Circadian Variation of Exercise Capacity in Patients with Prinzmetal's Variant Angina: Role of Exercise-induced Coronary Arterial Spasm

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SUMMARY Thirteen patients with Prinzmetal's variant angina performed treadmill exercise tests in the early morning and in the afternoon of the same day. The attacks with ST elevation were induced repeatedly in all 13 patients in the early morning, but in only two patients in the afternoon. Propranolol did not suppress the exercise-induced attacks in all 13 patients. Diltiazem suppressed the attacks in all 13 patients and phentolamine in eight of the nine patients.

Coronary arteriograms demonstrated that spasm occluding completely or almost completely the large coronary artery supplying the area of myocardium showing ST elevation appeared during the attacks and disappeared along with the attacks after nitroglycerin administration in all four patients in whom the attacks were induced by arm exercise in the catheterization laboratory.

We conclude that there is circadian variation of exercise capacity in patients with Prinzmetal's variant angina caused by coronary arterial spasm induced by exercise in the early morning but not in the afternoon.

ANGINA PECTORIS is a clinical syndrome caused by transient myocardial ischemia due to an imbalance between myocardial oxygen supply and demand. Exercise-induced angina (exertional angina) has been explained by increased myocardial oxygen consumption in the presence of fixed stenosis of large coronary arteries.1, 2 Prinzmetal's variant angina — which occurs at rest particularly at night and in the early morning and is associated with ST-segment elevation on the ECG3 — is difficult to explain on the above basis and there is now increasing evidence that spasm of a large coronary artery is responsible for the attack.4-9

Prinzmetal9 and other workers4-10 emphasized that this form of angina is not provoked by exercise, but there are reports indicating that some patients with this syndrome have attacks associated with ST-segment elevation which are induced by exercise.11-14

We have reported that coronary arterial spasm and Prinzmetal's variant angina can be induced by stimulation of α-adrenergic receptors.7 Because sympathetic discharge occurs in response to exercise,15, 16 it is possible that the attacks associated with ST-segment elevation can be induced by exercise in patients with Prinzmetal's variant angina.

The present study examines whether attacks associated with ST-segment elevation can be induced by exercise in patients with Prinzmetal's variant angina and by what mechanism the attacks occur.

Materials and Methods

Patients

We studied 13 patients with Prinzmetal's variant angina. All patients had attacks of chest pain associated with ST-segment elevation on the ECG which recurred at night or in the early morning more than five times per week at the time of the study. A summary of clinical data, including age, sex, ECG at rest and during attack, and coronary arteriograms, is given in table 1. None of the patients had prior myocardial infarction, heart failure, chronic obstructive lung diseases or other severe complications.

Exercise Stress Test

All medications were discontinued at least 5 days before the study except nitroglycerin, which was discontinued at least 2 hours before the study. All patients had been tested on a treadmill at least once before the study. They had been kept in bed in the fasting state until 5:00-8:00 a.m., when they were carried in a wheelchair to the ECG room. After control 12-lead ECG and blood pressure were taken, the patients exercised at 2.5 mph at a grade of 12% for up to 3 minutes on a motor-driven treadmill with constant ECG monitoring.

This procedure reproducibly induced attacks of chest pain associated with ST-segment elevation in all patients.

Treadmill exercise test was repeated at 3:00-4:00 p.m. of the same day at 3.0 mph at a grade of 12% for up to 4.5 minutes. The patients had strolled around the wards between morning and afternoon.

