Fragmented QRS Is Associated with Improved Predictive Value of Exercise Treadmill Testing in Patients with Intermediate Pretest Likelihood of Significant Coronary Artery Disease

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Background: The predictive value of exercise treadmill testing (ETT) remains inadequate in diagnosing patients with suspected coronary artery disease (CAD) and needs to be improved.

Objective: The aim of this study was to investigate whether the presence of fQRS on 12-lead ECG would increase the PPV of ETT in patients with an intermediate likelihood of CAD.

Methods: fQRS, defined as the presence of notched R or S waves without accompanying typical bundle branch block or the existence of an additional wave-like RSR' pattern in the original QRS complex (with a duration of <120 ms), was assessed in 95 patients with positive ETT. Coronary angiogram (CA) was performed in all patients, divided into two groups as the significant CAD group and nonsignificant CAD group according to coronary artery lesions. The differences between the groups in terms of the presence of fQRS and clinical characteristics were investigated.

Results: The mean age of patients was 51.3 ± 11.3 years, and 74 of them were males (77.9%). fQRS was present in 47 (49.5%) patients, and significant CAD was demonstrated in 51 subjects (53.7%) among the enrolled subjects. fQRS was more prevalent in the significant CAD group compared to nonsignificant CAD group ($P < 0.001$). The presence of fQRS increased the PPV of positive ETT from 53.7% to 85.1%. In addition, fQRS was associated with the increased risk of significant CAD in multivariate analysis ($OR = 2.839$, $P < 0.001$).

Conclusion: In clinical practice, the presence of fQRS in patients with positive ETT may support clinicians during the decision-making process with regard to the referral for a coronary angiography.

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fragmented QRS; exercise stress test; coronary artery disease

INTRODUCTION

Coronary artery disease (CAD) is associated with increased mortality and morbidity despite advances in its diagnosis and treatment.¹ Clinical assessment of patients with suspected CAD often includes noninvasive tests. An exercise treadmill testing (ETT) is usually the first-line test in this context.² Current guidelines state that "further

testing is most useful in patients in whom the cause of chest pain is truly uncertain (i.e., the probability of CAD is between 20% and 70%)."¹ ETT has limited sensitivity and specificity for detecting CAD, and its positive predictive value (PPV) is lower in females, diabetics, asymptomatic, and young subjects.^{1,3–5} Consequently, patients are often referred for cardiac imaging tests, which are typically more complicated, costly, and invasive

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than ETT. Patients are also exposed to ionizing radiation using some imaging modalities. Some of the subjects referred for invasive coronary angiography following a positive ETT are found to have normal coronary arteries or insignificant CAD. There is a need for some additional parameters to ETT to make more accurate and timely diagnoses of CAD in patients in order to improve the standard of medical care, while reducing the growing economic burden on the health care system.

Fragmented QRS is defined as the presence of notched R or S waves without accompanying typical bundle branch block or the existence of an additional wave-like RSR' pattern in the original QRS complex (with a duration of <120 ms).⁶ In patients with CAD, fQRS was reported to be associated with myocardial scarring in several studies.^{6,7} The presence of fQRS has also been shown to be an independent risk factor of cardiac events and lower event-free survival in CAD patients.⁶⁻⁸

To our knowledge, no studies have investigated the impact of fQRS on the predictive value of ETT in patients with an intermediate likelihood of significant CAD. We aimed to evaluate whether adding fQRS to ETT would increase its PPV in patients with an intermediate likelihood of significant CAD.

METHODS

Ninety-five patients who admitted to the out-patient cardiology clinic with chest pain and considered to have intermediate pretest likelihood of significant CAD, and referred for diagnostic coronary angiography based on positive ETT, were enrolled in our study between January 2011 and September 2014. Pretest likelihood of significant CAD of the subjects was evaluated according to current guidelines.¹ Patients with previous history of CAD, left bundle block or right bundle block on ECG (QRS duration >120 ms), incomplete right bundle block, left ventricular ejection fraction <50%, established chronic kidney disease with estimated GFR values <60 mL/min, clinical or electrocardiographic findings suggestive of unstable angina or ACS, or with contraindications to the implementation of ETT or coronary angiography were excluded from the study. All patients were

older than 18 years at the time of the study and gave informed consent. The study complies with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee. Presences of hypertension (blood pressure $\geq$ 140/90 mmHg or taking antihypertensive drugs), diabetes [(HbA1c $\geq$ 6.5% and/or fasting plasma glucose $\geq$ 126 mg/dL (7.0 mmol/l) and/or 2-hour plasma glucose $\geq$ 200 mg/dL and/or intake of oral antidiabetic medication and/or application of insulin)], hyperlipidemia (HL), family history of premature CAD (male and female first-degree relatives <55 years and <65 years, respectively), tobacco use were evaluated and recorded.

fQRS

Fragmented QRS was defined as the presence of notching in R or S waves or additional R waves in the original QRS complex (<120 ms) and without typical bundle branch block pattern in at least two contiguous leads corresponded to a major coronary artery area on resting 12-lead surface ECG (Fig. 1).⁶⁻⁸

Exercise ECG

Standard ETT was performed with Bruce protocol according to "ACC/AHA Practice Guidelines on Exercise Testing" and positive ETT was defined as horizontal or down-sloping exercise-induced ST-segment depression $\geq$ 1.0 mm at 0.08 seconds after the J-point.² Patients with positive ETT (n = 94) were enrolled in the study.

