The Prognostic Value of a QRS Score during Exercise Testing

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Summary

Background: Values of a QRS score have been positively related to the number of narrowed coronary arteries and to the extent of myocardial ischemia in radionuclide imaging techniques.

Hypothesis: This study was conducted to evaluate the potential prognostic information of abnormal values of this QRS score during treadmill exercise testing in patients with established coronary artery disease (CAD).

Methods: In all, 309 patients (258 men, 51 women, mean age 56.1 ± 10.0 years) with documented CAD, underwent a treadmill exercise test and coronary arteriography at baseline. Subsequently, they were prospectively followed to a maximum of 36 months (mean follow-up 23 ± 13 months, median 25 months).

Results: During the follow-up period, 20 patients (6.5%) died from acute myocardial infarction. Abnormal QRS score values were found to be significantly and independently associated with cardiac mortality (QRS ≤ -4 : relative risk 11.7; 95% confidence interval = 2.5–55.4; $p = 0.002$).

Conclusions: Taking into consideration the importance of exercise testing in the management of ischemic heart disease, the use of this QRS score could be of clinical value in predicting the outcome of patients with documented CAD.

Key words: prognosis, coronary artery disease, exercise testing, QRS score

Introduction

Coronary artery disease (CAD) is known to be the leading cause of death worldwide.¹ Exercise testing (ET) has been used for many years, and its use has contributed significantly to the management of patients with known or suspected CAD.² Many modifications have been proposed for improving the diagnostic accuracy of ET. Among them, a QRS score has been used, which combines exercise-induced changes in the amplitude of Q, R, and S waves, also known as Athens QRS score.³ So far, this index has been positively related, not only to the number of narrowed coronary arteries, but also to the extent of myocardial ischemia in radionuclide imaging techniques.⁴ Furthermore, from the diagnostic point of view, this score was proposed as a clinically useful predictor for the presence or absence of significant coronary stenosis.⁵

In clinical practice, however, risk assessment and prognostic stratification direct all patient management decisions. In turn, each therapeutic intervention aims at a favorable modification of a patient's future risk.² The aim of this study was to determine whether the above-mentioned QRS score, reported to provide additional information about the functional status of the ischemic myocardium, could provide prognostic information as well. To challenge this hypothesis, we conducted a specifically designed prospective study, aiming to evaluate the potential prognostic information of abnormal QRS-score values in patients with established CAD.

Methods

Between January 1999 and June 1999, 582 consecutive patients with documented CAD, who were referred for assessment, were screened as to their eligibility for the study. Patients with either a CAD diagnosis based on coronary arteriography, with or without angina, or a documented history of myocardial infarction (MI), were included in the study. The documentation of a previous MI was based on the applicable guidelines at the time of recruitment, for example, at least two of (1) typical chest pain, (2) typical electrocardiographic (ECG) changes, (3) typical rise in biochemical markers.⁶ Sig-

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nificant CAD was diagnosed when there was a diameter narrowing of $\geq 50\%$ in the lumen of a major coronary artery.⁷ The exclusion criteria were (1) conditions that render the assessment of the QRS score not feasible or unreliable (e.g., left or right ventricular hypertrophy [LVH or RVH], left or right bundle-branch block [LBBB or RBBB], ventricular preexcitation);³ (2) patients with a known history of valvular or congenital heart disease, cardiomyopathy, myocarditis, pericarditis, or pulmonary hypertension; (3) patients with second- or third-degree heart block, or sick sinus syndrome when they presented with a baseline ECG demonstrating severe bradycardia (< 50 beats/min) or atrial fibrillation causing symptoms or hemodynamic compromise; (4) patients with uncontrolled cardiac arrhythmias (atrial fibrillation or flutter, supraventricular or ventricular tachycardia), causing symptoms or hemodynamic compromise; (5) patients with a permanent pacemaker; (6) patients with symptomatic systolic heart failure (New York Heart Association [NYHA] II–IV); (7) patients who refused to undergo coronary arteriography; (8) patients who had a history of percutaneous coronary intervention and/or coronary artery bypass graft surgery; (9) psychosocial and geographic reasons making study participation impractical. Of the 582 screened patients, 332 were eligible to be included in the study and underwent a treadmill ET, as well as coronary arteriography and left ventriculography at baseline. Subsequently, all patients were followed to a maximum of 36 months (follow-up visits at 6, 12, 24, and 36 months) with regard to their outcome; 23 patients (6.9%) were lost to follow-up. The remaining 309 patients (258 men, 51 women, mean age 56.1 ± 10.0 years) were followed until the first occurrence of cardiac death, or until 36 months were completed (mean follow-up 23 ± 13 months, median 25 months). The study protocol was in accordance with the Declaration of Helsinki and was approved by the ethics committee of our institution. Each patient gave written informed consent before participation in the study. Baseline characteristics of the study population are shown in Table I.

