Detection of Multivessel Disease Post Myocardial Infarction Using an Exercise-Induced QRS Score

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Objective: The aim of this study was to investigate the ability of Athens QRS score values to detect stenoses in other coronary arteries than the obstructed ones (which caused the myocardial infarction [MI]) in patients with a history of MI.

Methods: We studied 125 patients (93 males and 32 females, mean age 54 ± 7 years [range 45–68 years]) with a history of MI (46 patients with anterior MI, 54 patients with inferior MI, 25 patients with lateral MI). All patients underwent treadmill exercise testing and coronary arteriography.

Results: Athens QRS score values were inversely related to the extent of CAD: -0.5 ± 0.3 mm for patients with 1-VD (obstructed vessel), -3.4 ± 2.2 mm for patients with 2-VD (obstructed vessel and stenosis in another vessel), and -5 ± 1.8 mm for patients with 3-VD (obstructed vessel and stenoses in two more vessels). The ROC curves for the detection of multivessel disease showed that the area under the curve for QRS score values < -3 mm is significantly higher than the curve for ST-segment depression ≥ 1 mm (0.948 vs 0.792, $P < 0.001$).

Conclusions: Values of the Athens QRS score less than -3 may distinguish single- from multivessel coronary artery disease in patients with a history of MI.

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QRS score, exercise testing, coronary artery disease, myocardial infarction.

Exercise testing is an important diagnostic tool in assessing patients with coronary artery disease (CAD).¹ Especially in patients with a prior history of myocardial infarction (MI), this method plays an important role in determining the prognosis of the disease.¹

It is known that mortality within the first year after a myocardial infarction ranges from 6% to 20%, followed by an annual mortality rate of 3–4%.^{2,3} Approximately 11% of patients with a new myocardial infarction experience another myocardial infarction within the first year, and 16% of this population experience a second myocardial infarction within 2 years.⁴ The occurrence of postinfarction angina, symptoms and signs of heart failure, complex ventricular arrhythmias, as well as mechanical complications (left ventricular free wall or papillary muscle rupture) are related with poor prognosis. However, the majority of the patients

recovering from a myocardial infarction have an uncomplicated course. In spite of that, the literature contains studies showing that a significant portion of these patients have actually severe underlying CAD.⁵

Exercise testing is indicated for patients with a history of a recent uncomplicated acute myocardial infarction, mainly for prognostic reasons. It aims to stratify them in two groups: (1) high risk patients, who are going to benefit from an aggressive therapeutic strategy (e.g., percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass grafting [CABG]), and (2) low risk patients, for whom a conservative medical treatment policy is more likely to be implemented.^{6,7} ET is usually carried out either before the patient leaves the hospital using the modified Bruce protocol, or 3 to 4 weeks after hospitalization using the unabridged, maximal Bruce protocol.⁸

The relatively low sensitivity and specificity of the standard exercise testing ischemic marker (ST-segment deviation), led to studies that examined the alterations of the amplitudes of Q, R and S deflections during exercise testing—the relations of these changes to myocardial ischemia were addressed as well.^{9,10} On the contrary, other investigators challenge the credibility of these findings.^{11,12} However, a QRS index was proposed,¹³ which is calculated based on Q, R, and S changes in leads aVR and V5 during exercise testing, and is independent of ST-segment changes. This index serves as a new indirect diagnostic ischemic criterion. Values of the score equal to or higher than 5 mm discriminate the normal subjects from patients with CAD, with a sensitivity ranging from 75% to 86% and a specificity ranging from 73% to 79%.^{13,14} The comparison of coronary arteriography findings with the respective Athens QRS score values showed that negative values are always related to CAD. Furthermore, as the QRS score values became more negative, the number of the obstructed coronary arteries increased, which suggests that this score is also related with the severity of CAD.

The purpose of this study was to investigate the possible relationship between abnormal QRS score values and the presence of lesions in other coronary arteries, besides the obstructed ones, which caused myocardial infarction in patients with a history of myocardial infarction.

METHODS

Overall, 125 patients with a recent myocardial infarction (93 males and 32 females) were studied. The mean age was 54 ± 7 years. The criteria used for the diagnosis of myocardial infarction were based on the applicable guidelines at the time of recruitment,³⁴ for example, at least 2 out of (1) typical chest pain, (2) typical ECG changes, (3) typical raise of biochemical markers.

