Comparison of Exercise QRS Amplitude Changes in Patients with Slow Coronary Flow Versus Significant Coronary Stenosis

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SUMMARY

Exercise Q, R, and S wave amplitude changes, called the QRS score, have been reported to be a marker of exercise-induced myocardial ischemia. Therefore, in this study, using the exercise QRS score, we sought to determine if slow coronary flow (SCF) phenomenon is associated with the exercise-induced myocardial ischemia.

This retrospective study included 23 patients evaluated for suspected coronary artery disease and found to have SCF (group I) and 19 subjects with angiographically-defined significant coronary artery stenosis (group II). All study subjects underwent treadmill exercise testing using the modified Bruce protocol. For each subject the amplitude of the Q, R, and S waves in leads aVF and V5 was measured manually using calipers before and immediately after exercise. The QRS score was calculated by subtracting the Q, R, and S wave differences in leads aVF and V5.

There was no difference between the two groups with respect to demographic properties. The peak heart rate achieved, baseline and peak systolic-diastolic blood pressure, exercise duration, and the metabolic equivalent values were similar in both groups. The maximum ST-segment depression ratio was significantly lower in patients with SCF than those of significant coronary stenosis (0.8 ± 0.4 vs 1.3 ± 0.5 P = 0.001, respectively). However, the exercise QRS score was found to be similar in both groups (3.3 ± 2.3 vs 2.1 ± 3.0 P = 0.2, respectively).

The data suggest that SCF phenomenon may alone lead to myocardial ischemia even in the absence of obstructed major epicardial coronary arteries as detected by similar exercise QRS scores to those of significant coronary artery stenosis. (Jpn Heart J 2004; 45: 419-428)

Key words: Slow coronary flow, Athens QRS score, Ischemia

NORMAL coronary arteries are found in as many as 10% to 30% of patients being evaluated for typical angina or angina-like chest pain and suspected coronary artery disease (CAD).1-3) Within the spectrum of patients with typical angina
or angina-like chest pain and normal epicardial coronary arteries, slow coronary filling, which is characterized by abnormally slow antegrade progression of contrast during coronary arteriography, is not an uncommon finding during routine coronary arteriography.

This angiographic phenomenon was first reported in 1972 by Tambe, et al4) and who had demonstrated ischemic result during exercise testing, hemodynamic abnormalities, and left ventricular enlargement with segmental dyskinesis in six patients with anginal complaints. However, since that time only a limited number of studies have focused on the etiology and clinical significance of this unique angiographic finding. Although this entity of so-called 'slow flow' is known, its relevance to the occurrence of ischemia is not well known and in these patients exercise-induced QRS changes have not yet been studied.

Treadmill exercise testing is one of the most common noninvasive methods used to detect myocardial ischemia although it is not always accurate in diagnosing significant CAD due to false negative and false positive results. Exercise-induced ST segment depression and chest pain are generally used as indicators of significant CAD. However, exercise-induced ST-segment depression only has a sensitivity of 50% to 70% and a specificity of 70% to 90% as a diagnostic indicator.5-7) For this reason, Michaelides, et al8) developed the Athens QRS score, which combines exercise-induced changes in amplitude of Q, R, and S waves in order to improve the accuracy of an exercise electrocardiogram in the detection of coronary artery disease. In this study, we measured the exercise Athens QRS score in patients with SCF and compared it to those with significant coronary stenosis to determine if SCF phenomenon is associated with myocardial ischemia.

**METHODS**

This retrospective study included 23 patients with typical angina or angina-like symptoms being referred for evaluation of suspected coronary artery disease and who were found to have SCF but otherwise normal epicardial coronary arteries and 19 patients with angiographically-documented significant coronary artery stenosis on angiographic evaluation.

The SCF was defined according to the TIMI frame count (TFC) method.9) Subjects with a TFC greater than two standard deviations (SD) from the normal published range for the particular vessel were accepted as having SCF. Significant coronary stenosis was defined if greater than 70% narrowing was present in at least one major epicardial coronary artery during angiography.

Patients with a history of previous myocardial infarction, percutaneous coronary intervention, valvular heart disease, mitral valve prolapse, cardiomyopathy,
left ventricular hypertrophy, bundle branch block, and systemic disorders were excluded.