Two hours after oral administration of diltiazem 90 mg and propranolol 60 mg (all 13 patients), and phenoxybenzamine 30 mg (four patients), and 5 minutes after intramuscular injection of phentolamine 0.2 mg/kg of body weight (nine patients) — each drug given on separate mornings within 1 week and with a
Table 1. Summary of Clinical Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>ECG at rest</th>
<th>ECG during attack</th>
<th>Coronary arteriogram (%) stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in V2-3</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation or depression in II, III, aVF</td>
<td>Normal RCA 50% LAD</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>F</td>
<td>T inversion in V1-4</td>
<td>ST elevation in V1-4</td>
<td>75% LAD</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>T inversion in V1-4</td>
<td>ST elevation in V1-4</td>
<td>80% LAD</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in V2-4</td>
<td>75% LAD</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in V2-4</td>
<td>80% LAD</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in V1-4</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in V2-4</td>
<td>50% LAD</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in V1-4</td>
<td>80% LAD</td>
</tr>
<tr>
<td>10</td>
<td>52</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in V1-4</td>
<td>Normal</td>
</tr>
<tr>
<td>11</td>
<td>63</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in II, III, aVF</td>
<td>80% RCA</td>
</tr>
<tr>
<td>12</td>
<td>48</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in V2-4</td>
<td>90% LAD</td>
</tr>
<tr>
<td>13</td>
<td>57</td>
<td>M</td>
<td>Normal</td>
<td>ST elevation in V2-4</td>
<td>95% LAD</td>
</tr>
</tbody>
</table>

Abbreviations: LAD = left anterior descending coronary artery; RCA = right coronary artery.

randomized sequence of administration — each patient repeated the same exercise at the same hour of the separate morning so we could examine the effects of these drugs on the exercise-induced attacks associated with ST-segment elevation.

The effects of these drugs on the attacks were judged as completely effective when exercise-induced chest pain and ST-segment elevation were completely suppressed; as partially effective when exercise-induced ST-segment elevation improved by more than 0.1 mV; as not effective when exercise-induced ST-segment elevation improved by less than 0.1 mV; and aggravated when exercise-induced ST-segment elevation was aggravated by more than 0.1 mV on the lead showing maximum ST-segment deviation 1 minute after the exercise. In this study, an attack was defined as chest pain associated with ST-segment elevation on the ECG.

Isoproterenol Infusion Test

The infusion of isoproterenol (10–15 μg/min for 1–3 minutes) was done with the patient in the supine position with constant monitoring of ECG and blood pressure to be compared with the results of the exercise test.

ECG was recorded with a six-channel electrocardiograph and blood pressure was taken sphygmomanometrically. Continuous electrocardiographic monitoring during the exercise was done telemetrically using bipolar transthoracic lead CMs.

Coronary Arteriography

Coronary arteriography was done using the Judkins technique with constant monitoring of ECG and blood pressure. No premedication was given.

In seven of 13 patients this was done before and immediately after arm exercise, and after nitroglycerin administration at 6:00–8:00 a.m., after the patients had been kept in bed in the fasting state, and in the remaining six patients at 1:00–4:00 p.m., after they had strolled around the wards during the morning.

After control coronary arteriograms were taken, the patients performed the arm-exercise test in the supine position using a spring pull exerciser (about 9 kg when expanded to 145 cm) 40–50 times per minute for up to 3 minutes. Coronary arteriography was done immediately after the exercise and then nitroglycerin (0.6 mg) was given sublingually. Repeat coronary arteriography was again performed 3–5 minutes after nitroglycerin administration. The catheter was withdrawn immediately to the thoracic aorta each time the dye injection into the coronary artery was finished. The relationship between focal spot, table top, patient position and height of the image intensifier was kept constant to maintain reproducibility of the magnification factors during the procedures.

Informed consent was obtained from each patient for the treadmill exercise test, drug studies and coronary arteriography.

Results

Exercise Stress Test

Treadmill exercise test done at 5:00–8:00 a.m. reproducibly induced attacks associated with ST-segment elevation in all patients. The test, however, did not induce attacks when done at 3:00–4:00 p.m. of the same day, except in patients 12 and 13, who had fixed stenosis at the proximal portion of the left anterior descending coronary artery of 90% and 95%, respectively. This occurred despite increases in heart rate and blood pressure after exercise that were more pronounced in the afternoon than in the morning.
because the duration of exercise was 1.5–3 times longer and the speed of exercise 1.2 times greater in the afternoon than in the morning.

Representative cases are shown in figures 1 and 2. In patient 1, treadmill exercise induced the attack associated with ST-segment elevation in leads V2-3 at 6:00 a.m., but not at 3:00 p.m. of the same day, although increases in heart rate and blood pressure after exercise were more pronounced in the afternoon than in the early morning because the duration of exercise was two times longer and the speed of exercise 1.2 times higher in the afternoon than in the early morning (fig. 1). In patient 2, the exercise induced the attack associated with ST-segment elevation in leads II, III and aVf at 7:00 a.m., but not at 3:00 p.m. of the same day, although increases in heart rate and blood pressure after exercise were more pronounced in the afternoon than in the morning because the duration of exercise was three times longer and the speed of exercise 1.2 times higher in the afternoon than in the morning (fig. 2).

