

Value of Fragmented QRS Complex on 12-lead ECG as a Valuable Marker of Myocardial Damage of CAD Patients

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Abstract

Background: Presence of Fragmented QRS (fQRS) on a 12-lead Electrocardiogram (ECG) was associated with various cardiac diseases. This phenomenon could represent as an electrical disruption of conduction system following myocardial damage due to coronary artery disease (CAD). We aimed to investigate the value of fQRS to detect the myocardial scar as detected by SPECT Myocardial Perfusion Imaging (MPI).

Methods: A cross-sectional study of patients who were either being evaluated for CAD or had a history of CAD and underwent Cardiac SPECT. The fQRS defined as morphologies of QRS wave (< 120 ms), which included an additional R wave (R'), notching in the nadir of S wave, or > 1 R' (fragmentation) in 2 contiguous leads, corresponding to a major coronary artery territory. Pathological Q wave, paced rhythm, typical right or left bundle branch block pattern with QRS duration of ≥ 120 ms were excluded. MPI was interpreted by visual analysis and semi-quantitative scores on 17-segment assessment according to standard nomenclature.

Results: Total of 72 patients (49 males, mean age 54.7 ± 9.8 years). fQRS was found in 46 patients (64%). The frequency of myocardial scar was significantly higher in patients with fQRS (89% vs. 15%, $p < 0.05$). Sensitivity, specificity, positive and negative predictive value of fQRS for any of myocardial scar as detected by SPECT analysis were 91%, 81%, 89%, and 84%, respectively. From regional scar analysis, fQRS has sensitivity and specificity of 87% and 90% for anterior wall, 76% and 80% for inferior wall, 73% and 79% for lateral wall. LVEF was significantly lower in patients with fQRS (36.9 ± 2.1 vs. 53.2 ± 2.2 , $p < 0.05$).

Conclusion: The fragmented QRS could serve as an important ECG marker to detect and localize the myocardial damage in patients with known or suspected CAD. Regional fQRS patterns denote the presence of regional myocardial scar and are a valuable diagnostic marker of CAD with good sensitivity and specificity.

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Introduction

Coronary artery disease (CAD) is known as a leading cause of death in many countries. In United States, it is estimated more than 17 million people suffered from CAD¹. Meanwhile in Indonesia, according to RISKESDAS 2013, prevalence of CAD reaches 1,5% of the entire

population, and is expected to continue to rise in coming years². The considerably high global incidence of CAD with its impact on morbidity, mortality, and treatment costs shows the importance of simple, accessible, and cost-effective diagnostic tools. The most universal modality that meets almost all of the mentioned attributes is electrocardiography (ECG)³.

Electrocardiogram (ECG) is the first useful diagnostic tool, readily available, and commonly used to diagnose coronary artery disease. Previous studies have shown that any change in QRS wave morphology is related to ventricular conduction disturbance and could be caused by myocardial damage due to ischemia or infarction of the ventricle⁴. Previously, pathological Q wave on a 12-lead ECG is a well-known marker for detecting prior Myocardial Infarction (MI) but some studies found that Q-waves do not always appear on post-MI ECG and can regress or even disappear over time in 25–60% of patients⁵. Thus, an increasing interest has developed in fragmented QRS (fQRS) and its relationship with previous MI. Some researchers have claimed that fQRS might show regional myocardial damage in non-Q wave MI patients and is associated with a higher all-cause mortality and cardiac event rate^{6,7}.

Fragmentation of QRS may represent a heterogeneous left ventricular activation state. The presence of left ventricular depolarization changes may manifest as fQRS appearance on 12-lead ECG⁸. The existence of a preliminary deflection of visible R waves can occur as result of a shift from the QRS wave vector to the right and posterior because of early depolarization process. The presence of a notch or a slurred of the S wave may represent the activation pattern of the precordial lead (to the left of the transition zone), similar to the activation pattern of the left bundle branch block. Therefore, the delayed conduction of QRS waves arising from the presence of block or slowing of the conduction pathway will lead to fragmented QRS pattern⁹.

