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Exercise-Induced QRS Changes (Athens QRS Score) in Patients With Coronary Artery Disease : A Marker of Myocardial Ischemia

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Abstract

Previous studies have shown a good correlation between exercise-induced changes of Q-, R-, and S-waves (Athens QRS score) and the number of the obstructed coronary arteries. The present study was undertaken to test the hypothesis that abnormal Athens QRS score is related to exercise-induced myocardial ischemia.

Patients who had exercise radionuclide ventriculography ($n=150$) or thallium-201 scintigraphy ($n=124$) within 1 month of cardiac catheterization were studied. Athens QRS score was calculated based on the exercise-induced changes of the Q-, R-, and S-waves. Changes in Athens QRS score were compared to the number of obstructed coronary arteries, segmental contraction abnormalities, and exercise-induced myocardial perfusion defects.

Athens QRS score and coronary artery disease : The Athens QRS score was decreased as the number of obstructed coronary arteries increased (normal coronary arteries 3.7 mm, confidence interval 1.0 to 3.9, one vessel disease 1.2 mm, two vessel disease −0.6 mm, three vessel disease −1.3 mm, $p<0.001$).

Athens QRS score and segmental contraction abnormalities : The Athens QRS score decreased as the number of segmental contraction abnormalities increased (no segmental contraction abnormalities 2.5 mm, confidence interval 1.0 to 3.9, one segmental contraction abnormality −0.4 mm, two segmental contraction abnormalities −1.5 mm, three segmental contraction abnormalities −2.6 mm, $p<0.001$).

Athens QRS score and reversible myocardial perfusion defects : The Athens QRS score was decreased as the number of exercise-induced myocardial perfusion defects increased (no perfusion defect 2.4 mm, confidence interval 0.9 to 3.9, one perfusion defect −0.7 mm, two perfusion defects −2.6 mm, three perfusion defects −3.3 mm, $p<0.001$).

Abnormal values of the Athens QRS score were better correlated with the number of exercise-induced segmental contraction abnormalities or the myocardial perfusion defects than the number of obstructed coronary arteries ($p<0.001$).

Exercise-induced changes in Athens QRS score were directly related to the number of obstructed coronary arteries, to exercise-induced segmental contraction abnormalities and to exercise-induced myocardial perfusion defects. However, Athens QRS score changes were more closely related to the number of exercise-induced segmental contraction abnormalities or to the exercise-induced myocardial perfusion defects than to the number of obstructed coronary arteries. The data suggest that exercise-induced QRS changes, Athens QRS score are related to exercise-induced myocardial ischemia.

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Key Words

exercise, ischemia (myocardial), perfusion defects, Athens QRS score, contraction abnormalities

INTRODUCTION

An electrocardiographic (ECG) index based on exercise-induced Q-, R-, and S-wave changes was introduced as the Athens QRS score for the detection of coronary artery disease[1]. Abnormal values of Athens QRS score were directly related to the number of obstructed coronary arteries.

We hypothesized that changes of the Athens QRS score were secondary to exercise-induced myocardial ischemia. However, the presence of ischemia in the previous study was not documented with radionuclide techniques. If our original hypothesis is correct, then it is expected that changes of the Athens QRS score with exercise in patients with coronary artery disease will be best related to the exercise-induced segmental contraction abnormalities on radionuclide ventriculography, or with exercise-induced reversible myocardial perfusion defects as defined by exercise thallium-201 scintigraphy, than to the number of obstructed coronary arteries. The present study was undertaken to test this hypothesis.

Table 1 Demographic characteristics, cardiac catheterization, radionuclide ventriculography, and myocardial scintigraphy data

	Ventriculography	Scintigraphy
Number of patients	150	124
Age (yrs)	56.4±12	58.2±11
Male/female	101/49	98/26
History of previous myocardial infarction	18	16
Cardiac catheterization		
Vessel disease		
0	40 (26.7%)	17 (13.7%)
1	32 (21.3%)	37 (29.8%)
2	40 (26.7%)	31 (25.0%)
3	38 (25.3%)	39 (31.5%)
Left ventricular ejection fraction	54±8	51±7
Segmental contraction abnormalities/myocardial perfusion defects		
0		
1	93 (62.0%)	68 (54.8%)
2	22 (14.7%)	22 (17.8%)
3	25 (16.6%)	18 (14.5%)
	10 (6.7%)	16 (12.9%)

MATERIALS AND METHODS

Two hundred seventy-four patients who had diagnostic cardiac catheterization and exercise radionuclide ventriculography or thallium-201 scintigraphy at The Ohio State University Medical Center were studied.