The ECG criteria used to locate a myocardial infarction were: septal when Q waves were present in leads V1-V2; anterior when they were present in leads V3-V4; anteroseptal if present in V1-V4; lateral when present in leads I, aVL, and V6; anterolateral when present in leads I, aVL, and V3-V6; extensive anterior when present in leads I, aVL and V1-V6; high lateral when present in leads I and aVL; inferior when present in leads II, III, and aVF, and anteroinferior, or apical, when present in

leads II, III, aVL; and in one or more of the V1-V4 leads.^{36,37}

All patients underwent a treadmill exercise testing using the multistage Bruce protocol 1 month post myocardial infarction. One week after the exercise testing the studied patients underwent coronary arteriography and left ventriculography.

Patients with left or right bundle branch block, left or right ventricular hypertrophy, ventricular preexcitation, valvular, or congenital heart disease, as well as patients receiving digitalis, were excluded from the study. The protocol was approved by our hospital's Ethics Committee, and written informed consent was obtained from all participants. Clinical characteristics of studied patients are shown in Table 1.

Exercise Testing

Exercise testing was carried out on a Quinton 5000 treadmill system (Quinton Instruments Co., Seattle, WA) according to the multistage Bruce protocol. During the procedure leads V₁, aVF, and V₅ were continuously monitored. A 12-lead electrocardiographic tracing was recorded every minute. Cuff blood pressure was measured every minute and before every stage change. Exercise endpoints included achieving target heart rate, development of maximal ST-segment depression of 3 mm or greater, excessive blood pressure (BP) increase (systolic BP equal or greater of 230 mmHg and diastolic BP equal or greater of 130 mm Hg), development of severe angina, incapacitating fatigue, dyspnea, and severe ventricular arrhythmias. All medications were discontinued for at least five half-lives before exercise testing performance.

Table 1. Clinical Characteristics of Studied Patients

Number of patients	125
Men/women	93/32
Age	54 ± 7
Arterial hypertension	12 (10%)
Hypercholesterolemia	58 (46%)
Diabetes mellitus	7 (6%)
Smokers	62 (50%)
Myocardial infarction	
Anterior	46 (37%)
Inferior	54 (43%)
Lateral	25 (20%)

Values are mean ± SD or n (%).

ST-segment Criteria

An exercise test result was considered positive if there was (1) a horizontal or downsloping ST-segment depression of at least 1 mm, 60 msec beyond the J point or (2) an upsloping ST-segment depression of 1.5 mm or greater, 80 msec beyond the J point, or (3) an ST-segment elevation of at least 1 mm.¹⁵ In patients with abnormal resting ST segments, we used the criterion of 2 mm additional exercise-induced ST-segment depression to characterize an exercise test positive.³⁵

An exercise ECG was considered negative (based on ST-segment changes) when the patient achieved at least 85% of the maximal predicted heart rate in the absence of ischemic ST-segment changes. Exercise ECGs without ischemic ST-segment changes, which were terminated at a heart rate <85% of the predicted maximal heart rate were considered inconclusive.

The interpretation was carried out by two independent investigators who were unaware of the angiographic findings. Intraobserver and interobserver variability for ST-segment changes was 0.3 ± 0.1 and 0.3 ± 0.3 mm, respectively.

The Athens QRS Score

Exercise-induced changes of individual waves of the QRS complex detected coronary artery disease with a low specificity or sensitivity. Therefore, they were incorporated into a composite expression, the QRS score, with the anticipation that a false-negative response of a wave would be negated by the true-positive responses of the other two, and specificity would improve.

The derivation of the QRS score was based on the following observations: (1) With an increasing number of obstructed coronary arteries the value of DR in leads aVF and V5 decreases, whereas the values of DQ and DS in the same leads increase, resulting in a progressive decrease in the value of the Athens QRS score. (2) The Athens QRS score derived from both leads aVF and V5 was better related to the number of obstructed coronary arteries than the Athens QRS score derived exclusively from lead V5.¹³

From the exercise test, the ECGs of patients in the standing position before and immediately after exercise were used. The amplitudes of Q, R, and S waves were measured in leads aVF and V5 from the isoelectric line to the peak of the R wave and to

the notch of Q and S waves. The amplitude of each wave was then approximated to the nearest 0.5 mm increment. Measurements were taken from the averaged beat, which was automatically provided by the computerized commercially available exercise system (Quinton 5000). Average beats consisted of a 20-second average of displayed leads and were updated every 10 seconds. However, when it was thought that the QRS complex of the averaged beat was not representative of the QRS complexes of the tracing ($n = 9$ [7%]), the Athens QRS score was calculated from three randomly selected consecutive beats. Measurements of the Q-, R- and S-wave amplitudes were performed by two of the investigators without prior knowledge of the results of the coronary arteriography.