The fragmentation of the QRS complex on 12 leads ECG examination could be found in many heart diseases such as ventricular aneurysm, idiopathic dilated cardiomyopathy, myocardial fibrosis, sarcoidosis, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy and myocarditis¹⁰. The incidence of fQRS in CAD patients is significantly associated with left ventricular dysfunction and decreased perfusion of the myocardium. The presence of QRS fragmentation

in the ECG is associated with the existence of ischemia, infarct or fibrosis and results from damage to the signal transduction and depolarization processes in the Purkinje fiber of the ventricles^{7,11}. Fragmentation of QRS may originate from an abnormal area of myocardium where ventricular activation is delayed and asynchronous which causes notching in the QRS complex¹². Nevertheless, this warrants further investigation because fragmented QRS is a relatively new marker with contradictory results reported in different studies.

Single-Photon Emission Computed Tomography (SPECT) is an accurate non-invasive modality for investigation of coronary artery disease with high sensitivity and specificity, and it also has a good prognostic value¹³. The quantitative analysis of myocardial wall movement abnormalities using SPECT is an accurate modality for assessing the presence of severe and extensive coronary artery disease¹⁴.

Stress Myocardial Perfusion Imaging (MPI) by Technetium-99m sestamibi-based Single Photon Emission Computed Tomography is routinely performed to identify the extent of a prior myocardial injury and the presence of physiologically significant myocardial ischemia in patients with known or suspected coronary artery disease¹⁵. Stress SPECT-based technique has also demonstrated superior accuracy and clinical utility in identifying the presence and size of myocardial infarction scar^{11,15}.

We aimed to investigate the value of Fragmented QRS complex to detect and localize the myocardial scar in patients with coronary artery disease by using Stress Myocardial Perfusion Imaging (MPI) with Technetium-99m sestamibi-based Single Photon Emission Computed Tomography (SPECT).

Methods

Study design and population

This is a cross-sectional study that included patients who were either being evaluated for CAD or had a history of CAD who underwent SPECT Myocardial Perfusion Imaging at Adam Malik General Hospital from Januari 2017 to March 2018. We conducted data collection through anamnesis, physical examination, laboratory examination, ECG, cardiac exercise test, echocardiography, and other supporting modalities. The