Patients were referred for exercise radionuclide ventriculography or thallium-201 scintigraphy by the physician responsible for their care; the decision to utilize one mode of exercise versus the other was related to the physician's preference and not to the difference in patient population.

Exercise testing and radionuclide ventriculography

Exercise radionuclide ventriculography was performed in 150 patients on a supine ergometric bicycle within 1 month of coronary arteriography. Demographic characteristics, cardiac catheterization and exercise data are shown in **Table 1**.

Maximal graded supine bicycle exercise was performed starting at a workload of 200 kpm/min and was increased by 200 kpm/min every 3 minutes. Exercise was continued until the development of severe angina (28 patients), dyspnea (6 patients), fatigue (96 patients), severe ventricular arrhythmias (9 patients), decrease in systolic blood pressure $>$ 20 mmHg (3 patients), or ST segment depression $>$ 3 mm (8 patients). ECG recordings were obtained every minute during exercise and for 5 minutes after exercise. Blood pressure was measured every 2 minutes during the exercise and the recovery period. A horizontal or downsloping ST segment depression of at least 1 mm at 60 msec after the J point or an upsloping ST segment depression $>$2 mm at 80 msec after the J point or in the presence of ST segment depression at rest, an additional 2 mm of ST segment depression, were considered ischemic responses[2].

Radionuclide ventriculography was performed at rest and during exercise with use of the gated equilibrium technique. *In vivo* red blood cell labeling was accomplished using 24 to 30 mCi of technetium-99m pertechnetate. The camera was positioned to obtain the left anterior oblique view that maximized the separation of ventricular images. Gated images were obtained over a 2-minute interval, at 20 frames per cardiac cycle, at rest, and during the last 2 minutes of each stage of supine bicycle exercise[3–6].

The left ventricular time-activity curve was generated by using a conventional software program (Medical Data Systems, Ann Arbor, Michigan) employing semiautomatic edge detection and computer-determined background subtraction. The left ventricular ejection fraction was automatically calculated directly from the time-activity curve. Wall motion was qualitatively evaluated by two independent experienced observers without knowledge of the cardiac catheterization data. The left anterior oblique studies at rest and at peak exercise were viewed side by side to detect an exercise-induced abnormality of wall motion in three anatomic walls: septal, inferoapical, and posterolateral. A segment was considered ischemic when a normal segment at rest became abnormal with exercise or when an already abnormal segment at rest showed further deterioration with exercise.

Wall motion for each region was graded as follows : 0=normal, 1=tardokinesis, 2=hypokinesis, 3=severe hypokinesis, 4=akinesis, 5=dyskinesis. Agreement between the observers about the normal or abnormal wall motion was reached in 92% of the cases. Differences in the remainder of the regions were resolved by joint review and arbitration of the studies by a third observer[6].

Exercise testing and thallium-201 scintigraphy

Exercise testing and thallium-201 scintigraphy was performed in 124 patients within 1 month of coronary arteriography. Demographic characteristics, cardiac catheterization and exercise thallium-201 imaging data are shown in **Table 1**. Exercise testing was performed on a treadmill according to the multistage Bruce protocol. ECG recordings were obtained every minute during the exercise and for 5 minutes during the recovery period. Blood pressure was measured every 2 minutes and before every stage change by sphygmomanometry. Exercise was terminated because of severe angina (16 patients), leg fatigue (90 patients), dyspnea (4 patients), severe ventricular arrhythmias (6 patients), decrease in systolic blood pressure >20 mmHg (2 patients), and a maximal ST segment depression $>$ 3 mm (6 patients).