All subjects underwent treadmill exercise testing using the modified Bruce protocol. Before testing, all subjects were instructed to not eat, drink, or smoke for 3 hours before the testing. Angina, fatigue, diagnostic ST-segment depression, or persistent arrhythmias were considered reasons for discontinuing the exercise test. The ST-segment level was measured 60 ms after the J point in all 12 leads. The heart rate, ECG, and blood pressure were recorded at the onset and immediately after exercise. For each subject the amplitude of the Q, R, and S waves in leads aVF and V5 was measured manually, using calipers, before and immediately after exercise. Q, R, and S-wave amplitudes were measured by two observers blinded to the clinical details. Each measurement is presented as the mean of 3 randomly selected consecutive beats. The postexercise Q-, R-, and S-wave differences (DQ, DR, and DS, respectively) were obtained. The Athens QRS score was calculated by subtracting the Q-, R-, and S-wave differences in leads aVF and V5 as follows: Athens QRS score (mm) = (DR-DQ-DS) aVF + (DR-DQ-DS) V5. QS complexes were treated like Q or S waves. Definitive positive criteria for exercise testing were defined as: horizontal or downsloping ST segment depression ≥ 1 ms, or upsloping ST segment depression, ≥ 2 mm in any lead, present within the first 2 minutes of the recovery period.

**Statistical analysis:** Statistical analysis was performed with SPSS for Windows (version 10.0). Data are presented as the mean ± SD. The unpaired Student t test was used for continuous variables and the chi-square test was used for categorical changes. A P value < 0.05 was considered to indicate statistical significance.

**RESULTS**

The baseline characteristics of both groups are presented in Table I and the results of exercise testing are shown in Table II. Neither rhythm disturbance nor haemodynamic abnormality occurred during exercise testing. The peak heart rate achieved, baseline and peak systolic-diastolic blood pressure, test duration, and metabolic equivalent (MET) values were similar in both groups. All subjects completed the test successfully. Exercise-induced typical angina or angina-like symptoms such as palpitations, shortness of breath, and fatigue occurred in both groups (12 and 13 subjects, respectively). The maximum ST-segment depression ratio was significantly lower in patients with SCF than in those with significant coronary stenosis (0.8 ± 0.4 vs 1.3 ± 0.5 mm, P = 0.001, respectively) (Figure 1). A definitive positive test was detected in 17 of 23 patients with SCF. The tests of the remaining 6 patients were uncertain but they showed typical angina during exercise or had ST-segment depression on basal ECG. However, the exercise
Table I. Baseline Characteristics of the Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>51 ± 5</td>
<td>49 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Men/women</td>
<td>15/8</td>
<td>12/7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean heart rate, beats/min</td>
<td>78 ± 9</td>
<td>80 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 ± 5</td>
<td>28 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertensives, n</td>
<td>5</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers, n</td>
<td>6</td>
<td>8</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = statistically not significant

Table II. Exercise Test Results for Both Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>METs, mL/kg/dk</td>
<td>9.8 ± 0.8</td>
<td>9.4 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline SBP, mmHg</td>
<td>128 ± 9</td>
<td>132 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>Peak SBP, mmHg</td>
<td>146 ± 10</td>
<td>142 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline DBP, mmHg</td>
<td>77 ± 8</td>
<td>81 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Peak DBP, mmHg</td>
<td>85 ± 4</td>
<td>87 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Peak heart rate, beats/min</td>
<td>153 ± 10</td>
<td>151 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>% Heart rate achieved</td>
<td>93 ± 5</td>
<td>94 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Total exercise duration (min.)</td>
<td>9.4 ± 1.0</td>
<td>9.0 ± 0.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

METs = metabolic equivalents; NS = statistically not significant; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Figure 1. Exercise-induced maximum ST segment depression ratio in patients with slow coronary flow (group I) and coronary artery stenosis (group II).
QRS score was found to be similar in both groups (3.3 ± 2.3 vs 2.1 ± 3.0 mm, \( P = 0.2 \), respectively) (Figure 2).