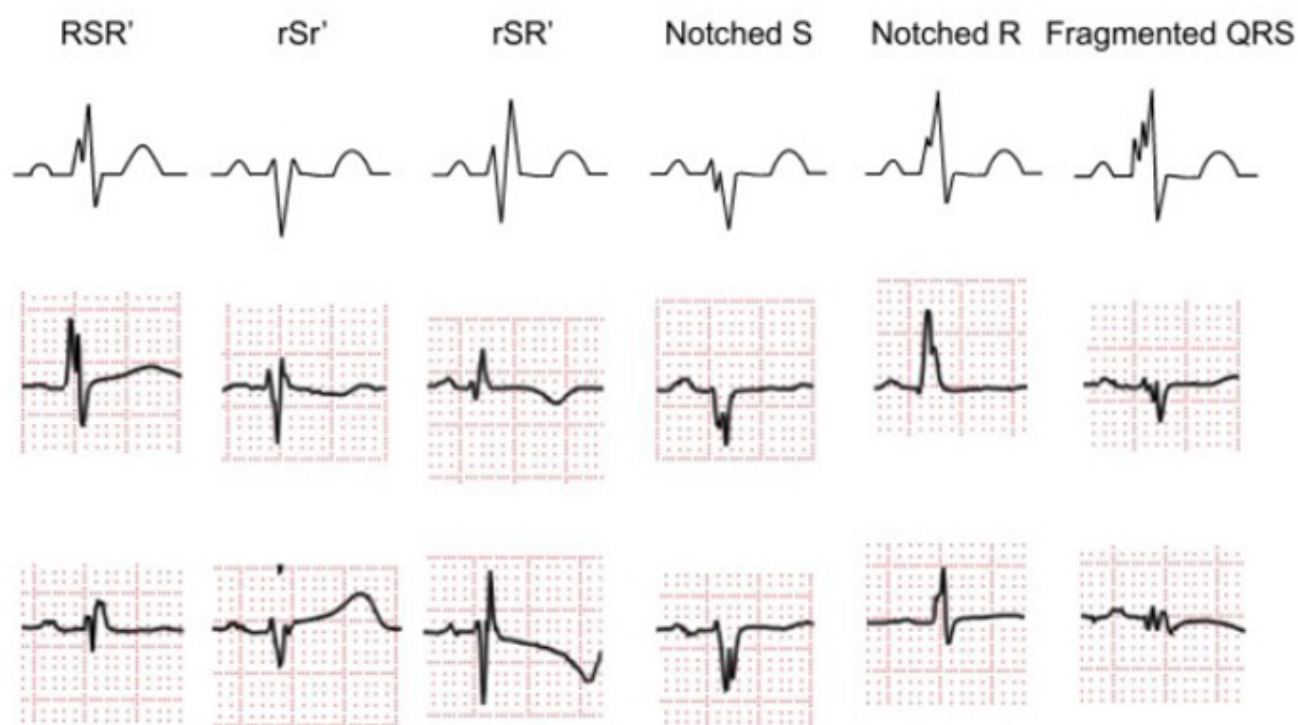


Figure 1. Various morphologies of QRS fragmentation on a 12-lead ECG¹¹

demographics of all patients, including risk factors for CAD (age, sex, hypertension, smoking, type II diabetes mellitus, dyslipidemia) were recorded.

Exclusion criteria were ECG findings of pathological Q wave, paced rhythm, typical right or left bundle branch block pattern with QRS duration of ≥ 120 ms and patients who are unable to complete an optimal SPECT examination. Written informed consent was obtained from all patients before the SPECT study. The study protocol was approved by the ethics committee of the University.

ECG criteria for Fragmented QRS

The measurement of QRS complex fragmentation was performed at just before the SPECT examination was conducted. Resting baseline 12-lead ECG (100 Hz, 25 mm/s, 10 mm/mV; *Fukuda Denshi, Tokyo, Japan*, model FX-8322 R) was obtained and analyzed by two independent readers who were blinded to the SPECT findings. The fragmented QRS defined as morphologies of QRS wave (<120 ms), which included an additional R wave (R'), notching in the nadir of S wave, or >1 R' (fragmentation) in 2 contiguous leads, corresponding

to a major coronary artery territory (Figure 1)¹¹. The presence of fQRS in ≥ 2 contiguous anterior leads (V1 to V5) was assigned to myocardial scar in anterior segments or in the left anterior descending territory. The lateral leads (I, aVL, and V6) was assigned to myocardial scar in lateral segments or left circumflex territory. The inferior leads (II, III, and aVF) was assigned to myocardial scar in the inferior segments or in the right coronary artery territory.

SPECT Acquisition and Analysis

Patients were advised not to take beta-blockers, calcium channel blockers, aminophylline or caffeine 24-hour before the test. All patients underwent a rest/stress (low-dose/high-dose) Technetium-99m sestamibi single-day stress protocol. Dobutamine was used as pharmacologic stress agents. Dobutamine was infused at incremental doses of 5, 10, 20, 30 and 40 mg/kg per minute at 3-min intervals, until symptoms or target heart rate is achieved. Patients who are unable to complete an optimal cardiac SPECT examination (severe complaints, hemodynamic deterioration or malignant ECG changes during examination) were also be excluded.

