Exercise-Induced Cyclic Episodes of S-T Segment Elevation in a Patient with Variant Angina

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SUMMARY
A unique case of variant angina is described in which cyclic S-T segment elevation was reproducibly induced by exercise. The treadmill test revealed cyclic S-T segment elevation to occur from the first minute onward, recurring with a cycle length of 2 min throughout the exercise while the work load was being increased. Similar cyclic episodes were also induced by the cold pressor test, and the ambulatory electrocardiogram demonstrated spontaneous episodes of S-T segment elevation with a similar cycle length in early mornings. Coronary arteriography revealed a fixed lesion in the mid-portion of right coronary artery with a 90% narrowing associated with coronary spasm leading to subtotal occlusion. The cyclic episodes were abolished by the administration of the calcium antagonist diltiazem. The spontaneous phasic activity of coronary arterial muscle is discussed as a possible cause or mechanism.

Additional Indexing Words:
Variant angina  S-T elevation  Treadmill test  Coronary spasm

A s described in Prinzmetal's original articles,1),2) some patients with variant angina show the occurrence of cyclic episodes of S-T elevation at rest. These are often seen to occur in sequences with regular intervals of less than 30 min.31–5) However, clinical observation of cyclic S-T segment elevation induced by exercise has not been reported. We report here an unusual case of variant angina with periodic S-T segment elevation that was reproducibly induced by exercise and persisted in spite of increasing work load. This particular case may provide us with a valuable insight into a potential mecha-
Case Report

Past and present history: This patient was a 64-year-old bookseller who suffered from severe back pain of 1 hour duration when he was walking uphill one morning 13 months prior to his admission. Three months before he was referred to the National Cardiovascular Center for further evaluation and medical management, he had experienced a similar attack lasting for 10 min, induced by mowing the lawn in the morning. During the same period he also experienced throat discomfort of less than 1 min on several occasions during his daily activities, or was awakened by momentary chest discomfort in the early morning. But he did not remember feeling definite chest pain or pressure while sleeping.

The patient’s past history indicated long-standing diabetes mellitus which had been successfully controlled by oral medication for 20 years. Another risk factor was a history of cigarette smoking (3 packs/day) for 40 years.

Physical and laboratory findings: Physical examination disclosed no significant abnormal findings. X-ray examination of the chest revealed a heart of normal size, and the electrocardiogram at rest showed rS or rSr' pattern in leads III and aV\(_F\) with negative T waves which were suggestive of an old inferior infarction. Fasting blood sugar level was 90 mg/100 ml. No abnormalities were seen in other laboratory examinations.

Clinical course: After admission, the patient was put on activity ad lib within the room, but he did not complain of any anginal pain. On the 5th hospital day the patient underwent a graded treadmill exercise test using the CASE monitoring system (Marquette Electronics). During the early phase of stage 0 (speed: 2.5 Km/h, grade: 0%), the electrocardiogram showed S-T segment elevation in leads II, III, and aV\(_F\) and reciprocal S-T segment depression in leads V\(_2\) to V\(_4\), however the patient had no complaints. These S-T segment changes disappeared during continued exercise and then reappeared. These changes were repeated with same amplitude of S-T segment changes with a recurring cycle length of 2 min while the work load was increased from stage 0 through stage 1/2 (2.5 Km/h, 5%), stage 1 (2.5 Km/h, 10%), and stage 2 (3.5 Km/h, 10%) to stage 3 (4.5 Km/h, 10%) (Fig. 1). A 24 hour ambulatory electrocardiogram recorded on the 7th to 8th hospital day revealed more than 60 recurring episodes of S-T segment elevation in the early morning. Most of them were of short duration and periodic occurrence with a predominant cycle length of about 2 min, interspersed with a few episodes of longer duration and cycle length. He was symptom
Fig. 1. A) ECG recording during treadmill exercise without drug. B) The trendgrams of displacement (depression or elevation at junctional point of RST segment) and slope of S-T segment obtained from the record of the treadmill test using CASE system (Marquette Electronics). They show cyclic S-T segment elevation in lead aVF and reciprocal S-T segment depression in lead V1 during and immediately after exercise while the work load was increased from stage 0 (2.5 Km/h, 0%) to stage 3 (4.5 Km/h, 10%). The periodicity is regular with a cyclic length of about 2 min.

free throughout these episodes. A cold pressor test (immersion of hands into cold water for 15 sec) also induced the same cyclic pattern of asymptomatic S-T segment elevation in the same leads as detected in the exercise test (Fig. 2). This episode was not reproduced after taking sublingual isosorbide dinitrate 5 mg. After a small dose of calcium antagonist (diltiazem 30 mg q.i.d.) was given, the second treadmill test was done, which revealed the same cyclic S-T segment elevation throughout exercise from stage 1 to stage 3 (Fig. 3A). Then the regimen of diltiazem was increased to 60 mg q. 6 h. The treadmill test revealed that S-T segment elevation without cyclic change appeared only when the work load increased to stage 5 (5.5 Km/h, 14%) and lasted for 4 min after the end of exercise (Fig. 3B).