Thus, there is marked circadian variation of exercise capacity in most patients with Prinzmetal's variant angina and the attacks are induced even by mild exercise in the early morning but not even by strenuous exercise in the afternoon.

Effects of Various Drugs on Exercise-induced Attacks

Propranolol, a β-adrenergic blocking agent, was not only ineffective in suppressing the attacks in all 13 patients, but aggravated the attacks in eight of them (61.5%), although increases in heart rate and blood pressure after exercise were suppressed the most by propranolol.

However, diltiazem, a calcium antagonistic coronary vasodilator, suppressed the attacks completely in 11 of 13 patients (84.6%) and partially in the remaining two patients. Thus, diltiazem was effective in suppressing the attacks in 100% of the patients. Phenoxybenzamine and phentolamine, both α-adrenergic blocking agents, suppressed the attacks completely in three of four patients and in six of nine.
patients, respectively, and partially in one of four patients and in two of nine patients, respectively. Thus, these agents were effective in suppressing the attacks in 100% and 88.9% of the patients, respectively.

Figures 3 and 4 show representative cases. Diltiazem, phenoxybenzamine and phentolamine completely suppressed the attacks associated with ST-segment elevation, but propranolol aggravated the attacks, although increases in heart rate and blood pressure after exercise were suppressed the most by propranolol.

Isoproterenol Infusion Test

The attacks did not occur during the infusion of isoproterenol, a β-adrenergic stimulant which increases myocardial oxygen consumption, except in patient 6, although heart rate increased to more than 130 beats/min during the infusion in all patients.

Coronary Arteriograms

The attacks associated with ST-segment elevation on the ECG were induced by arm exercise in three (patients 2, 3 and 4) of seven patients (2–8) who performed this test in the morning in the catheterization laboratory. Coronary arteriograms demonstrated that spasm occluding completely or almost completely the large coronary artery (normal right coronary artery in patient 2, left anterior descending coronary artery with 75% fixed stenosis in patient 3 and with 80% fixed stenosis in patient 4) supplying the area of myocardium showing ST-segment elevation appeared during the attacks and disappeared along with the attacks after nitroglycerin administration in all three patients.

In two (5 and 6) of the remaining four patients (5–8) in whom the attacks could not be induced by arm exercise, spasm of a large coronary artery (left anterior descending coronary artery with 75% fixed stenosis in patient 5 and with 80% fixed stenosis in patient 6) delaying the visualization of the peripheral portions also appeared after arm exercise and disappeared after nitroglycerin administration. Thus, coronary arterial spasm was induced by arm exercise in five of seven patients (71.4%) in the morning.
The representative cases are shown in figures 5 and 6. In patient 2, the right coronary artery appeared spastic and its diameter was small on the control coronary arteriogram (fig. 5A). During the attack which was induced by 1 minute of arm exercise and was associated with ST-segment elevation in lead III, severe spasm appeared and occluded the right coronary artery completely at the proximal portion (fig. 5B). After nitroglycerin administration, which promptly relieved the attack, the spasm disappeared and the right coronary artery was markedly dilated and normal (fig. 5C).

In patient 5, the left coronary artery was promptly visualized, including its peripheral portions, on the control coronary arteriogram (fig. 6A). The coronary arteriogram taken after 3 minutes of arm exercise showed that spasm appeared at the proximal portion of the left anterior descending coronary artery and delayed the visualization of its peripheral portions (fig. 6B). After nitroglycerin administration, the spasm disappeared and the left coronary artery was markedly dilated compared with the control (fig. 6C).

In the afternoon, arm exercise could induce the attacks only in patient 13, who had 95% fixed stenosis of the left anterior descending coronary artery at the midportion (figs. 7A and 7C). In this patient the attack associated with ST-segment elevation in lead V_4 was induced by 2 minutes of arm exercise. During the attack, spasm appeared at the site of the organic stenosis, occluding completely the left anterior descending coronary artery (fig. 7B), and disappeared along with the attack after nitroglycerin administration (fig. 7C).

