in a patient. Same subject had a fragmented QRS on ECG in V2, V3, V4 and V5 derivations.

Table I. Comparison of patients characteristics between two groups.

	non-fQRS (n=60)	fQRS (n=42)	<i>p</i>
Age	62.20 ±9.12	63.07±10.24	0.653
Gender			0.788
female	23 (38.3%)	15 (35.7%)	
male	37 (61.7%)	27 (64.3%)	
Diabetes mellitus	20 (33.3%)	15 (35.7%)	0.803
Hyperlipidemia	34 (56.7%)	25 (62.5%)	0.774
Smoking	14 (23.3%)	7 (17.5%)	0.412
Family history	28 (46.7%)	18 (45%)	0.704
Hypertension	42 (70%)	27 (67.5%)	0.544
Prior percutaneous intervention	10 (16%)	11 (26%)	0.242
Q wave	3 (5%)	6 (14%)	0.104

Table II. Comparison of myocardial perfusion findings in patients with and without FQRS.

MPI findings	fQRS (-) , n=60	fQRS (+), n=42	<i>p</i>
Normal perfusion (n)	78.3% (47)	23.8% (10)	<0.001
Ischemia (n)	11.7% (7)	54.8% (23)	<0.001
Scar (n)	6.7% (4)	9.5% (4)	0.054
Scar and ischemia (n)	3.3% (2)	11.9% (5)	0.05

Table III. Functional parametres of left ventricle.

MPI findings	fQRS (-) , n=60	fQRS (+), n=42	<i>p</i>
EF	63.15±9.54	58.18±14.26	0.067
EDV	70 (58-91)	84 (58-103)	0.094
ESV	25 (18-40)	37 (20.5-44.75)	0.098
SMS	2 (0-7)	6 (0-16)	0.025
STS	0 (0-3)	5 (0-8.5)	0.062

EF, ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; SMS, summed motion score; STS, summed thickening score.

Discussion

The present study demonstrated that the fQRS was an independent predictor of reversible perfusion defects on MPI in patients who had an intermediate degree of coronary stenosis. We found that fQRS had a correlation with SDS and SSS which were the parameters of ischaemia.

fQRS was defined as unexpected fragmentation of morphology of QRS complex⁷. Although the pathophysiology of fragmentation is not understood completely, there are several assumptions. The experimental studies¹¹ confirmed that after myocardial infarction, significant myocar-

dial necrosis, with islands of viable myocardial tissue merge in abundant connective tissue. It was speculated that chronically ischaemic myocardium displays slow activation because of the partial depolarization and is probably responsible for abnormal conduction around the scarred myocardium causing multiple spikes within QRS complexes¹². It was reported¹⁰ that the incidence of both ischaemia and scarring on MPI were higher in patients with fQRS than in patients without fQRS. Previous studies^{7,9,13} had shown that fQRS could be a sign of myocardial scarring as detected by MPI, and it had a higher sensitivity and negative predictive value than those of the patholog-

Table IV. Univariate and multivariate analyses for predictor of myocardial perfusion abnormalities.

	Univariate			Multivariate		
	<i>p</i>	OR	95%CI	<i>p</i>	OR	95%CI
fQRS	<0.001	11.569	4.525-29.583	<0.001	11.181	3.900-32.057
Age	0.853	1.004	0.963-1.046			
Gender	0.123	1.923	0.838-4.411			
Diabetes mellitus	0.545	0.774	0.338-1.774			
Hyperlipidemia	0.105	0.517	0.233-1.149			
Smoking	0.268	0.566	0.207-1.548			
Family history	0.188	0.586	0.265-1.299			
Hypertension	0.812	1.107	0.479-2.558			
EF	0.002	0.938	0.901-0.977	0.446	1.067	0.903-1.261
EDV	0.004	1.027	1.009-1.045	0.291	0.948	0.859-1.047
ESV	0.002	1.046	1.017-1.077	0.182	1.176	0.927-1.492