Exercise testing was carried out on a Quinton-5000 treadmill system (Quinton Instruments Co., Seattle, Wash., USA) according to the multistage Bruce protocol. The procedure and the interpretation were performed according to applicable guidelines² by two independent investigators who were blinded to clinical and/or other findings. During the procedure, leads V₁, aVF, and V₅ were monitored continuously. A 12-lead ECG 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, excessive blood pressure (BP) increase (systolic BP ≥ 230 mmHg and diastolic BP ≥ 130 mmHg), development of severe angina, incapacitating fatigue, dyspnea, and severe ventricular arrhythmias. All medications were discontinued for at least five half-lives before the patients underwent exercise testing. An exercise test result was considered positive if there was (1) a horizontal or downsloping ST-segment depression of at least 1 mm, 60 ms beyond the J point; (2) an upsloping ST-segment depression of ≥ 1.5 mm, 80 ms beyond

the J point; or (3) an ST-segment elevation of at least 1 mm. 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 maximum were considered inconclusive. The Duke Exercise Treadmill Score was calculated as follows: Duration of exercise in min $- (5 \times \text{maximal net ST-segment deviation in mm}) - (4 \times \text{angina index})$.⁸ The QRS score was calculated as follows:

$$\text{QRS score} = (\Delta R - \Delta Q - \Delta S) aVF + (\Delta R - \Delta Q - \Delta S) V_5,$$

where $\Delta R/\Delta Q/\Delta S = R/Q/S$ at rest $- R/Q/S$ at peak-exercise.³ The QRS score was derived from leads aVF and V₅ because, according to the relevant original paper, it was better related to the number of obstructed coronary arteries than the QRS score derived from other leads or their combinations.³ The calculation of the QRS score from leads aVF and V₅ has been tested in other cohorts by independent investigators with similar results.^{4, 5} Coronary arteriography and left ventriculography were performed according to the applicable guidelines.⁷ The interpretation was performed by two investigators who were blinded to exercise testing results.

Statistical Analysis

To evaluate the discriminative ability of the QRS score, receiver operator characteristics (ROC) curves were constructed. Logistic regression analysis was used to evaluate univariate risk ratios of the studied variables (covariates). All tests of statistical significance were two-tailed and were considered to be significant at a 0.05 level of statistical significance. Kaplan-Meier curves of stratified QRS scores were constructed using the Kaplan-Meier method.

TABLE I Patient baseline characteristics according to QRS-score values

	QRS-score values		p Value
	> -4 mm (n = 198)	≤ -4 mm (n = 111)	
Age (years, mean $\pm$ SD)	54.7 ± 10.0	57.8 ± 9.7	NS
Males/females (n)	145/31	113/20	NS
Hypertension (n, %)	23 (13)	19 (14)	NS
Smokers (n, %)	83 (47)	65 (49)	NS
Diabetes (n, %)	39 (22)	27 (20)	NS
Hypercholesterolemia (n, %)	65 (37)	46 (35)	NS
Chest pain (n, %)	79 (45)	59 (44)	NS
History of MI (n, %)	58 (33)	41 (31)	NS
Receiving beta blockers (n, %)	49 (28)	41 (31)	NS
Receiving CCBs (n, %)	53 (30)	37 (28)	NS

Abbreviations: MI = myocardial infarction, SD = standard deviation, CCBs = calcium-channel blockers.