We compared the coronary arteriograms taken in the early morning (patients 2–8) with those taken in the afternoon (patients 1, 9–13) in these patients. As shown in figures 5 and 6, the tone of the large coronary artery was increased and its diameter small on the control coronary arteriogram. Nitroglycerin dilated the artery markedly in the early morning in all patients except 7 and 8, who had been nervous before coronary arteriography.

However, in the afternoon the large coronary artery was already dilated and its tone low on the control coronary arteriogram; nitroglycerin dilated the artery little further, as shown in figures 7 and 8.

To document quantitatively the differences in the tone of the large coronary artery observed in the early morning and afternoon, we measured the diameters at the proximal, mid- and distal portions of the right cor-

**Figure 3. Effects of diltiazem, propranolol and phenoxybenzamine on the exercise-induced attack in patient 1.** Propranolol aggravated the attack while diltiazem and phenoxybenzamine suppressed the attack. See text for details. BP = blood pressure.
Discussion

Because attacks of Prinzmetal’s variant angina occur most often in the early morning and least often in the afternoon,17,18 we performed treadmill exercise tests both in the early morning and in the afternoon of the same day in patients with this syndrome. The treadmill exercise test induced the attacks repeatedly in the early morning in all patients, but did not provoke the attacks in the afternoon of the same day, except in two patients who had severe organic stenosis of a large coronary artery, although the exercise was longer and heavier in the afternoon than in the early morning. Thus, there is marked circadian variation of exercise capacity in patients with Prinzmetal’s variant angina.

Propranolol, a β-adrenergic blocking agent which reduces myocardial oxygen consumption1,2,16,20 and has been widely used in the treatment of exertional angina,1,2,18-21 was not only ineffective in suppressing the attacks induced by exercise in all the patients, but also aggravated the attacks in more than half of the patients.

Diltiazem,22 a calcium antagonistic drug which
dilates large coronary arteries by blocking the entry of calcium ions into the coronary vascular smooth muscle cells\(^{17, 23, 24}\) and which is effective in the treatment of Prinzmetal's variant angina\(^ {17, 25, 26}\) suppressed the attacks in all the patients. Phenoxybenzamine and phentolamine, both \(\alpha\)-adrenergic blocking agents, suppressed the attacks in most of the patients.

The attacks did not occur during the infusion of isoproterenol, a \(\beta\)-adrenergic stimulant which increases myocardial oxygen consumption, except in one patient.

This evidence strongly suggests that the exercise-induced angina associated with ST-segment elevation in patients with Prinzmetal's variant angina is caused by coronary arterial spasm and that \(\alpha\)-adrenergic receptors play a role in the production of the spasm.

In fact, in all four patients in whom the attacks were induced by arm exercise, it was demonstrated by coronary arteriography that spasm of a large coronary artery supplying the area of myocardium showing ST-segment elevation on the ECG appeared during the attacks and disappeared along with the attacks after nitroglycerin administration.

Thus, coronary arterial spasm plays an important role in the production of exercise-induced angina associated with ST-segment elevation in patients with Prinzmetal's variant angina.

The present study also shows that the tone of the large coronary artery is high and its diameter small in the early morning in patients with Prinzmetal's variant angina. Under these conditions, exercise can readily induce severe spasm resulting in the attack,
Figure 6. Left coronary arteriograms taken in the early morning in patient 5. A) Control. The left coronary artery was promptly visualized, including its peripheral portions. B) After arm exercise the spasm appeared at the proximal portion of the left anterior descending coronary artery (arrow) and delayed the visualization of its peripheral portions. C) After nitroglycerin administration the spasm disappeared and the artery was markedly dilated compared with the control.

while nitroglycerin dilates the artery markedly.

In the afternoon the large coronary artery is already dilated and its tone is low. Under these conditions, exercise can induce little spasm and no attacks occur except in patients with severe organic stenosis of a large coronary artery in whom only a slight degree of spasm would occlude the artery, resulting in the attack, as demonstrated in patient 13.