The Q-, R- and S-wave values of the ECG immediately after exercise were subtracted from the values prior to exercise. The differences were called delta Q (δQ), delta R (δR), and delta S (δS). Delta Q and δS were subtracted from δR . These values of leads aVF and V5 were summed to form the QRS score (in millimetres) according to the formula:¹³

QRS score

$$= (\delta R - \delta Q - \delta S)aVF + (\delta R - \delta Q - \delta S)V5$$

A QS complex was treated as either a Q- or an S wave.

Athens QRS score values <+5 mm were considered abnormal.

Intraobserver and interobserver variability for the Athens QRS score values was 0.3 ± 0.2 and 0.4 ± 0.3 mm, respectively.

Coronary Arteriography and Left Ventriculography

All patients underwent left ventriculography in the 30-degree right anterior oblique projection at 40 frames/sec. The area-length method¹⁶ was used for the calculation of the left ventricular ejection fraction. All patients underwent selective coronary arteriography using the percutaneous (Judkins) technique. The left coronary artery was visualized in the 60-degree left anterior oblique, in the 30-degree right anterior oblique, and in the left lateral with 30-degree cranial angulation positions. The right coronary artery was visualised in the 60-degree left anterior oblique and the 30-degree right anterior oblique positions. Significant coronary artery disease was diagnosed when there was a diameter narrowing of $\geq 70\%$ in the lumen of the left anterior

descending, the left circumflex, the right coronary artery, or a diameter narrowing $\geq 50\%$ of the left main coronary artery. The interpretation was performed by two investigators who were unaware of exercise testing results.

Statistical Analysis

Values are expressed as mean $\pm$ SD. Chi-square test, *t*-test, and one-way analysis of variance with Bonferroni analysis for pairwise comparisons between group means, as appropriate, were used to compare the studied variables in the different study groups. In order to evaluate the discriminative ability of the QRS score and of exercise-induced ST-segment deviation, ROC curves were constructed for the different study subgroups. All tests of statistical significance were two-tailed and were considered to be significant at a 0.05 level of statistical significance. Statistical analyses were performed with SPSS statistical software (version 8.0, SPSS, Chicago, IL).

RESULTS

The exercise test parameters of patients with MI who were included to the study, as well as the correlations between these parameters and the hemodynamic findings, are summarized in Table 2.

Based on coronary arteriography, 48 (38%) patients had 1-vessel disease, 43 (34%) had 2-vessel disease, and 34 (27%) had 3-vessel disease. The relationship between infarct location and diseased artery in the 48 patients with 1 vessel disease was

as follows: 19 patients had an anterior myocardial infarction, 14 patients had an inferior myocardial infarction, and 15 patients had a lateral myocardial infarction. All patients with an anterior myocardial infarction had a left anterior descending artery lesion. Of the 14 patients with an inferior myocardial infarction, 13 had a right coronary artery lesion, and 1 had a left circumflex lesion. Of the 15 patients with a lateral myocardial infarction, 13 had a left circumflex artery lesion, while 2 had a lesion of the diagonal branch of the left anterior descending artery.

The correlation between ET parameters and hemodynamic findings shows that the three patient groups, with 1-vessel, 2-vessel, and 3-vessel disease, did not exhibit statistically significant differences ($P = \text{NS}$) with regard to age (51 ± 8 , 55 ± 7 , and 57 ± 6 , respectively), duration of exercise (438 ± 105 , 416 ± 102 , and 396 ± 80 sec, respectively), maximal heart rate (160 ± 18 , 154 ± 17 , and 148 ± 20 beats/min, respectively), maximal ST depression (1.6 ± 0.5 , 2.0 ± 0.3 , and 2.1 ± 0.2 mm, respectively), and ejection fraction (52 ± 3 , 50 ± 2 , and $49 \pm 4\%$, respectively).