TABLE II Exercise testing parameters, coronary arteriography and left ventriculography parameters, and study endpoints according to QRS-score values

	QRS-score values		
	>−4 mm (n = 198)	≤−4 mm (n = 111)	p Value
Exercise testing parameters			
Duration of ET (s)	552 ± 121	438 ± 174	0.001
Double product (beats.mmHg.min ^{−1})	28536 ± 4950	25992 ± 5474	0.001
Maximum ST deviation (mm)	0.81 ± 0.94	1.38 ± 1.09	0.001
Chest pain during ET (n, %)	38/176 (21.6)	50/133 (37.6)	0.001
QRS score (mm)	2.2 ± 3.0	−5.5 ± 3.4	NA
Rest QRS (mm) & % change	16 ± 4.3 (−87.5)	17 ± 4.9 (+132.5)	NA
Duke score	3.5 ± 7.1	−2.3 ± 9.2	0.001
Coronary arteriography and left ventriculography parameters			
1-VD (n, %)	102 (58)	44 (33)	0.001
2-VD (n, %)	55 (31)	28 (21)	0.001
3-VD (n, %)	19 (11)	61 (46)	0.001
LVEF (%; mean ± SD)	55.1 ± 7.1	45.5 ± 7.2	0.001
Study endpoints			
Cardiac death (n, %)	0 (0)	20 (15)	0.001

Abbreviations: ET = exercise test, LVEF = left ventricular ejection fraction, VD = number of vessel disease, NA = not applicable, SD = standard deviation.

Results

The results of ET parameters, QRS score, Duke score, coronary arteriography, left ventriculography, as well as the study endpoints are listed in Table II. During the follow-up period, 20 patients (6.5%) died from MI. All deaths, sudden or non-sudden, that occurred in the context of this study were due to cardiac causes. All 20 study patients who died within the 3-year follow-up period, had been submitted to our institution¹⁶ or to other affiliated institutions,⁴ and the cause of death was documented as “cardiac” in their death certificates by qualified medical personnel.

The ROC curve of the prognostic value and the discrimination ability of the QRS score with regard to cardiac death resulted in an area under the curve of 0.867. The sensitivity and specificity of the QRS-score values ≤ −4 were 70.0 and 80.3%, respectively (Fig. 1). The respective univariate risk ratio for cardiac death was 34.9 (95% confidence interval [CI] 4.7–256.9). The ROC curves of other strong univariate predictors and standard findings are presented in Table III.

The Kaplan-Meier curves showed that patients could be classified into two categories based on their QRS-score values: the high-risk group and the low-risk group, with QRS-score values of below and above −4, respectively. For the occurrence of cardiac death using the QRS cut-off −4, the relative risk (RR) was 21.2 (95% CI 5.0–89.6) with an odds ratio of 26.3 (95% CI 5.9–111.1) (Fig. 2).

QRS-score values of survivors were significantly higher than in those who experienced cardiac death during the follow-up period (−0.6 vs. −7.7, $p < 0.001$). All variables studied were examined by univariate Cox regression analysis to

detect those which were related to long-term cardiac mortality (Table IV). Age ($p = 0.061$), duration of ET ($p < 0.001$), maximal heart rate achieved during ET ($p = 0.068$), double product ($p = 0.017$), maximal ST-segment deviation during ET ($p = 0.014$), QRS-score values ≤ −4 ($p < 0.001$), Duke score ($p < 0.001$), number of diseased vessels on coronary angiography ($p = 0.001$), and left ventricular ejection fraction ($p < 0.001$) were found to be associated with cardiac mortality, and thus they were subsequently included in a multivariate Cox proportional regression model. By multivariate Cox pro-

FIG. 1 Receiver operator characteristic curve of the prognostic value and the discrimination ability of the QRS score in regard to cardiovascular (CV) death. The area under the curve was 0.867. The sensitivity and specificity of the QRS score at −4 were 70.0 and 80.3%, respectively. The risk ratio at QRS = −4 was 34.9 (95% confidence interval 4.7–256.9).