**DISCUSSION**

Treadmill exercise testing is one of the most common noninvasive diagnostic methods for detecting ischemic heart disease and exercise-induced ST-segment depression is the principal parameter used. However, the value of this marker was proven to be limited due to varying sensitivity and specificity.\(^5\)\(^-\)\(^7\) Therefore, Michaelides, et al\(^8\) proposed a new parameter, called the QRS score, to improve the efficacy of exercise testing. They showed that exercise-induced changes in the QRS complex provide a useful index not only for diagnosis but also for assessment of the severity of coronary artery disease.

The clinical utility of the exercise-induced ECG waves changes has been widely studied. Previous studies have showed that during exercise testing the Q wave amplitude may decrease, particularly in left anterior descending coronary artery stenosis, as a result of abnormal septal activation.\(^10\)\(^,\)\(^11\) Wothuis, et al\(^12\) studied ECG waveform changes in subjects at low risk for cardiovascular disorders.
and found that the average R wave amplitude increases during early exercise and then decreases during maximum effort and the average S wave amplitude becomes greater as exercise progresses. Also, Charlap, et al. showed that the S wave amplitude decreases during occlusion of LAD angioplasty. Van Campen, et al. reported that an abnormal QRS score reflects myocardial ischemia and the QRS score decreases as the number of vessels increases.

Typical angina or angina-like chest pain with or without objective evidence of myocardial ischemia with angiographically normal coronary arteries and no evidence of epicardial coronary artery spasm is usually designated syndrome X. In some of these patients, stress ECG abnormalities, pathologic lactate extraction during isoproterenol infusion or atrial pacing, or inadequate increase in coronary flow during dipyridamole infusion can be detected. However, such abnormalities are generally not detectable in basal conditions, and can be induced only through adequate physical and/or pharmacological stress. We therefore hypothesized that exercise-induced ischemia in microvascular areas may affect the QRS score in patients with SCF and our data suggest that the exercise QRS score is not different in patients with SCF than in those with significant coronary stenosis although the maximum ST segment depression ratios are different. In other words, the similarity of the exercise QRS score of patients with SCF and those with significant coronary artery stenosis indicates that this phenomenon may alone lead to myocardial ischemia. The exact mechanism is not known, however, microvascular disorders and vasomotor changes frequently detected in this group of patients may be the responsible mechanisms.

From the clinical standpoint, patent coronary arteries and angina pectoris are poorly understood entities and within this spectrum, SCF and otherwise normal coronary arteries have distinct significance. Whether this pattern of flow is associated with myocardial ischemia is unclear. Although it is often considered to be an incidental angiographic finding, individual case reports and small clinical studies have identified some clinical consequences of SCF. This term was first defined by Tambe, et al. in 6 cases with typical or atypical chest pain. All 6 patients had an abnormal resting ECG, 1 of whom may have had a previous inferior myocardial infarction, and 3 of the 6 had ischemic exercise tests. They suggested abnormally high small-vessel resistance due to impairment of coronary microcirculation. In 1986, Mosseri, et al. revealed fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, and endothelial degeneration in the microvascular circulation from right ventricular biopsy specimens of 6 patients with SCF. Echocardiographic study showed all patients had myocardial hypertrophy and 2 also had left ventricular enlargement. In addition, Mangieri, et al. evaluated left ventricular biopsy samples from 10 patients with SCF, none of whom had cardiac or systemic illness, and found endothelial thickening due to
cell edema, capillary damage, and decreased luminal diameter. They proposed that histopathologic abnormalities in microvascular structures cause or at least facilitate the increase in microvascular resistance. Later, Kurtoglu, et al.,(22) using a TFC method, showed that dipyridamole, which has a vasodilator effect on microvascular coronary arteries, normalized SCF. Goel, et al.(23) showed that definitively positive exercise testing was more common in SCF than in the normal coronary flow group. Cesar, et al.(24) found ST depression in 11.7% of patients with SCF. In another study carried out in patients with chest pain and normal epicardial coronary arteries, a link between slow run-off of coronary dye and exercise-induced regional functional and perfusion abnormalities at scintigraphic examination, often in absence of symptoms and ECG abnormalities, was shown. Moreover, Przybojewski and Becker(26) described myocardial infarction due to SCF in a 51-year-old woman with a previous history of palpitations and episodes of retrosternal pain. Later, Kooper, et al.(27) reported three cases with angina pectoris and ST segment elevation after treadmill exercise testing in the presence of only slow flow.