Table 1. Baseline characteristics

Variables	Fragmented QRS (fQRS)		P value
	With (n=46)	Without (n=26)	
Age (mean ± SD), years	56,2 ± 8,4	51,9 ± 11,5	0,1 ^a
Gender (n, %)			
Male	38(82)	11(42)	0,001 ^b
Female	8(18)	15(58)	
CAD risk factors (n, %)			
Hypertension			0,8 ^b
Type 2 Diabetes Mellitus	22(48)	12(46)	
Dyslipidemia	26(56)	8(30)	0,03 ^b
Smoker	39(84)	17(65)	0,06 ^b
Post PCI	38(82)	13(50)	0,003 ^b
Post CABG	6(13)	3(11)	0,8 ^b
	4(8)	0(0)	0,29 ^c

SD=Standard Deviation; PCI=Percutaneous Coronary Intervention; CAD=Coronary Artery Disease; CABG=Coronary Artery Bypass Grafting; ^aStudent's t-test; ^bChi Square Test; ^cFisher's Exact Test

Table 2. SPECT analysis results between groups

Variables	Fragmented QRS		P value
	With	Without	
LVEF (%)	36,9 ± 2,1	53,2 ± 2,2	0,002
Rest LVESV (mean±SD), ml	138,1 ± 82	97,5 ± 64,1	0,02 ^a
Stress LVESV (mean±SD), ml	139 ± 86,1	91 ± 57,6	0,006 ^a
Myocardial scar, n (%)	41 (89)	4 (15)	< 0,001

SD = Standard Deviation; LVEF = Left Ventricle Ejection Fraction; LVESV = Left Ventricle End Systolic Volume; ^aStudent's t-test

The ECG-gated acquisition was performed on post-stress images at 8 frames per R-R interval, acquired within 20 to 45 minutes after peak stress Tc-99m administration. Gated SPECT images were obtained with ECG-gated rotating, 90° fixed dual-head gamma camera (*Philips Medical System, Cleveland*). Tomograms were reconstructed by different axis, including projection in vertical long-axis, horizontal long-axis, and short-axis planes. Motion correction software was used when needed, as determined by the reader. The rest and stress acquisitions were analyzed using an automated AutoQuant software (*Cedars-Sinai Medical Center, Los Angeles, California*) (Figure 2).

SPECT images were evaluated visually and semiquantitatively by nuclear medicine specialists who

was an independent blinded reader. A semiquantitative Sum Stress Score (SSS), Sum Rest Score (SRS), and Sum Difference Score (SDS) were calculated on 17-segment analysis using 5-point scale (0 = normal, 1 = equivocal or mildly abnormal, 2 = moderately abnormal, 3 = severely abnormal, and 4 = absent tracer uptake). Individual epicardial coronary artery regional segments were scored according to standard nomenclature¹⁶. The left anterior descending artery (7 segments) represented by anterior leads; the left circumflex artery (5 segments) represented by lateral leads; and the right coronary artery (5 segments) represented by inferior lead (Figure 3). A myocardial scar was defined by a total regional SSS and SRS ≥ 3 and a regional SDS ≤ 2, corresponding to a major coronary artery region.

Statistical Analysis

Categorical variables were presented as the number or frequency (n) and percentage (%). Continuous variables were expressed as mean and standard deviation (SD). Categorical variables were analyzed by using Chi-squared (χ^2) and Fisher's exact test whereas continuous variables were analyzed by Independent T or Mann-Whitney test. Normality test was done using one sample Kolmogorov-Smirnov (n >50) or the Shapiro-Wilk (n <50). Sensitivity was defined as the number of true-positive tests divided by the total number of patients with myocardial scar defined by SPECT. Specificity was defined as the number of true-negative tests divided by the total number of patients without myocardial scar. Positive and negative predictive values were also calculated. Positive predictive value is the probability that subjects with a positive screening test truly have the disease and calculated as (true positive)/(true positive + false positive). Negative predictive value is the probability that subjects with a negative screening test truly do not have the disease and calculated as (true negative)/(false negative + true negative). P-value < 0,05 is considered to be statistically significant. All statistical analysis were done using SPSS software for *Windows*.