There was a statistically significant difference ($P < 0.05$) between men and women with 3-vessel disease (30/4), and between patients with 1-vessel and 2-vessel disease with regard to the maximal systolic blood pressure achieved during ET (170 ± 10 mm Hg vs 186 ± 12 mm Hg, $P < 0.05$).

Angina or angina-like symptoms occurred during ET with statistically significant difference ($P < 0.05$), between patients with 3-vessel disease,

Table 2. Exercise Testing Parameters of Studied Patients. Correlation with Catheterization Data

	Patients With			P Value
	1-VD (n = 48)	2-VD (n = 43)	3-VD (n = 34)	
Men/women	35/13	28/15	30/4	<0.05
Age	51 ± 8	55 ± 7	57 ± 6	NS
Exercise duration (sec)	438 ± 105	416 ± 102	396 ± 80	NS
Maximal heart rate (beats/min)	160 ± 18	154 ± 17	148 ± 20	NS
Maximal systolic blood pressure (mm Hg)	186 ± 12	178 ± 10	170 ± 10	<0.05
Maximal ST depression (mm)	1.6 ± 0.5	2.0 ± 0.3	2.1 ± 0.2	NS
Athens QRS score (mm)	-0.5 ± 0.3	-3.4 ± 2.2	-5 ± 1.8	<0.001
Angina	7 (15%)	14 (33%)	13 (38%)	<0.05
Myocardial infarction				
Anterior	19 (41%)	16 (35%)	11 (24%)	
Inferior	14 (26%)	21 (39%)	19 (35%)	
Lateral	15 (60%)	6 (24%)	4 (16%)	
Ejection fraction	52 ± 3	50 ± 2	49 ± 4	NS

VD = vessel disease. Values are mean $\pm$ SD or n (%).

patients with 2-vessel disease, and patients with 1-vessel disease (38%, 33%, and 15%, respectively).

Of the 125 patients studied, 46 (37%) had an anterior MI, 54 (43%) had an inferior MI, and 25 (20%) had a lateral MI. Of the 46 patients with an anterior MI, 19 (41%) had 1-vessel disease, 16 (35%) had 2-vessel disease, and 11 (24%) had 3-vessel disease. Of the 54 patients with an inferior MI, 14 (26%) had 1-vessel disease, 21 (39%) had 2-vessel disease, and 19 (35%) had 3-vessel disease. Finally, of the 25 patients with a lateral MI, 15 (60%) had 1-vessel disease, 6 (24%) had 2-vessel disease, and 4 (16%) had 3-vessel disease.

It becomes evident in Figure 1, that ST-segment depression during exercise testing occurred in 71 of 125 patients (sensitivity 57%), whereas abnormal Athens QRS score values occurred in 110 of 125 patients (sensitivity 88%). This observation indicates that the QRS score values are strongly related to the hemodynamic findings in comparison to the other exercise testing parameters.

Mean value of QRS score in patients with multivessel disease was significantly lower compared to patients with single-vessel disease (-4.9 ± 2.3 vs -0.5 , $P < 0.001$). The ROC curves of the diagnostic value, the area under the curve, and the relative P values of QRS score values ≤ -3 , and of ST-segment depression ≥ 1 to detect multivessel disease, are presented in Figure 2.

DISCUSSION

The present study shows that the QRS score can be used for patients with a history of myocardial

Figure 1. Sensitivity of ST-segment depression and Athens QRS score values.

infarction to detect single- or multivessel disease. This is a novel indication for this score that has been investigated in the past only as a marker of ischemia to detect CAD. The results of the present study show that QRS score values diagnostically approach the number of the diseased coronary vessels, so that negative values correlate with lesions in other than the occluded arteries.

Up to this point, the usefulness of ET for patients with MI was mainly focused in the prognostic area. This means that uncomplicated patients were referred to ET in order to identify a high risk subgroup, which is more likely to benefit from the aggressive therapeutic strategy by means of coronary angioplasty or bypass grafting.

According to the available literature, the studied ET parameters in patients with a history of MI are confined mainly to ST-segment changes. Theroux and associates⁸ reported that ST depression ≥ 1 mm during ET is a highly prognostic indicator for sudden death during the first year after a myocardial infarction. Sami et al.¹⁷ concluded that there is an increased risk of cardiac arrest and the recurrence of MI in patients who were not able to complete the test due to chest pain and ST depression ≥ 2 mm.