Thallium-201 scintigrams were acquired using standard techniques previously described[3,5,7]. Two mCi of thallium-201 were injected intravenously 1 minute before exercise termination. Exercise and redistribution scintigrams were obtained 10 minutes and 4 hours post thallium-201 injection, respectively, in anterior, 45° left anterior oblique and 90° left lateral projections using a Picker Dynamo camera with a low energy, all-purpose collimator. A 10-minute image was collected in each view with an information density of 3,000 counts over the highest myocardial activity. The 64×64 matrix images were processed digitally using interpolative background subtraction and quantitative horizontal profile activity curves as previously described by Watson *et al.*[8] All images were photographed in black and white on 8×10 inch film.

Matching views from exercise and reperfusion studies were displayed as pairs and interpreted by two observers without knowledge of the cardiac catheterization or electrocardiographic findings.

Each image was divided into three segments;

1) Anterior image: anterolateral, apical, inferior

2) Left anterior oblique image : septal, inferoapical, posterolateral

3) Left lateral image: anterior, anteroapical, inferoposterior[3,9–11]

Stress-induced perfusion defect was defined as an area of myocardium exhibiting decreased activity compared to a normally appearing wall. Fixed defect was defined when relative change in defect activity between stress and redistribution images was present. Partially reversible defect was defined when incomplete filling occurred in the area of stress-induced defect on the redistribution image. Completely reversible defect was defined when normalization of the stress-induced defect on the redistribution image occurred.

Athens QRS score

The postexercise Q-, R-, and S-wave amplitude values were subtracted from the baseline, and the corresponding Q-, R-, and S-wave differences (ΔQ, ΔR, and ΔS, respectively) were obtained[1]. The Athens QRS score was calculated by subtracting the Q- and S-wave differences from the R-wave difference in leads $aV_F + V_5$. Athens QRS score (mm) $=(\Delta R - \Delta Q - \Delta S)\ aV_F + (\Delta R - \Delta Q - \Delta S)V_5$. QS-complexes were treated like Q- or S-wave. Measurements of the Athens QRS score post-exercise thallium studies were performed in the supine position.

Coronary arteriography and left ventriculography

All patients underwent left ventriculography in the 30-degree right anterior oblique projection and selective coronary arteriography by the percutaneous (Judkins) or brachial (Sones) technique. Angiograms were evaluated by two cardiologists independently. Significant coronary artery disease was diagnosed when there was a diameter narrowing ≧70% in the lumen of a major vessel or their major branches, or ≧50% stenosis in the left main coronary artery.

Statistical analysis

Statistical evaluation was performed using two-way analysis for variance with multiple comparisons.

RESULTS

Athens QRS score values and coronary artery disease

Among the 274 patients studied, 57 (20.8%) had normal coronary arteries and 208 (75.9%) had coronary artery disease (60 one, 71 two and 77 three vessel disease).

The Athens QRS score decreased as the number of obstructed coronary arteries increased (normal coronary arteries 3.7 mm, confidence interval 1.0 to 3.9, one obstructed coronary artery 1.2 mm, two obstructed coronary arteries −0.6 mm, three obstructed coronary arteries −1.3 mm, $p<0.001$, **Table 2**).

Athens QRS score and segmental contraction abnormalities

The Athens QRS score decreased as the number of segmental contraction abnormalities increased (no segmental contraction abnormalities 2.5 mm, one segmental contraction abnormality −0.4 mm, two segmental contraction abnormalities −1.5 mm, three segmental contraction abnormalities −2.6 mm, $p<0.001$, **Table 2**).

The lower confidence interval for the Athens QRS score in patients with normal coronary arteries or normal radionuclide studies was 1.0. Thus, values <1.0 were considered abnormal. Abnormal values of the Athens QRS score were better correlated with the number of exercise-induced segmental contraction abnormalities than to the number of obstructed coronary arteries. Thus, 3 of the 40 patients (7.5%) with normal coronary arteries, 13 of 32 (40.6%) with one, 21 of 40 (52.5%) with two, and 28 of 38 (73.7%) with three vessel disease had abnormal Athens QRS score, whereas 15 of 93 patients (16.1%) without segmental contraction abnormalities, 19 of 22 patients (86.4%) with one, 22 of 25 (88.0%) with two, and 9 of 10 (90.0%) with three segmental contraction abnormalities had abnormal values of the Athens QRS score, $p<0.001$ (**Fig. 1**).