Results

86 patients were enrolled in our study, 14 patients (16%) were excluded from our analysis because of pathological Q wave (n = 6), typical RBBB or LBBB (n = 3), and

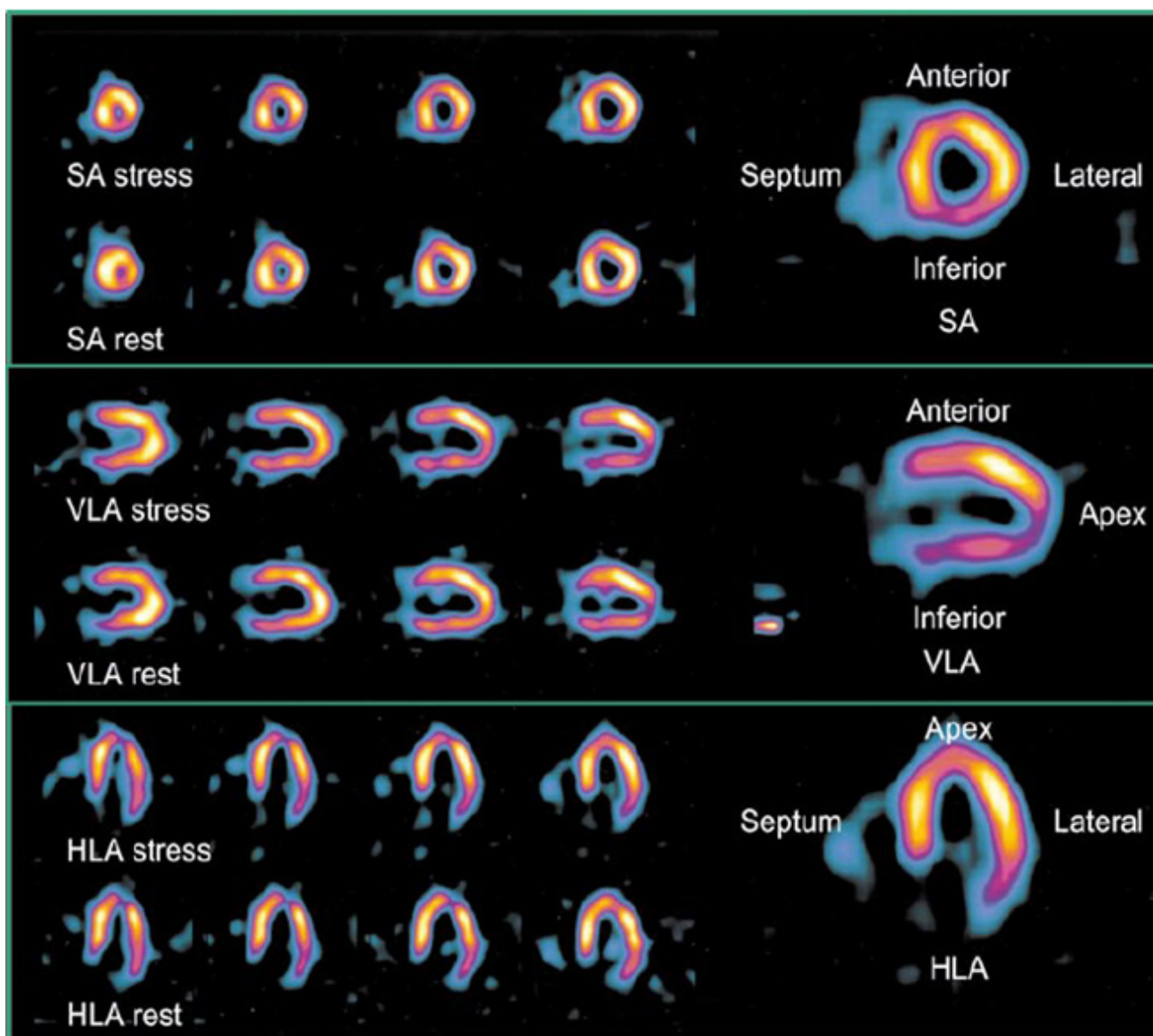


Figure 2. Myocardial perfusion visual analysis by SPECT¹⁶

unable to complete an optimal SPECT examination ($n = 5$). Total of 72 patients 49 were males and mean age was $54,7 \pm 9,8$ years. The appearance of fQRS on 12-lead ECG was found in 46 patients (64%). Most of patients with fQRS were males compared with non-fQRS group (82% vs 42%, $p=0.001$). The mean age of patients in fQRS group were somewhat older although the difference between two groups was not statistically significant.