Figure 2. The ROC curves for the detection of multivessel disease and the diagonal reference lines are presented. The area under the curve for QRS score values < -3 (thick black line) is 0.948, 95% CI = 0.907–0.909, ($P < 0.001$). The area under the curve for ST-segment depression ≥ 1 mm (dotted line) is 0.792, 95% CI = 0.707–0.877, ($P = 0.001$).

It is also known that ST elevation in the resting ECG in Q-leads relates to extended infarctions,¹⁸ whereas if the ST elevation occurs during ET, it represents dyskinesia in the infarcted area^{19–22} and the resultant dysfunction of the left ventricle.

The relationship between the ST elevation in Q-leads during ET after a MI and the myocardial viability has been challenged. Gerwirtz and associates²³ found a positive relationship using nuclear techniques. Bodi et al.²⁴ studied a group of patients 1 week and 6 months after MI using ET and coronary arteriography. They concluded that 1 month after the MI, there was a lower percentage of viable myocardium in patients with ST elevation at rest, as well as in patients with ST elevation during ET in comparison with patients without ST elevation in non-Q leads at rest or during ET. After 6 months though, there was no significant difference between the two groups.

Nakaho et al.²⁵ studied the clinical significance of ST elevation ≥ 1 mm in Q-leads during ET and concurrent ST depression ≥ 1 mm in other leads (mirror image) in patients with a history of MI and 1-vessel disease. Using PET, they found that patients with both parameters exhibited a viable myocardium inside the infarcted area, whereas patients with ST elevation in Q-leads but without a mirror image during ET did not exhibit viable myocardium. The prospective sensitivity, specificity, and accuracy of this finding were 84%, 100%, and 94%, respectively.

Other studies²⁶ showed that Q-wave prolongation during ET is an indicator of viability inside the area surrounding a myocardial scar.

Besides ST changes during ET, other parameters that have been studied include the duration of the test, the achieved level of METS, and the double product, which predict the myocardial consumption of O₂ (MVO₂).²⁷ The aforementioned parameters represent markers of myocardial dysfunction.

Given that the severity of CAD is a significant parameter for survival^{28,29} and considering that the coronary arteriographies of patients with a recent MI usually reveals multivessel disease in 50–75% of them,^{5,19,22,30} studies have been conducted that correlate ST changes during ET after MI with the severity of the disease.

Fuller et al.³¹ and Schwartz et al.⁵ concluded that ST depression ≥ 1 mm, the occurrence of angina, or both during ET after a MI, identify the subgroup of patients with multivessel disease,

whereas the hemodynamic parameters (double-product, achieved workload) do not correlate with the extent of the disease. In both studies, the sensitivity for the discrimination of multivessel disease ranges from 55% to 67%, the specificity is 90%, and the positive prognostic value is 90%. Fuller et al.³¹ found that 73% of patients with a normal ET had 1-vessel disease. On the contrary, Schwartz et al.⁵ reported that more than 50% of patients with a normal ET had multivessel disease. Accordingly, a positive ET after MI identifies many patients with multivessel disease, but a negative test does not indispensably exclude this contingency.

Previous studies showed that the QRS score has been proven to be more sensitive in comparison to ST changes (86% vs 62%) for the discovery of myocardial ischemia^{13,14} and in clinical trials it is used as a strong indicator of an abnormal ET.^{32,33}

In conclusion, it seems that the Athens QRS score has not been analyzed in previous studies with regard to the presence of viable myocardium and the extent of myocardial ischemia in patients with MI. This study shows that values of the QRS score ≤ -3 mm can be useful for the discrimination between single- and multivessel disease after myocardial infarction, which, in turn, may contribute to the decision making with regard to the implementation of the optimal therapeutic strategy for these patients, for example, medical or interventional.

The results of this study lead to the following conclusions: the follow-up of patients after myocardial infarction using exercise testing comprises a valuable and irreplaceable diagnostic tool for the identification of the severity of coronary artery disease, and for the determination of prognosis of patients with a previous myocardial infarction.

ST-segment changes occurring during exercise testing in patients with a history of MI exhibit low sensitivity for the identification of ischemia. The QRS score contributes to the optimal approach of patients with a history of myocardial infarction, not only by increasing the sensitivity of exercise testing, but also by tracing the presumptive number of the diseased coronary arteries.

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