OR: odds ratio; CI, confidence interval; fQRS, fragmented QRS; EF, ejection fraction; EDV, end diastolic volume; ESV, end systolic volume.

ical Q wave. These studies were focused on the predictive value of fQRS for myocardial scarring, although fQRS denoted the presence of a higher SSS, SRS and SDS which are signs of both myocardial scarring and ischaemia^{7,8,10}. In contrast to these findings, several studies^{14,15} failed to show a relationship between fQRS and myocardial scarring. Recently, Dabbagh Kakhi et al¹⁶ showed correlations only between fQRS and SSS and between fQRS and SRS, and they concluded that fQRS was a predictor of myocardial scarring rather than myocardial ischaemia. All of these population studies included consecutive patients with known or suspected CAD who were referred for MPI.

In the present study we chose a group of patients who were being evaluated for the functional significance of coronary stenosis. All of our patients had an intermediate degree of coronary stenosis in one or two coronary arteries. Eight patients had myocardial scarring, and seven patients had a combination of myocardial scarring and ischaemia. fQRS was not significantly different between patients with versus without scarring. We speculated that this was because our patients cohort was a relatively small study population and was evaluated for ischaemia specifically. On the other hand, we showed a significant correlation between fQRS and myocardial ischaemia. fQRS has been shown to be related with myocardial fibrous tissue, manifesting after prior MI or various diseases. Chronic ischaemia has been documented to cause myocardial patchy fibrosis^{17,18} and we

believe that this could lead to emergence of fQRS on ECG in patients with myocardial ischaemia. Our results support the study of Pietrasik et al¹⁹ who proposed that fQRS could be used to identify ischaemic myocardium. They showed that fragmentation of QRS in patients with resolved Q waves had an increased risk of cardiac events. They claimed that presence of fQRS might identify scarring within hibernated/viable and less stable myocardium.

Another study declared that fQRS was more common among metabolic syndrome patients, and the presence of fQRS was associated with subclinical left ventricular dysfunction in metabolic syndrome patients²⁰.

The decision for revascularization requires objective evidence of ischaemia and not just visual anatomical assessment of stenosis. It was shown that coronary stenosis between 50% and 70% had a wide variability in functional significance based on FFR measurement²¹. Multiple factors such as the length of stenosis, number of stenoses in the vessel, location of the lesion, and left ventricular hypertrophy, can lead to functionally significant coronary stenosis. Additionally, insufficient collateral circulation can contribute to a setting of myocardial ischaemia. Erdogan et al²² found that fQRS was independently related to poor collateral circulation in patients with chronically total coronary occlusion. In their study, they showed that patients with poor collateral coronary circulation had a higher rate of fQRS than the patients with good collateral circulation.

In our study the presence of fQRS was related to left ventricular dysfunction. Both myocardial ischaemia and scarring can cause deterioration of wall motion and wall thickening. The finding that the myocardium exhibited depression of contractile function when myocardial ischaemia is severe or prolonged is expected. A previous study²³ also found that fQRS was related to left ventricular systolic and diastolic dysfunction.

In our study there were 10 patients with fQRS for whom MPI was evaluated as normal. A recent population-based study about the incidence and prognosis of fQRS detected fQRS in 19.7% of the middle-aged population; but in subjects without a known cardiac disease, fQRS was not related to adverse outcomes²⁴.

In this study, we had several limitations. A major limitation of our study was the small number of patients. Second, we did not have follow-up information for the patients in terms of prognosis. Because of the retrospective design of the study, we could not correlate the findings of MPI with FFR.

Conclusions

The presence of fQRS on ECG is associated with myocardial ischaemia in patients with an intermediate degree of coronary stenosis. Evaluating the functional significance of coronary stenosis with consideration of fQRS on ECG can be an additional parameter contributing to clinical decision making for coronary intervention. However, these findings should be supported by additional large prospective studies.

Conflicts of interest

The authors declare no conflicts of interest.

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