Table 2 Exercise-induced changes of Athens QRS score in relation to segmental contraction abnormalities, and reversible myocardial perfusion defects

Segmental contraction abnormalities	Athens QRS score	Myocardial perfusion defects	Athens QRS score
0	2.5±6.9 mm (1.0 to 3.9)	0	2.4±6.1 mm (0.9 to 3.9)
1	−0.4±3.4 mm (−1.8 to 1.0)	1	−0.7±3.5 mm (−2.2 to 0.8)
2	−1.5±3.7 mm (−3.0 to 0)	2	−2.6±3.4 mm (−4.2 to −1.0)
3	−2.6±3.6 mm (−3.5 to −0.7)	3	−3.3±3.3 mm (−5.0 to −1.6)

Mean ±1 standard deviation. Values in parentheses represent confidence intervals.

The exercise parameters in patients who were studied with exercise radionuclide ventriculography are shown in **Table 3**.

Athens QRS score values and reversible myocardial perfusion defects

The Athens QRS score decreased as the number of exercise-induced myocardial perfusion defects increased (no perfusion defect 2.4 mm, one perfusion defect −0.7 mm, two perfusion defects −2.6 mm, three perfusion defects −3.3 mm, $p<0.001$, **Table 2**).

Abnormal values of the Athens QRS score were better correlated with the number of ischemic perfusion defects than with the number of obstructed coronary arteries. Thus, 1 of 17 patients (5.9%) with normal coronary arteries, 15 of 37 (40.5%) with one, 18 of 31 (58.1%) with two, and 28 of 39 (71.8%) with three vessel disease had abnormal values of the Athens QRS score ($p<0.001$), whereas 12 of 68 patients (17.6%) without reversible perfusion defects, 18 of 22 patients (81.8%) with one, 17 of 18 patients (94.4%) with two, and 15 of 16 patients (93.8%) with three ischemic perfusion defects developed abnormal Athens QRS score with exercise, $p<0.001$ (**Fig. 2**).

Table 3 Exercise parameters in patients studied with radionuclide ventriculography or thallium-201 myocardial scintigraphy

	Radionuclide ventriculography			Myocardial scintigraphy		
	Abnormal values of Athens QRS score (*n*=65)	Normal values of Athens QRS score (*n*=85)	*p* value	Abnormal values of Athens QRS score (*n*=63)	Normal values of Athens QRS score (*n*=61)	*p* value
Exercise duration (sec)	462±132	495±144	<0.01	446±128	518±116	<0.01
Max heart rate (bpm)	141±32	148±28	NS	148±21	156±26	NS
Max systolic blood pressure (mmHg)	173±17	181±15	NS	175±18	182±17	NS
Max ST depression (mm)	1.02±0.65	0.69±0.62	<0.03	1.35±0.72	0.77±0.71	<0.05
Time in sec to 1 mm ST depression	352±118	393±122	<0.02	358±121	403±188	<0.05

Mean ±1 standard deviation.
Max=maximal; NS=not significant.

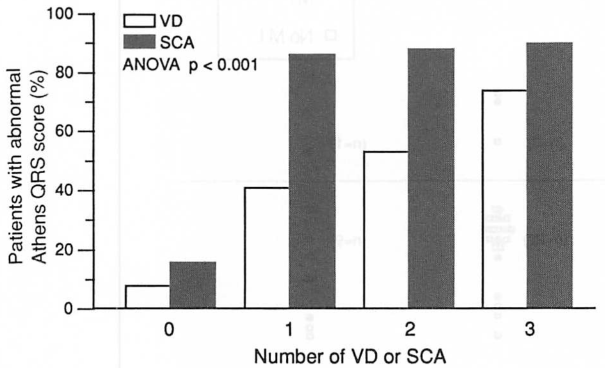

Fig. 1 Relationships between exercise-induced abnormal values of Athens QRS score, number of vessel disease (VD) and segmental contraction abnormalities (SCA)

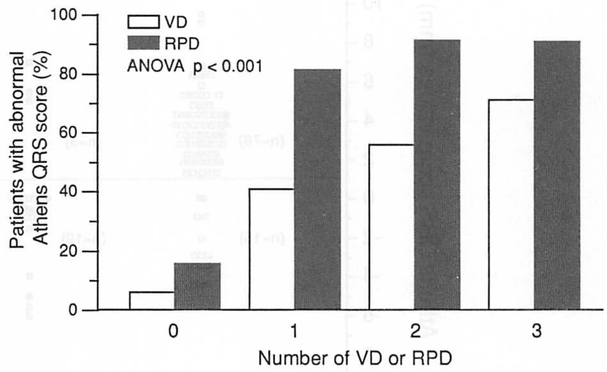

Fig. 2 Relationships between exercise-induced abnormal values of Athens QRS score, number of vessel disease and reversible myocardial perfusion defects (RPD)
Abbreviation as in Fig. 1.