Coronary Angiography

Coronary angiogram (CA) was performed in all patients. Selective CA was performed in multiple projections in all patients with positive ETT, according to standard Judkins technique using the femoral and radial approaches. Coronary angiograms were evaluated by two experienced cardiologist blinded to clinic status, exercise test results and other data of the study subjects. Significant CAD was defined as $\geq$ 70% stenosis in $\geq$ 1 major coronary artery ($\geq$ 2 mm in diameter) or $\geq$ 50% in the left main artery, determined by visual interpretation. Patients were divided into two groups as patients with significant CAD and nonsignificant CAD.

Figure 1. Example of fragmented QRS on 12-lead surface ECG.

Table 1. Patient Characteristic with Respect to Presence of Significant Coronary Artery Disease

	Significant CAD (n = 51)	Nonsignificant CAD (n = 44)	P Value
Age (years)	53.8 ± 10.7	48.3 ± 11.4	0.018*
Gender (n, %)			
Male	41 (55.6)	33 (44.6)	
Female	10 (47.6)	11 (52.4)	0.528
DM (n, %)	18 (75)	6 (25)	0.015*
HT (n, %)	28 (66.7)	14 (33.3)	0.024*
Hyperlipidemia (n, %)	11 (73.3)	4 (26.7)	0.096
Family history (n, %)	19 (67.9)	9 (32.1)	0.073
Tobacco use (n, %)	28 (62.2)	17 (37.8)	0.113
fQRS present (n, %)	40 (85.1)	7 (14.9)	
fQRS absent (n, %)	11 (22.9)	37 (77.1)	<0.001*

CAD = significant coronary artery disease; DM = diabetes mellitus; Family history = history of premature coronary artery disease; fQRS = fragmented QRS complex; HT = hypertension; *P < 0.05.

In this study, all patients had positive ETT results, the presence of significant CAD identified a "true positive" test and absence of significant CAD indicated a "false positive" test. PPV was calculated as true positive divided by the sum of true positive plus false positive multiplied by 100%. PPV was calculated for the entire study group; for ETT and fQRS.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). The values were expressed as mean ± standard deviation or percentage. Variables were analyzed for the presence of normal distribution using the test Kolmogorov-Smirnov test. Differences of variables between the groups were assessed using the independent Student *t*-test. Associations between categorical variables were evaluated using the chi-square or Fisher's exact tests. Multiple logistic regression analysis was used to assess the ability of independent variables in the diagnosis of significant CAD. A P value <0.05 was considered to be statistically significant.

RESULTS

The mean age of patients was 51.3 ± 11.3 years and there were 74 males (77.9%) and 21 females (22.1%) among enrolled subjects. fQRS was present in 47 (49.5%) subjects and angiography indicated significant CAD was demonstrated in 51 subjects (53.7%) among the entire study population (Fig. 2).

Compared to nonsignificant CAD group, patients with significant CAD were older (53.8 ± 10.7 vs 48.3 ± 11.4, P = 0.018) and had more prevalence of DM and HT (75% vs 25%, P = 0.015 and 66.7% vs 33.3%, P = 0.024). There was no statistically significant difference between patients with significant CAD and those nonsignificant CAD, in regards to gender, history of hyperlipidemia, family history of premature CAD and tobacco use (Table 1).

The frequency of fQRS was significantly higher in patients with significant CAD compared to nonsignificant CAD (85.1% vs 14.9%, P < 0.001; Table 1). The relationship between all the investigated clinical and laboratory parameters and presence of significant CAD was evaluated using multiple logistic regression analysis. Only the presence of fQRS was found to be statistically significant in

Figure 2. Study population respect to presence of significant coronary artery disease and fQRS.

Table 2. The Relationship between Variables and Significant CAD

	Odd Ratio	P Value	95% Confidence Interval	
Age	0.024	0.308	0.978	1.074
DM	1.100	0.096	0.091	1.214
HT	0.390	0.488	0.225	2.037
fQRS	2.839	<0.001*	0.020	0.175

CAD = significant coronary artery disease; DM = diabetes mellitus; fQRS = fragmented QRS complex; HT = hypertension; *P < 0.05.

the constructed model. The presence of fQRS was significantly associated with increased the risk of significant CAD (OR = 2.839, P < 0.001; Table 2).