TABLE III Areas under the receiver operator characteristics curves of the QRS score and other strong univariate predictors and standard findings

Test result variable(s)	Area	Std. error ^a	Asymptotic sig. ^b	Asymptotic 95% CI	
				Lower bound	Upper bound
QRS score	0.867	0.051	0.000	0.863	0.948
LVEF (%)	0.760	0.060	0.000	0.747	0.856
ET duration	0.751	0.043	0.000	0.742	0.834
Number of VD	0.732	0.035	0.000	0.625	0.736
Duke score	0.699	0.034	0.000	0.677	0.786
STmax	0.552	0.049	0.441	0.456	0.612

^a Under the nonparametric assumption.^b Null hypothesis: true area = 0.5.

Abbreviations: CI = confidence interval, STmax = maximum ST deviation. Other abbreviations as in Table II.

FIG. 2 Kaplan-Meier curves classifying patients into two risk categories based on their QRS-score values. Dotted line is for QRS > -4. CI = confidence interval.

portional hazard regression analysis, with all the aforementioned variables included as covariates, QRS-score values ≤ -4 and left ventricular ejection fraction were found to be significantly and independently associated with cardiac mortality at follow-up (RR=11.7, 95% CI 2.5–55.4, $p=0.002$, and RR = 0.925, 95% CI 0.868–0.926, $p=0.017$, respectively).

Subsequently, the Cox proportional hazard regression analysis was challenged with a forward stepwise entry model for assessing the strength and independence of the QRS score in this context. By multivariate, forward stepwise Cox proportional hazard regression analysis, with all the aforementioned variables included as covariates, QRS score values ≤ -4 , left ventricular ejection fraction, and duration of exercise were found to be significantly and independently associated with cardiac mortality at follow-up ($p=0.0085$, $p=0.0001$, and $p=0.0014$, respectively) (Table V).

Discussion

Interpretation of Results—Possible Underlying Mechanisms

According to the results of this clinical study, the QRS score is an independent predictor of cardiac death in a high-risk cohort of patients with CAD. These findings can probably be explained by the mechanisms leading to Q-, R-, and S-wave changes during exercise. The Q-wave amplitude remains unchanged or fails to increase during exercise in patients with CAD. This has been related to abnormal septal activation, reflecting loss of contraction associated with ischemia.⁹ The S-wave amplitude increases with exercise both in normal sub-

TABLE IV Group (descriptive) statistics for cardiac death

	No death (n = 289)	Yes death (n = 20)
Age (years)	55.79 ± 9.97	60.05 ± 9.53
Duration of exercise (s)	512.73 ± 151.39	363.75 ± 172.15
Double product (beats.mmHg.min ⁻¹)	27630.75 ± 5282.122	24694.35 ± 5318.92
Maximum ST deviation (mm)	1.01 ± 1.03	1.62 ± 0.93
Duke score	1.45 ± 8.45	-5.77 ± 6.67
QRS score (mm)	-0.66 ± 4.65	-7.70 ± 5.25
Diseased coronary arteries (n)	1.25 ± 1.12	2.50 ± 0.51
LVEF (%)	51.51 ± 8.23	42.40 ± 9.37

Values are in mean ± SD.

Abbreviations as in Table II.

TABLE V Forward stepwise Cox proportional hazard regression model

	p Value	HR	95.0% CI	
QRS score	0.0085	4.70	1.48	14.86
LVEF (%)	0.0001	0.89	0.84	0.94
Duration of exercise	0.0014	0.99	0.99	1.00

Abbreviation: HR, hazard ratio. Other abbreviations as in Tables II and III.

jects and in patients with CAD. The less pronounced exercise-induced increase of the S-wave amplitude in patients with CAD is attributed to subendocardial ischemia.¹⁰ The R-wave amplitude remains unchanged or increases with exercise in patients with CAD. It has been suggested that exercise-induced increases in R-wave amplitude may be related to failure of the ischemic myocardium to respond to adrenergic stimulation or to an increase of intracardiac blood volume.¹¹