Exercise parameters in patients who were studied with thallium-201 myocardial scintigraphy are shown in **Table 3**.

Thirty-four of the patients had a history of myocardial infarction. The relationships of the Athens QRS score in patients with previous myocardial infarction to the number of vessel disease, exercise-induced segmental contraction abnormalities, or myocardial perfusion defects was not different compared to patients without previous myocardial infarction (**Fig. 3**).

One hundred sixty-five patients were treated with cardiovascular drugs. The sensitivity and specificity of Athens QRS score in patients treated and not treated with cardiovascular drugs were compared to exercise-induced segmental contraction abnormalities and to exercise-induced myocardial perfusion defects.

The sensitivity and specificity of Athens QRS score in relation to exercise-induced segmental contraction abnormalities were not statistically different in patients receiving therapy (sensitivity 86%, specificity 85%), compared to patients not receiving therapy (sensitivity 90%, specificity 82%). Likewise, the sensitivity and specificity of Athens QRS score in relation to exercise-induced myocardial perfusion defects were similar in patients receiving therapy (sensitivity 86%, specificity 84%) and patients not receiving therapy (sensitivity 95%, specificity 80%).

The specificities and sensitivities of ST segment response to exercise and Athens QRS score were compared with the results of the coronary arteriography, to exercise-induced myocardial perfusion defects and to exercise-induced segmental contraction abnormalities.

The specificity and sensitivity of ischemic ST segment response in relation to coronary angio-