Thus, there is circadian variation of the tone of the large coronary artery in patients with Prinzmetal's variant angina which seems to explain the circadian variation of exercise capacity in patients with this syndrome. We propose the following explanation as one mechanism responsible for the circadian variation in the tone of the large coronary artery.

The tone of vascular smooth muscle (including that of the coronary artery) depends quantitatively on the presence of calcium ions which are required for the activation of myofibrillar ATPase. Physiologically, a highly potent calcium antagonistic action is exerted by hydrogen ions. Accordingly, vasoconstriction occurs if calcium ions increase or hydrogen ions decrease, whereas vasodilation is produced by either calcium deficiency or an increased hydrogen concentration. In the early morning, metabolism decreases and hydrogen ions which are produced by metabolism also decrease, whereas in the afternoon metabolism increases and hydrogen ions increase. This may be intimately related to the circadian variation in the tone of the large coronary artery. Indeed, coronary arterial spasm and anginal attacks can be induced by hyperventilation and Tris-buffer in-
fission, which decrease hydrogen ions in patients with Prinzmetal's variant angina.26

However, there are undoubtedly many other factors that may play a role in the genesis of the circadian variation in the tone of the large coronary artery.

References
FIGURE 8. Left coronary arteriograms taken in the afternoon in patient 1. The artery was already dilated on the control coronary arteriogram (A) and nitroglycerin dilated it a little further (B).


FIGURE 9. Percent increase of the diameter of the large coronary artery after nitroglycerin administration in the early morning and afternoon in patients with Prinzmetal's variant angina. Note that the large coronary artery dilates after nitroglycerin administration markedly in the early morning but little in the afternoon. See text for details.
Coronary Arterial Spasm as a Cause of Exercise-Induced ST-Segment Elevation in Patients with Variant Angina

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SUMMARY Four patients with variant angina pectoris exhibited reproducible exercise-induced chest pain and ST-segment elevation. Coronary arterial spasm was documented with arteriography during exercise-induced ST-segment elevation (three patients) or after intravenous administration of ergonovine maleate (one patient). Our observations show that in patients with variant angina exercise can trigger coronary arterial spasm, thus inducing anginal pain and ST-segment elevation.

EXERCISE-INDUCED ST-segment elevation is an abnormal response which appears in association with ventricular aneurysm, severe ischemic heart disease, or variant angina. In the variant form of angina pectoris the role of coronary artery spasm is well established but it is not yet clear whether it may also play a role in exercise-induced angina and ST-segment elevation. In this paper we present four patients with spontaneous and exercise-induced ST-segment elevation. In these patients we demonstrated that spasm was the pathogenetic mechanism of exercise-induced angina and related electrocardiographic changes.

Subjects and Methods

Four patients suffering from variant angina and no previous myocardial infarction had exercise-induced ST-segment elevation. The clinical history and the results of the exercise test and coronary angiography are briefly described (see Case Report section). The patients were asked to perform a multistage bicycle exercise test in the supine position with an initial work load of 50 watts and subsequent increments of 25 watts every 3 minutes. A 12-lead ECG was obtained before and at termination of the exercise and at each minute during recovery. Leads V4, V5, V6 were monitored during exercise and recorded on paper every 30 seconds. The patients were exercised to symptomatic end points: typical anginal pain, dyspnea or exhaustion. After premedication with 10 mg of diazepam, coronary arteriography was performed using the method of Sones. In three patients (cases 2, 3 and 4) the exercise test was repeated in the same way during coronary arteriography and arteriograms were obtained during pain and electrocardiographic changes. In the remaining patient (case 1) 0.2 mg of ergonovine maleate was administered intravenously at 0.05 mg/min. In this patient coronary arteriograms were also obtained during ergonovine-evoked chest pain. In all cases nitroglycerin, administered sublingually, relieved the pain within 3 minutes. Drug therapy was stopped 12 hours before angiography and exercise tests. No patient was receiving β-blocking drugs. Informed consent was obtained from each patient before the study. The procedures did not result in any complications.

Case Reports

Case 1

A 51-year-old man presented with a 6-month history of spontaneous anginal attacks that occurred about once a month. He reported only one episode of chest pain during effort. The admitting physical examination was negative. The blood pressure was 130/80 mm Hg; the pulse rate was 76 beats/min and

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