Exercise Test in Variant Form of Angina Pectoris

Comparison of the Results with Spontaneous Attacks

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SUMMARY

Exercise tests were performed in 14 patients with untreated variant angina with frequent spontaneous attacks and in 15 patients after treatment abolished the attacks. (1) Anginal attacks associated with ST elevation were induced by exercise in 79% of untreated patients. By contrast, ST elevation was not observed in treated patients and ST depression was induced in 53% of the cases. (2) Exercise-induced ST elevation in untreated patients was shown in the same leads as the spontaneous attacks. (3) Exercise-induced ST elevation appeared initially during the recovery phase after exercise in 36% of untreated patients. Exercise-induced ST depression appeared during or immediately after exercise. (4) The reproducibility of exercise-induced ST elevation was low with repeated tests at different stages, but exercise-induced ST depression was consistently observed. (5) The exercise-induced ST depression and lack of ST changes in treated patients were highly suggestive of the presence and absence of organic coronary artery disease, respectively. However, the exercise-induced ST elevation in untreated patients did not differentiate between the presence or absence of organic stenosis of the coronary arteries. The results of exercise tests vary with the stage of variant angina. It is suggested that a coronary arterial spasm is a trigger mechanism for exercise-induced angina in cases of variant angina with frequent spontaneous attacks.

Additional Indexing Words:

Variant form of angina pectoris Exercise test Exercise-induced ST elevation Exercise-induced ST depression Coronary arterial spasm

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ATTACKS of variant forms of angina pectoris (variant angina) occur at rest or during ordinary activity and are usually not precipitated by exercise in Prinzmetal's original description.^{1),2)} However, recent papers³⁾⁻¹⁶⁾ have described that exercise-induced anginal pain is associated with ST elevation, as in the spontaneous attacks. Nevertheless, it is generally accepted that exercise-induced ST elevation is not a common phenomenon in variant angina.

Contrary to these descriptions, our clinical observations of patients with variant angina have shown that exercise can frequently induce anginal attacks associated with ST elevation. However, the occurrence of exercise-induced angina was not consistent in each patient. Thus, the discrepancy between our findings and other reports probably reflects the inconsistent results of exercise tests in patients with variant angina. In this report, we compare the results of exercise tests performed when spontaneous attacks frequently occurred with results after they subsided.

METHODS

Subjects: Twenty-one patients (20 male and 1 female subjects, 37-69 years old) with typical spontaneous angina with electrocardiographic evidence of ST elevation, were included in this study. Patients with clear evidence of myocardial infarction or a suspected, impending myocardial infarction were excluded. Patients were divided into untreated and treated groups. Exercise tests were performed on 14 untreated patients (untreated group). Eight subjects in the untreated group were given another exercise test after the spontaneous attacks were abolished by treatment. In 7 other subjects, the first exercise test was given after initiation of treatment, immediately after the spontaneous attacks were recognized. These 15 patients were included in the treated group.

Exercise test: Exercise tests were performed under continuous observation, using treadmill or bicycle ergometer. The treadmill exercise test was performed according to Bruce's protocol.¹⁷⁾ The bicycle ergometer exercise test was started at 300 KPM/min and increased at 300 KPM/min or 150 KPM/min every 3 min until the following signs of end point appeared. The end point of the exercise test was determined by progressively aggravating anginal pain, severe dyspnea, incapacitating leg fatigue, appearance of progressive ST elevation or depression of more than 0.1 mV, or attainment of 85% of the age-predicted maximal heart rate according to Lester and Sheffield's table.¹⁸⁾ The ECG was recorded continuously using either conventional 12 leads or modified Frank's leads,¹⁹⁾ from the preexercise period

until 10 min after cessation of the test.

The exercise tests were performed between 2 and 5 p.m. in the fasted state. Tests performed at other times were excluded from this study. The date of the exercise test was as close as possible to the day when spontaneous attacks associated with ST elevation were confirmed in untreated state. The exercise test was repeated on another day to evaluate the reproducibility of the test. After the control exercise test was performed in the untreated state, the patients were treated with calcium antagonists or long-acting nitrates. When spontaneous attacks subsided, another exercise test was performed. For patients who had severe spontaneous attacks necessitating immediate treatment, the exercise test before medication was omitted and the first test was performed after starting the treatment.

Coronary angiography: Coronary angiography (CAG) was performed in 11 patients by the Judkins technique after treatment completely abolished spontaneous attacks. Coronary artery stenosis of more than 75% was defined as significantly stenotic.

RESULTS

The results of the exercise tests and CAG are summarized in Table I.