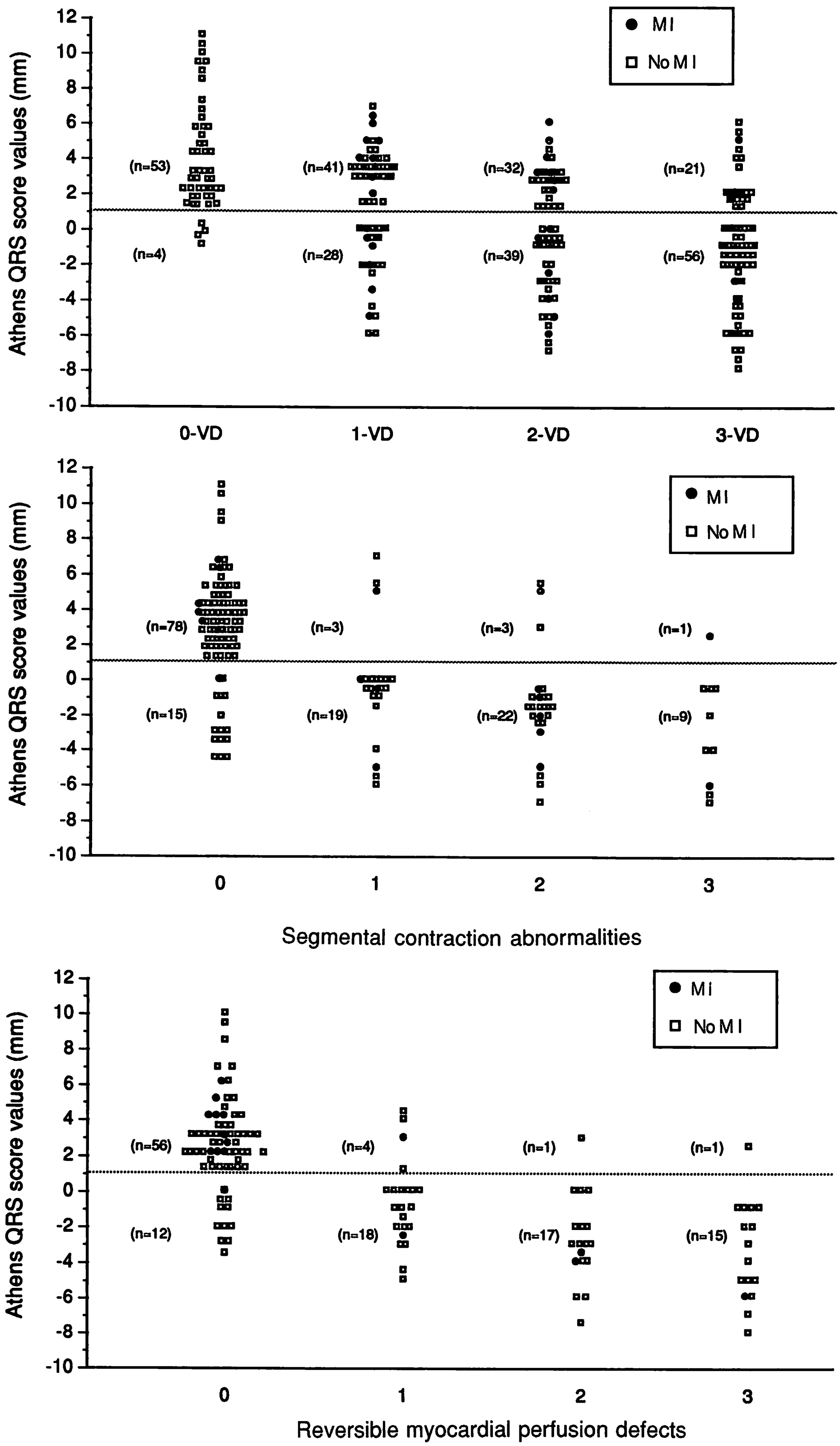

Fig. 3 Athens QRS scores plotted against the number of vessel disease (*upper*), exercise-induced segmental contraction abnormalities (*middle*) and exercise-induced myocardial perfusion defects (*lower*)

Patients with and without previous myocardial infarction (MI, no MI, respectively) are also shown.

graphy (sensitivity 31%, specificity 76%) were lower compared to those using Athens QRS score (sensitivity 57%, specificity 93%, $p<0.05$). Likewise, the sensitivities of ST segment ischemic response in relation to exercise-induced segmental contraction abnormalities (40%) and exercise-induced myocardial perfusion defects (45%) were lower compared to Athens QRS score (segmental contraction abnormalities 88%, myocardial perfusion defects 89%, $p<0.05$).

The specificities of ST segment ischemic response in relation to exercise-induced segmental contraction abnormalities (82%) and to exercise-induced myocardial perfusion defects (84%) were not different compared to Athens QRS score (segmental contraction abnormalities 84%, myocardial perfusion defects 83%).

DISCUSSION

Previous studies have shown that exercise-induced changes in the QRS complex (Athens QRS score) were directly related to the number of obstructed coronary arteries[1]. The present study demonstrated that exercise-induced changes of the Athens QRS score were best correlated with the number of exercise-induced segmental contraction abnormalities as defined by radionuclide ventriculography or to the reversible myocardial perfusion defects as defined by thallium-201 scintigraphy, than to the number of obstructed coronary arteries. These findings suggest that exercise-induced abnormal values of the Athens QRS score were related to exercise-induced myocardial ischemia.

Exercise-induced changes in the QRS complex

Analysis of exercise-induced changes in the Q-, R-, and S-wave amplitude provides the framework for understanding exercise-induced changes in the Athens QRS score of normal subjects and patients with coronary artery disease.

Q-wave amplitude remained unchanged or failed to increase with exercise in patients with coronary artery disease[12]. Failure to increase or decrease Q-wave amplitude with exercise in patients with coronary artery disease has been related to abnormal septal activation reflecting loss of contraction associated with ischemia that results from narrowing of the left anterior descending coronary artery[13,14].

R-wave amplitude remained unchanged or increased with exercise in patients with coronary artery disease. The explanation of this phenomenon is not completely understood. It has been suggested, however, that exercise-induced increases in R-wave amplitude may be related to an increase in intracardiac blood volume, or failure of the ischemic myocardium to respond to adrenergic stimulation[15–20].