From the risk factors of CAD, Type II Diabetes Mellitus (DM) and smoker were significantly different between these groups. Frequency of smoker was

significantly higher in patients with fQRS (82% vs 50%, $p=0.003$). 26 patients (56%) with type II DM in fQRS group and 8 patients (30%) in non-fQRS group ($p=0.03$). We found no statistically significant difference between those with and without fQRS regarding hypertension, dyslipidemia and history of PCI or CABG (Table 1).

SPECT results between fQRS and non-fQRS groups

Patients of the fQRS group had a significantly lower

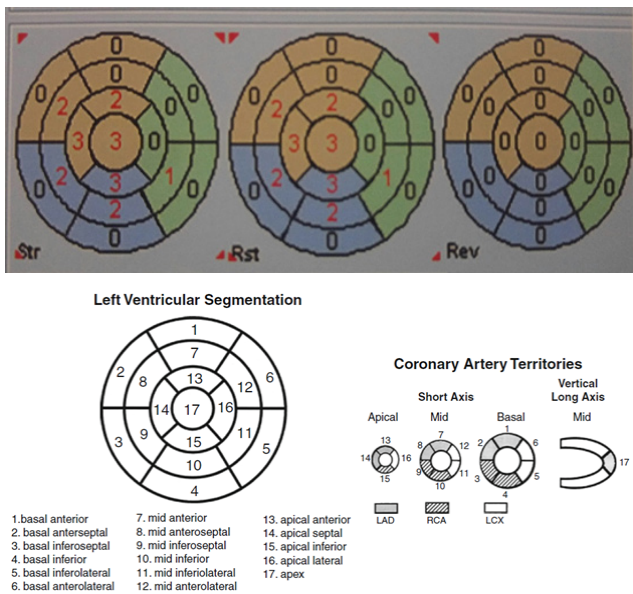


Figure 3. Semiquantitative scoring analysis on 17-segment standard nomenclature¹⁶

Left Ventricular Ejection Fraction (LVEF) compared with non-fQRS group, $36,9 \pm 2,1$ % vs. $53,2 \pm 2,2$ %, ($p=0.002$). The fQRS group had higher mean Left Ventricular End Systolic Volume (LVESV) than non-fQRS group either at resting phase or Dobutamine-load phase. The differences between the two groups were statistically significant. The LVESV at resting phase in patients with fQRS was $138,1 \pm 82$ ml and $97,5 \pm 64,1$ ml in patients without fQRS ($p=0.02$). Meanwhile, LVESV at Dobutamine-load in patients with fQRS was $139 \pm 86,1$ ml and $91 \pm 57,6$ ml in patients without fQRS ($p=0.006$). Incidence of myocardial scar as detected by SPECT was significantly higher in fQRS group compared with non-fQRS group. (82% vs. 15%, $p<0.001$) (Table 2).

Fragmented QRS and regional scar analysis

Sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of fQRS for any of myocardial scar as detected by SPECT analysis were 91%, 81%, 89%, and 84%, respectively. For each regional scar analysis, anterior fQRS has sensitivity, specificity, PPV and NPV of 87%, 90%, 91 %, and 85 % for anterior wall. Inferior fQRS has sensitivity, specificity, PPV and NPV of 76%, 80%, 74%, and 82% for inferior wall. Lateral fQRS has sensitivity, specificity,

PPV and NPV of 73%, 79%, 62%, and 86% for lateral wall (Figure 4).