Michealides, et al.(8) reported that an Athens QRS score of 5 mm predicted CAD with sensitivity ranging from 73% to 86% and a specificity ranging from 73% to 79%, values which were higher than that of ST segment depression (62% and 70). Accordingly, Cin, et al.(28) using a cut off point of < 5 mm for mild to moderate risk patients and a cut off point of < 3 mm for high risk patients showed that in patients with a QRS score < 5 mm, CAD is significant and extensive during coronary angiography and concluded that there is a significant relationship between the QRS score and the extent of CAD. Michealides, et al.(29) have also showed exercise-induced QRS changes in Athens QRS is directly related to the number of obstructed coronary arteries, to exercise-induced segmental contraction abnormalities, and to exercise-induced myocardial perfusion defects, and concluded that the Athens QRS score is related to exercise-induced myocardial ischemia. Koide, et al.(30) showed that exercise-induced maximum ST-segment depression, QT dispersion immediately after exercise, and the Athens QRS score are independent predictors of significant coronary stenosis. In our study, the Athens QRS score was found to be lower than 5 mm in both groups.

The accuracy of exercise-induced significant ST-segment depression is clinically inadequate because a significant number of patients who do not have exercise-induced chest pain or significant ST-segment depression have coronary stenosis.31) It has been shown that horizontal or downsloping ST depression measured at the J junction during exercise or recovery, or both, is the most powerful predictor of severe coronary artery disease. With the use of a cut off point of 0.075 mV for ST depression, horizontal or downsloping ST depression alone...
yielded a sensitivity of 50% and specificity of 71% for the prediction of severe disease.\textsuperscript{32)}

The Athens QRS score was found to be unrelated to exercise-induced ST-segment depression and its sensitivity and specificity in predicting CAD were found to be higher than the ST-segment depression ratio.\textsuperscript{8)} In this context, although the maximum ST segment ratio was found to be lower in the SCF group than in those with coronary stenosis, a similar QRS score may indicate the presence of exercise-induced ischemia in patients with SCF.

\textbf{Study limitations:} There are limitations to this study that may influence the results. The major limitation is that other findings of true myocardial ischemia, including lactate production, transient ventricular wall motion abnormalities, and transient defect of thallium uptake were not studied. If these had been studied, the results would be much more supportive of the hypothesis regarding the presence of ischemia in these patients. In fact, this was a retrospective study, therefore, we could not study the other findings of ischemia, and we are aware of the difficulty in claiming that true myocardial ischemia occurs in patients with SCF only depending on the exercise QRS score. However, previously a close association has been detected between slow run-off of coronary dye and exercise-induced regional function and perfusion abnormalities at scintigraphic examination.\textsuperscript{24,25)} In accordance with Goel, \textit{et al}\textsuperscript{23)} we found a definitive positive exercise test ratio of 76% in patients with SCF. Accordingly, our study group has recently showed that endothelial functions and left ventricular diastolic functions are impaired in patients with SCF.\textsuperscript{33,34)} In addition, the other findings of true myocardial ischemia including abnormalities of left ventricular function, decreased coronary sinus oxygen saturation, abnormal myocardial lactate metabolism, abnormal coronary vasodilator reserve, and regional myocardial perfusion abnormalities during exercise or atrial pacing have already been shown in this group of patients.\textsuperscript{17-19,35-37)} Moreover, the Athens QRS score changes were found to be closely correlated with exercise-induced segmental contraction abnormalities, exercise-induced myocardial perfusion defects, and the number of obstructed coronary arteries.\textsuperscript{29)} On the other hand, only a small number of patients were included, thus, the observed results should not be extrapolated to all patients with SCF and it is not clear whether exercise-induced ischemia is permanent or returns to normal some time after.

\textbf{Conclusion:} In this study containing a small number of patients, the exercise QRS score was found to be similar in those with SCF but otherwise patent epicardial coronary arteries and those with obstructive CAD. These results suggest that SCF and otherwise patent epicardial coronary arteries may cause myocardial ischemia during a provocation test such as exercise testing. However, this should
be confirmed by further large-scale studies and the other objective findings of true myocardial ischemia also need to be investigated.

REFERENCES