S-wave amplitude increased with exercise both in normal subjects and in patients with coronary artery disease. The increase in S-wave amplitude, however, was less in patients with coronary artery disease compared to normal subjects. Exercise-induced increase in the S-wave amplitude in normal subjects is related to a rightward and posterior axis shift, which produces an increase in the amplitude in the lateral leads. The exercise-induced increase in the amplitude of the S-wave in patients with coronary artery disease is attributed to subendocardial ischemia[21,22].

Inasmuch as exercise-induced changes in the individual waves of the QRS complex detected coronary artery disease with a low specificity or sensitivity, the individual waves were incorporated into a composite expression (Athens QRS score); thus, a false negative response of one wave can be negated by the true positive responses of the other two[1].

It is known that exercise-induced myocardial ischemia may cause global or regional ventricular dysfunction in experimental animals and patients with coronary artery disease[3,5,22]. Several factors such as changes in preload, afterload and pharmacologic agents may alter left ventricular ejection fraction during exercise. Segmental contraction abnormalities of the left ventricular myocardium induced with exercise are more specific for exercise-induced myocardial ischemia than changes of global left ventricular ejection fraction[3–5,23–28].

Likewise, several studies have shown the usefulness of thallium-201 scintigraphy for detection of exercise-induced myocardial ischemia[29–36]. Exercise-induced perfusion defects which improve on the redistribution images are consistent with exercise-induced myocardial ischemia in patients with coronary artery disease[5,29–43]. In our Medical Center, radionuclide exercise studies are often performed after coronary arteriography while the patients are receiving therapy. Thus, the purpose of the exercise study in most of the instances was not for the diagnosis of coronary artery disease but for the evaluation of exercise-induced myocardial ischemia in patients with coronary artery disease while receiving antianginal therapy. Indeed, only 44 of the 207 patients with coronary artery disease had chest pain during exercise. This may explain the low incidence of positive radionuclide studies in patients with coronary artery disease. The Athens QRS score, however, was compared to exercise-induced myocardial ischemia (segmental contraction abnormalities or myocardial perfusion defects); thus, the low incidence of positive radionuclide test did not influence our results. Further, the sensitivity and specificity of Athens QRS score were similar in patients receiving therapy compared to patients without therapy.

Comparison of the Athens QRS score and ST segment ischemic response to the exercise-induced segmental contraction abnormalities or myocardial perfusion defects demonstrated that the sensitivity of the Athens QRS score was greater compared to the ST segment ischemic response. In our previous study, receiver operating curves were used to compare the sensitivity of different partitions of Athens QRS score and ST segment depression in patients with coronary artery disease at matched levels of test specificity determined by percentile estimation in normal subject[1]. At partition values corresponding to any specificity and sensitivity values of the Athens QRS score were higher than those for the ST segment depression.

The sensitivity and specificity of exercise radionuclide ventriculography and thallium-201 myocardial scintigraphy in the detection of coronary artery disease have been discussed extensively over the last two decades. Thus, the purpose of this study was not to define agreement of these diagnostic modalities in relation to the number of obstructed coronary arteries. Likewise, the sensitivity and specificity and limitations of Athens QRS score have been discussed extensively previously[1] and our purpose was not to repeat previous studies. The data, however, suggest that the Athens QRS score is best related to exercise-induced myocardial ischemia as defined by radionuclide techniques than to the number of obstructed coronary arteries. An abnormal Athens QRS score, therefore, is an indicator of exercise-induced myocardial ischemia.

Our purpose is not to introduce an index for the diagnosis of coronary artery disease in the era of intravascular echocardiography. Nevertheless, the Athens QRS score may prove to be an inexpensive, noninvasive index for stratification of patients with suspected coronary artery disease, before other more expensive studies are performed. Further, the Athens QRS score may be a useful index in the third world where modern technology is less available.

CONCLUSIONS

Abnormal values of the Athens QRS score are related to the number of obstructed coronary arteries, to the number of exercise-induced left ventricular segmental contraction abnormalities and to the number of reversible myocardial perfusion defects. Abnormal values of the Athens QRS score, however, were better related to the number of exercise-induced segmental contraction abnormalities or to the number of reversible myocardial perfusion defects than to the number of obstructed coronary arteries. The data support the hypothesis that abnormal values of the Athens QRS score are related to exercise-induced myocardial ischemia.

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