Demonstration of coronary spasm: On the 17th hospital day the patient underwent cardiac catheterization and selective coronary arteriography using the Judkins technique. Immediately after spontaneous S-T elevation was confirmed, right coronary arteriography was performed (Fig. 4A). It revealed subtotal occlusion at the mid right coronary artery (segment 36) with delayed filling of the distal portion of the vessel. After a chain of
spontaneous episodes subsided, right coronary arteriography was repeated. This revealed at the same site an organic narrowing of 90% with plaque but without delayed filling of the vessel's distal portion (Fig. 4B). The third right coronary arteriography, which followed right atrial pacing performed at a rate of 130 beats/min with concomitant S-T segment elevation, revealed the same subtotal occlusion at the same site with distal delayed filling (Fig. 4C). Sublingual nitroglycerin (0.3 mg) was then administered, and right coronary arteriography was done for the fourth time with demonstration of
Fig. 4. Right coronary arteriogram. A) Immediately after a spontaneous episode of S-T segment elevation. At the mid-portion of the artery, subtotal occlusion with slow filling of the distal portion of the vessel is observed. B) During the absence of S-T segment elevation. A 90% organic narrowing with plaque is seen at the mid-portion of the artery. Filling delay at the distal portion of the vessel was not observed. C) Immediately after an episode of S-T segment elevation induced by right atrial pacing at a pacing rate of 130 beats/min. It shows subtotal occlusion at the mid-portion of the artery with slow distal filling. D) During right atrial pacing after sublingual administration of nitroglycerin 0.3 mg. It shows a 90% organic narrowing without slow distal filling.

90% organic narrowing of the same portion without distal delayed filling (Fig. 4D). Then left coronary arteriography and left ventriculography were done in the usual manner. They revealed 75% luminal narrowing at the mid-portion of the left circumflex coronary artery (segment 13°) and reduced wall motion of the anterolateral and diaphragmatic left ventricular wall without ventricular aneurysm.

Thallium-201 myocardial imaging was performed simultaneously with the cold pressor test, which did not induce an episode of S-T segment change, and revealed hypoperfusion of radionuclide in the inferoposterior region of the left ventricle where radionuclide refilled in 2 hours. After several days of treatment with 60 mg diltiazem q. 6 h., the ambulatory electrocardiogram and cold pressor test were repeated with negative results. On the 59th hospital day the patient was discharged. He has remained asymptomatic for 4 months after discharge on this therapeutic regimen, and was able to perform a higher grade of exercise (5.5 Km/h, 18%) without significant S-T change.
and chest pain (Fig. 3C) even after discontinuing administration of diltiazem for several days.

**DISCUSSION**

It is well known that in patients with variant angina, episodes of S-T segment elevation at rest may occur at regular intervals, as was first described by Prinzmetal et al. However, the case reported here is a rare one in which cyclic S-T segment elevation was shown during exercise.

The following mechanism can be postulated as a cause of these cyclic episodes. The patient could have an abnormally high basal tone of the coronary artery which would cause it to be very sensitive to an agonist. Predisposed by this increased basal tone, certain endogenous substances, liberated by exercise, might initiate or enhance the phasic constriction of coronary arterial muscle under the influence of the autonomic nervous system, the activity of which might be altered even during early periods of exercise. The phasic constriction is superimposed upon a fixed stenosis of the coronary artery, leading to manifestation of S-T segment elevation.

There are some reports supporting the possibility of this hypothesis. Servi et al. reported 2 patients with variant angina who showed variable threshold of angina during exercise, and they suggested that this might have been due to differences in coronary artery tone at the start of exercise. In our case, the cyclic changes were seen during very light exercise with cycle lengths similar to those of spontaneous attacks observed in early mornings, and with the same degree of amplitude on each recurrence of S-T elevation independent of the level of work load. It is evident, therefore, that these findings are a manifestation of a decreased threshold for ischemic episodes with S-T elevations probably in association with easily inducible coronary artery constriction.

The phenomenon of cyclic reduction in coronary blood flow with cycle length of 3.5 to 20 min has been observed in experimental studies by Uchida et al. and Folts et al. They postulated that a fixed stenosis in a narrowed coronary artery promotes periodic in vivo platelet aggregation which transiently increases obstruction and decreases coronary blood flow. However, they noted that the platelet thrombus formation may have additional significance in some instances as a source of vasoconstriction of the human coronary artery. On the other hand, recent experiments on isolated human coronary arterial muscle performed by Ginsburg et al. and Ross et al. demonstrated spontaneous, rhythmic periods of constriction and relaxation with cycle lengths between 60 and 80 sec; this cyclic activity was shown to be enhanced
or initiated by several vasoactive substances such as noradrenaline or ergonovine, and abolished by verapamil or diltiazem. As suggested by their experiments, it is conceivable that any agent which produces partial depolarization of the coronary smooth muscle cells could, under certain circumstances, act to trigger powerful and rhythmic constrictions. This type of phenomenon might be considered as an experimental model of coronary spasm, especially that related to cyclic episodes of myocardial ischemia.

Ginsburg et al. also described how human coronary artery responded to vasoactive substances with a biphasic response, i.e. an initial rapid phase of constriction followed by a slow, tonic phase of constriction. The initial constriction can, depending on the agonist used, account for 70% of the overall maximal tension generated and might be caused by the release of intracellular calcium; the slow tonic response is presumably due to an influx of extracellular calcium through the calcium slow channel. Diltiazem eliminated the latter response with minimal effect on the initial rapid response. These experimental studies may partly explain our clinical observation that diltiazem abolished cyclic S-T changes during exercise but not S-T elevation of longer duration at higher work loads (Fig. 3B). Later when the patient was completely free from anginal attacks, S-T elevation was not induced at higher levels of exercise (Fig. 3C).

The cyclic constriction of coronary arteries as discussed here is seldom documented as a clinical manifestation of myocardial ischemia. Nevertheless, it is of prognostic importance that repetitive vasoconstriction, whether clinically detected or not, may result in endothelial damage and the development of atherosclerotic plaques, as suggested by Marzilli et al.121

REFERENCES

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