In our study the PPV of ETT was calculated as 53.7%. Among patients with positive ETT, presence fQRS on 12-lead surface ECG predicted significant CAD with a sensitivity of 78.4%, a specificity of 84.1% and a positive predictive value of 85.1%.

DISCUSSION

The main finding of this study was that the presence of fQRS on 12-lead surface ECG increased the positive predictive value of positive ETT from 53.7% to 85.1% in patients with intermediate pretest likelihood of significant CAD.

The frequency of fQRS on ECG has been previously reported to be 19.7% in a population-based study.⁹ fQRS had higher sensitivity (85.6%) and negative predictive value (92.7%) than did the

Q wave, and had a specificity 89% for detecting the myocardial scar in patients with CAD.^{7,8} The presence of fQRS has been shown to predict mortality in CAD patients and particularly in NSTEMI acute coronary syndrome patients.¹⁰⁻¹² There is evidence that the fQRS is an independent predictor of low LV EF and infarct burden acute MI patients.^{13,14} Moreover, all-cause mortality (34.1% vs 25.9%) and cardiac event rate (49.5% vs 27.6%) in CAD were revealed to be higher in patients with fQRS than in patients without fQRS, and the presence of fQRS was an independent predictor for cardiac events.¹⁵⁻¹⁷

In our study, the frequency of fQRS was higher among patients with significant CAD and independently predicted significant CAD in analysis. The relationship between fQRS and myocardial scar due to ischemia is well known and linked to inhomogeneous conduction in the myocardium, which results as a spike on the ECG.^{6,7} fQRS results from conduction abnormality around the fibrotic and scarred myocardium in patients with CAD.^{6,7} The increased frequency of fQRS in a significant CAD group, which has been found in this study, may be explained by the constant interaction between ischemia and inhomogeneous electrical conduction of myocardium.

We revealed that the presence of fQRS among patients with positive ETT was able to predict significant CAD with a sensitivity of 78.4%, a specificity of 84.1%, a positive predictive value of 85.1%, and a negative predictive value of 72.5%. In addition, the PPV of the ETT was found to be 53% in our study. Surprisingly, the presence of fQRS on a resting 12-lead surface ECG increased

the PPV of a positive ETT from 53.7% to 85.1% in patients with intermediate pretest likelihood of significant CAD. Now-a-days, ETT, commonly used as an initial noninvasive test for diagnosing suspected CAD, has substantial limitations in clinical practice. The PPT of ETT depends on the prevalence of CAD in the population tested and is particularly lower in females, diabetics, and asymptomatic and young subjects.³⁻⁵ The sensitivity and specificity of ETT is reported as 45–50% and 85–90%, respectively.¹⁸ Therefore, subjects suspected for CAD are often referred for cardiac imaging, which is more complicated and costly than ETT. Especially, subjects perfused coronary angiograms are exposed to ionizing radiation and complications related to invasive procedures. Some of the subjects referred for invasive coronary angiography following a positive ETT also may have normal coronary arteries or nonsignificant CAD. Hence, there is a growing interest in investigating additional parameters in order to improve the diagnostic accuracy of ETT. Previous studies assessed different parameters in this context. Rosenmann, et al. evaluated HfQRS in ETT and showed that HfQRS provided a sensitivity of 70% and specificity of 80% for the detection of angiographically significant coronary obstruction in a study that only examined women.¹⁹ In another study, Belardinelli, et al. examined cardiopulmonary exercise testing in diagnosing myocardial ischemia in subjects with chest pain for improving the accuracy of ETT.²⁰ They found that, compared with ETT, PPV improved significantly from 33% to 73%.²⁰ But the method used in the mentioned study is more complicated and impractical compared to a simple-sign “fQRS” on a surface ECG.

Because of clinical challenges in a noninvasive diagnosis with ETT of CAD, our results may suggest useful insights to clinicians. Detecting fQRS on an ECG is noninvasive, easily applied, cheap, and readily available and may help clinicians to recognize subjects suspected with CAD for coronary angiography more accurately.

Major limitation of the study is lack of patients with negative ETT where QRS fragmentation could be evaluated. Since we have included only patients with a positive stress test and have no control group with negative ETT, we could not evaluate the impact of fQRS on the sensitivity and specificity of ETT. The others limitations of the study are the lack of assessment of fQRS during exercise test, small sample size, cross-sectional design, and

absence of follow-up in terms of clinical events. Finally, as we visually evaluated CA to define the significance of CAD, the assessment of coronary artery hemodynamics, such as fractional flow reserve, was not carried out.

CONCLUSION

We have demonstrated that fQRS, during the noninvasive evaluation of patients with an intermediate likelihood of CAD, could increase the positive predictive value of ETT. According to these results, the presence of fQRS in patients with a positive ETT may support the clinician during the decision-making process with regard to subjects referred for coronary angiography.

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