Untreated group: In 12 of 14 (86%) patients, spontaneous attacks were

Table I. Summary of Results of Exercise Test and Coronary Angiography

group	untreated (14)	treated (15)
interval between spontaneous attack and exercise test	0-5 days	1 day—1 year
spontaneous attack	frequent	absent
ST changes	ST ↑ 11/14 ST(−) 3/14	ST ↓ 8/15 ST(−) 7/15
leads showing ST change	same as in spontaneous attack 11/11	V ₄ —V ₆ 8/8
appearance of ST changes	during or immediately after test 7/11 (ST ↑) during the recovery phase 4/11 (ST ↑)	during or immediately after test 8/8 (ST ↓)
reproducibility of exercise test	low (ST ↑)	high (ST ↓)
CAG	stenosis (+): ST ↑ 3 stenosis (−): ST ↑ 1 ST(−) 1	stenosis (+): ST ↓ 3 stenosis (−): ST(−) 3

ST ↑ = ST elevation; ST ↓ = ST depression; ST(−) = no ST change; CAG = coronary angiography.

recognized on the day when the exercise test was performed. In the remaining 2 patients, the exercise test was performed either 3 or 5 days after spontaneous attacks were recognized. Anginal attacks associated with ST elevation were induced by exercise in 11 (79%) patients and the exercise test was negative in the remaining 3 (21%) patients. There were no serious complications of the test necessitating immediate treatment. The average heart rate at the end of exercise test was 129/min (110–150/min) for patients with exercise-induced angina and 152/min (140–170/min) for patients with negative results.

Exercise-induced ST elevation was shown in the same leads as in the spontaneous attacks in all patients. Typical ECG records during exercise-induced and spontaneous attacks are shown in Fig. 1. ST elevation in the X and Z leads was observed in both conditions. It appeared during exercise and persisted in the post-exercise recovery phase in 7 patients. In 4 patients, ST elevation was not observed during exercise; however, it appeared after exercise. An example of the late appearance of ST elevation after the cessation of exercise is shown in Fig. 2. In this case, exercise was discontinued because of leg fatigue before the development of anginal pain. During the first 1 min of the recovery phase, ST elevation began in lead III and typical anginal pain occurred. A maximum ST elevation of more than 0.3 mV was observed 3 min after the cessation of exercise and anginal pain was relieved by nitroglycerin administration.

The exercise test was repeated in 5 patients. In 4 patients, ST eleva-

Fig. 1. ECG during spontaneous and exercise-induced angina in a 68 year old male patient with variant angina. ST elevation was observed in X and Z leads during both attacks.

Fig. 2. Exercise ECG in a 68 year old male patient with variant angina. ST elevation appeared at 1 min and reached maximum at 3 min of the recovery phase after exercise. ANG=anginal attack; NTG=nitroglycerin; H.R.=heart rate.

tion was induced in the second test. The other patient displayed ST depression. The threshold of exercise tolerance for ST elevation induction was not reproducible. The exercise test was performed 5 times on 1 patient. Although exercise-induced angina 4 out of 5 times, the exercise tolerance was different and the heart rate at the end point of exercise varied 100 to 140/min. On the final test, angina was not induced until the heart rate reached 150/min.

CAG was performed on 5 patients in the untreated group. Among 4 patients showing exercise-induced ST elevation, 1 displayed 2-vessel disease, 2 had single-vessel disease, and 1 had no significant stenosis. Another case showing no ST changes during the exercise test had no significant coronary artery stenosis.

Treated group: Patients were treated with either diltiazem (8 cases), nifedipine (2 cases) or nitrates with propranolol (5 cases). The interval between the beginning of treatment and the exercise test varied from 1 day to 1 year. Spontaneous attacks either completely subsided or were markedly decreased in all subjects by the time that the exercise test was performed.

Eight of 15 (53%) patients showed ST depression of more than 0.1 mV and the remaining 7 (47%) had negative exercise test results. There were no cases showing ST elevation. Exercise tolerance was greater after the treatment than before the treatment. The electrocardiographic leads showing ST depression were different from those showing ST elevation during spontaneous attacks. Maximal ST depression was seen in V_4 – V_6 . ST depression appeared either during or immediately after exercise and persisted until 3 to 5 min after the cessation of exercise. Fig. 3 shows ECG record during the exercise test from the case shown in Fig. 2, recorded after spontaneous attacks were eliminated by treatment with diltiazem. ST depres-

Fig. 3. Exercise ECG, recorded after spontaneous attacks were abolished by treatment with diltiazem. Pre-treatment records from the patient are shown in Fig. 2. ST depression appeared during exercise and persisted for 5 min into the recovery phase. ST elevation (as shown in Fig. 2) was not observed.

sion started during exercise, while ST elevation occurred only in the recovery phase (Fig. 2).

The exercise test was repeated in 4 patients showing exercise-induced ST depression. In all cases, ST depression was obtained in the second test and the threshold exercise tolerance for induction of ST depression was nearly identical with results of the first test.

CAG was performed in 6 patients in the treated group. All 3 patients showing ST depression during the exercise test had significant coronary artery stenosis, 2 with single-vessel disease and 1 with 2-vessel disease. All 3 patients showing no ST changes had no significant stenosis.