Inter-observer variability

The QRS Fragmentation measurement are often variably between observers. In this study, measurements of fQRS were performed by 2 observers. Inter-observer variability was measured by using Kappa test (Cohen's Kappa Coefficient). The value of Cohen's Kappa Coefficient (κ) on inter-observer variability is 0,791 which is considered to be good agreement between the observers ($p<0.001$).

Discussion

This cross-sectional study was conducted to investigate the diagnostic capability of fragmented QRS on 12-lead ECG as a marker to detect the presence of myocardial scar and its location as examined by Stress Myocardial Perfusion Imaging (MPI) with Technetium-99m sestamibi-based SPECT. SPECT MPI is a non-invasive nuclear-based modality that has ability of localizing the location of the ischemic region and assessing the extent and severity of cardiac damage with good sensitivity and specificity¹⁵.

The patients who were either being evaluated for CAD or had a history of CAD and underwent SPECT Myocardial Perfusion Imaging were enrolled in this study. We conducted data collection through anamnesis, physical and laboratory examination, ECG, cardiac exercise test, and other supporting modalities. The risk factors for CAD (age, sex, hypertension, smoking, type II diabetes mellitus, dyslipidemia) were also investigated. We found 13% patients with fQRS had history of PCI. 8% patients with fQRS had previous CABG. No significant difference between fQRS and non-fQRS groups regarding the history of PCI or CABG.

In our study, from the baseline characteristics, we found 46 people (64%) with fQRS. This did not differ greatly from the previous study that found the prevalence of fQRS in CAD patients was 58%¹⁷. We observed that most of patients with fQRS were males. Previous studies have reported that the occurrence of fQRS is 2-3 times higher in men than in women⁴. Type II Diabetes Mellitus (DM) and smoker were the

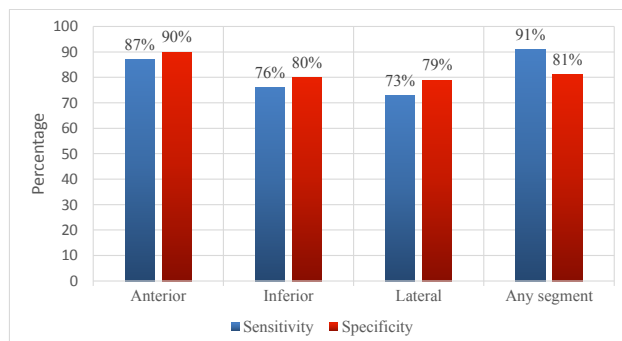


Figure 4. Sensitivity and specificity of fragmented QRS for each myocardial segment

risk factors that appeared to be significantly different between these groups.

Smoker was a significant risk factor in patients with fQRS in our study, this probably be due to patients with male-dominated fQRS, who tended to carry such risk factor. While incidence of hypertension and dyslipidemia were higher in patients with fQRS, but both were not statistically significant.

Our study findings demonstrated that fragmented QRS complexes on 12-lead ECG is a marker of myocardial perfusion abnormalities on stress SPECT study. Some previous studies have shown that fQRS became an important marker of ECG which exhibited a lower LVEF in CAD patients because its presence involves extensive areas of ischemia and myocardial damage^{18,19}. Our study also found similar results, patients with fQRS had significantly lower LVEF when compared to patients without fQRS. In addition, the LVESV, as an important parameter of LV, was significantly greater in patients with fQRS when compared with patients without fQRS in the resting phase and Dobutamine-load phase. The LVEF, stress and rest LVESV were measured using SPECT.