QRS-score values have been shown to be unrelated to exercise-induced ST segment and they have a higher predictive accuracy in patients with CAD, as reported in previous studies.³⁻⁵ In particular, negative (<0) scores were always associated with CAD, while a QRS score <5 mm predicted CAD with sensitivity ranging from 75 to 86% and specificity ranging from 73 to 79%, values significantly higher than those of ST-segment depression (62 and 70%). Moreover, applying the Bayes' theorem, the combination of an abnormal QRS-score and ST-segment depression resulted in the highest post-test risk for CAD, and a normal QRS score without ST-segment depression in the lowest post-test risk. Furthermore, the QRS score has been favorably related, not only to the number of narrowed and/or obstructed coronary arteries, but also to the number of segmental contraction abnormalities and exercise-induced myocardial perfusion defects.⁴ In fact, the latter correlation was stronger than the first one (correlation between the QRS score and the extent of reversible thallium-201 defects: $p < 0.001$). These findings imply that the QRS score provides useful information with regard to the functional status of the ischemic myocardium, which might explain its ability to prognosticate the outcome of patients with CAD and is also suggested by the results of the current study.

Prognosis and Exercise Testing—Possible Future Implications

Although initial studies have shown that subjects manifesting abnormal ST responses are at greater risk for subsequent cardiovascular events, further research demonstrated that other parameters are equally or even more important in revealing prognostic information. For example, individuals demonstrating high exercise tolerance ($10 \geq$ METs) generally enjoy an excellent prognosis, while ST-segment changes have not emerged as an independent predictor.¹³ More than a decade ago, the Duke treadmill score was derived and validated,⁸ incorporating exercise capacity with exercise-induced angina

and ST-segment changes. The prognostic value of the ET is maximized when multiple exercise findings are considered. However, even if combining different findings improves the ability of the test to stratify risk, the question remains as to whether or not high-risk patients might be missed. The results of our study suggest that ECG changes during ET might be of a significantly greater value than generally believed if, on top of the standard ST criteria, QRS changes are also interpreted correctly and taken into consideration. However, larger trials including different populations (e.g., suspicion for CAD, low/intermediate risk, women, postrevascularization) would be necessary to confirm this.

Exercise testing is indispensable for the detection of undisclosed MI, for the management of established heart disease, as well as for assessing the severity of impairment due to ischemia and for measuring the effectiveness of therapy. Furthermore, it defines the level at which it is safe to exercise in the context of cardiac rehabilitation. It is well known, of course, that many other accurate diagnostic techniques have been developed and made available in recent years. Compared with imaging procedures such as stress-echocardiography, single-photon emission computed tomography (SPECT), myocardial perfusion imaging, and coronary angiography, treadmill ET can be performed at a much lower cost.²

The authors believe that, in parallel to the aforementioned sophisticated and far more expensive methods, the full potential of the traditional treadmill ET should be employed rather than abandoned. This is particularly true in light of the health economics reality in developed countries. Moreover, in developing countries, treadmill ET might be the only, or almost the only available technique in everyday practice for diagnosing, assessing the severity and the response to therapy, as well as stratifying the risk of patients with CAD.

Limitations

The correlation between the QRS score and cardiac death should also be tested in a cohort without CAD, as well as in other CAD subpopulations (e.g., women, the elderly, patients with a history of percutaneous coronary intervention and/or coronary artery bypass graft surgery). Moreover, it might also be useful to compare the prognostic value of the QRS score with imaging data that were not provided in this study. Furthermore, the association of the QRS score with mortality could have been influenced if we had included, in multivariate analysis, a number of additional factors whose predictive value has been proven in previous studies but that were not available in our study (e.g., detailed biochemical or qualitative angiographic data). In this context, our analysis may have unintentionally overemphasized the hypothesized predictive role of the QRS score.

Conclusions

Abnormal QRS-score values were shown to have an independent ability in predicting cardiac mortality in patients with

CAD. Despite the remarkable advances in diagnostic imaging techniques, ET is still an affordable and widely available tool for the detection of exercise-induced myocardial ischemia. Taking into consideration the importance of ET in the management of ischemic heart disease, the use of this QRS score could be of clinical value in predicting the outcome of patients with documented CAD.

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