DISCUSSION

Variant angina is one of the unstable varieties of angina pectoris, in which an exercise test is usually contraindicated. In our study, subjects suspected of having an acute myocardial infarction or showing severe spontaneous attacks (such as those accompanying serious ventricular arrhythmias) were excluded. Under these restrictions, we found that the test could be performed safely in patients with variant angina with no serious complications.

Our study revealed that exercise tests induced anginal attacks in approximately 80% of patients with variant angina; only 20% of patients showed negative exercise test results. As in spontaneous attacks, exercise-induced angina was always associated with ST elevation. Yasue et al¹¹⁾ re-

ported that exercise tests performed in the early morning could easily induce anginal attacks in patients with variant angina. In some of our cases, the exercise test was performed in the morning with similar results. However, they were excluded from this study because the number of patients was small. Even with a test performed in the afternoon, angina attacks were induced in a high proportion of the patients. One reason for this high percentage may be that the test was performed at the time when spontaneous attacks were frequent. This period is defined as unstable angina and an exercise test is usually postponed until spontaneous attacks subside and the clinical situation is stable. We found that the reproducibility of exercise test results is low for repeated tests, suggesting that the underlying condition varies with time. When the exercise test is performed on a day when spontaneous attacks frequently occur, the attacks seem to be more readily induced by exercise than is generally believed. Our results indicate that Prinzmetal's original description^{1),2)} does not necessarily hold for many patients with variant angina during the stage when spontaneous attacks frequently occur. The ineffectiveness of exercise in precipitating attacks seems not to be an essential feature of variant angina.

It is strongly suggested that coronary artery spasms are an important pathogenetic mechanism of spontaneous angina in variant angina. Many investigators have presented evidence of coronary arterial spasms during spontaneous attacks. Recent papers^{11),20)} show coronary arterial spasms with CAG during exercise-induced angina in cases with variant angina where exercise seems to trigger the spasm. Our results seem to support the spasm theory for the mechanism of exercise-induced angina. Firstly, exercise-induced angina was always associated with ST elevation and its location was always same as in spontaneous attacks. Secondly, inconsistent exercise test results were observed. At the time when spontaneous attacks frequently occurred, exercise could easily induce anginal attacks associated with ST elevation. However, the reproducibility of the test was low after the spontaneous attacks subsided. Furthermore, the fact that the results of exercise tests were different in the morning and in the afternoon supports coronary arterial spasm theory. By contrast, exercise-induced ST depression is highly reproducible, and an imbalance of myocardial oxygen demand and supply is presumably the underlying mechanism. The inconsistency of exercise-induced ST elevation cannot be explained by classic myocardial oxygen imbalance theory. Finally, there were several cases showing ST elevation in the late recovery phase after exercise. This phenomenon has been previously reported by Weiner et al.⁷⁾ and Lahiri et al.¹²⁾ The late occurrence of ST elevation is difficult to explain by myocardial oxygen imbalance, since myo-

cardial oxygen demand should be decreased in this stage.

The mechanisms for coronary arterial spasm induction by exercise are not clear. Stimulation of alpha-adrenergic receptors has been proposed as a mechanism underlying spontaneous attacks of variant angina.²¹⁾⁻²³⁾ Exercise predominantly stimulates beta-adrenergic receptors. How alpha-adrenergic receptors are stimulated by exercise is not well explained. At the time when spontaneous attacks frequently occur, alpha-adrenergic receptors may be hypersensitive, inducing a coronary arterial spasm by non-specific stimulation. It is well known that variant angina is precipitated by various non-specific stimuli such as ordinary daily activities, hyperventilation, a cold pressor test or a Valsalva maneuver. Exercise exerts a profound influence on autonomic nervous activity. Beta-adrenergic activity is enhanced during exercise and vagal tone is increased in the recovery phase after exercise. These serial changes may affect a preexisting alpha-adrenergic hypersensitivity and precipitate attacks. Enhancement of alpha-adrenergic activity may also occur in the recovery phase after exercise, via reflex mechanisms associated with an increase of vagal tone and a decrease of beta-adrenergic activity. Circulating metabolic factors produced by exercise are another candidate for a trigger mechanism. However, these factors are not satisfactory for explaining every aspect of exercise-induced ST elevation.

When spontaneous attacks disappeared after treatment, ST depression induced by exercise was observed in some cases. This is probably due to increased myocardial oxygen demand. This is a consistent result of exercise tests and maximal ST depression is usually observed during or immediately after exercise, when myocardial oxygen demand is supposed to be maximal. It is of clinical importance that exercise-induced ST depression after treatment is highly suggestive of organic coronary artery disease, while a lack of ST changes probably excludes the presence of severe coronary artery disease. By contrast, presence or absence of organic coronary artery disease cannot be determined from exercise-induced ST elevation.

Thus, results of exercise test vary with time in patients with variant angina. Exercise tests should be performed repeatedly in patients with variant angina and the results should be evaluated in the light of the clinical course of the patients. We believe that repeated exercise tests are a valuable non-invasive tool for the estimation of functioning coronary arteries.

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