Previous experimental study confirmed that after MI, significant myocardial necrosis, with islands of viable myocardial tissue merge in abundant fibrous tissue. The islands of chronically ischemic myocardium display slow activation because of the partial depolarization and is probably responsible for abnormal conduction around the scarred myocardium and causing multiple spikes within QRS complexes¹². The presence of fQRS is associated with an existence of myocardial scar after myocardial infarction, therefore fQRS could detect prior silent myocardial infarction and remote myocardial scar

as detected by cardiac SPECT imaging^{9,20}. Our study supported this finding, the incidence of myocardial scar on SPECT analysis was significantly higher in patients with fQRS than in patients without fQRS. We could relate that the fragmentation of QRS complex could be a sign of myocardial scarring in CAD patients. This finding may also be the cause of lower left ventricular ejection fraction in patient with fQRS.

Some studies revealed that the initial R-wave deflection observed is due to shifting of the QRS vector to the right and posterior as a result of early depolarization, with relatively normal conduction through the upper septum and the right ventricle in left ventricular that has a high scar load^{21,22}. Similarly, notching or slurring in the S wave may represent the activation pattern in precordial leads (leftward to the transition zone) similar to the activation pattern in left bundle-branch block. Thus, the terminal conduction delay of QRS forces arising from the area of conduction block or slowing results in an fQRS of ventricular activation. Therefore, different morphologies of the QRS on the surface ECG may represent various directions of myocardial activation pattern, depending on the extent and location of scar tissue in the left ventricle.

According to prior study, male sex and type II DM were the predictors of more severe stenosis, bigger infarcts size and lower left ventricular ejection fraction^{23,24}. While other study revealed that CAD patients with fQRS appear to have a worse coronary collateralization system, thus affecting the extent of infarction^{17,25}. Our findings are also consistent with this study, considering that fQRS group predominantly were males and type 2 DM patients.

From the regional scar analysis, our study found that presence of fQRS complexes on an ECG had good sensitivity, specificity, PPV and NPV for predicting the presence of a corresponding focal regional myocardial scar. The extent of global and regional perfusion abnormalities is an important predictor of fQRS complex patterns on the ECG. Moreover, patients with fQRS also demonstrated greater LV volumes and lower global LV systolic function. This is further reassurance to the presence of LV remodeling after MI. Hence the prompt detection of fQRS patterns on 12-lead ECG may improve our early detection of patients with suspected CAD or prior MI.

Limitations of study

Smaller number of patients compared with previous study was the limitation of our study. Not all of the patients were diagnosed by coronary angiography as the gold standard in diagnosing CAD. In the future, further study with larger number of CAD patients who were diagnosed by coronary angiography needed, resulting in better analysis and can also determine the relationship between the fQRS on the 12-lead ECG with other parameters obtained from coronary angiography modality.

Conclusions

The fragmented QRS could serve as an important ECG marker to detect and localize the myocardial damage in patients with known or suspected CAD. Regional fQRS patterns denote the presence of regional myocardial scar and are a valuable diagnostic marker of CAD with good sensitivity and specificity.

Ethical Clearance

No: 155/TGL/KEPK FK USU-RSUP HAM/2018 from Health Research Ethical Committee, Medical Faculty of Universitas Sumatera Utara / H. Adam Malik General Hospital

Publication Agreement

The authors of this article give permission to Indonesian Journal of Cardiology (IJC) to publish this article in its journal if this article is accepted.

Conflict of Interest

The authors indicate no conflict of interest.

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List of Abbreviations

CABG : Coronary Artery Bypass Grafting
 CAD : Coronary Artery Disease
 DM : Diabetes Mellitus
 ECG : Electrocardiogram
 fQRS : Fragmented QRS
 LV : Left Ventricle
 LVEF : Left Ventricle Ejection Fraction
 LVESV : Left Ventricle End Systolic Volume
 MI : Myocardial Infarction
 MPI : Myocardial Perfusion Imaging
 ms : millisecond
 NPV : Negative Predictive Value
 PPV : Positive Predictive Value
 RISKESDAS : Riset Kesehatan Dasar
 SD : Standard Deviation
 SDS : Sum Difference Score
 SPECT : Single Photon Emission Computed Tomography
 SRS : Sum Rest Score
 SSS : Sum Stress Score

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