Prinzmetal’s Variant Form of Angina Pectoris
Re-evaluation of Mechanisms

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SUMMARY
Thirty-five patients with typical Prinzmetal’s variant angina were studied by coronary cineangiography. There was no demonstrable stenosis of the major coronary arteries in 19 patients. Nine patients with single coronary stenosis underwent aortocoronary bypass and had recurrence of the symptoms postoperatively.

Administration of nifedipine effected complete cessation of the symptoms among patients formerly treated medically. Although surgical treatment did not effect permanent relief of pain, all patients initially treated surgically experienced relief of pain when nifedipine was administered.

The pathophysiology of variant angina remains obscure. Our results suggest that neurohumoral factors exert more of an effect on the myocardial cell than on the coronary vessels.

Additional Indexing Words:
Aortocoronary bypass
Neurohumoral factor
Nifedipine
Coronary vasodilators
Coronary spasm

PRINZMETAL and his coworkers described a variant form of angina in which recurring attacks of pain occurred almost exclusively at rest, particularly in the early morning, were rarely provoked by exercise, were associated with transient ST-segment elevation, and were related to an obstructive lesion of a single major coronary artery. Since that time there has been some disagreement among workers in the field over the definition of this syndrome. In spite of the low incidence of ischemic heart disease among Japanese, 200 cases of the variant form of angina have been reported from Japan. The development of cardiac arrhythmias in many patients with variant angina further emphasizes the clinical significance of this syndrome.

Patients and Definitions
Thirty-five patients were studied. For this report, the patients were classified according to ST-segment deviation at rest and during exercise. Group a includes 27 patients in whom ST-segment elevation occurred only at rest (fig. 1). Group b includes eight patients in whom ST-segment elevation occurs at rest and ST depression during exercise (fig. 2). Enzyme studies on all patients were within normal limits.

Results
Coronary Cineangiography
All patients were studied by cineangiography. Nineteen patients (54.3%) had no significant stenosis of a coronary artery. Sixteen patients (45.7%) were found to have stenosis of more than 50% in one of the major coronary arteries. In nine of the latter, the site of stenosis corresponded with the site of ST elevation on the ECG. These patients all had single vessel disease with good perfusion distal to the stenosis. All of these nine patients underwent an aortocoronary bypass procedure. The site of the stenosis in the other seven patients did not correspond to the site of ST-segment elevation on their ECGs and these patients were not treated surgically.

Medical Treatment
Glycerol trinitrate (0.3–0.6 mg sublingually) was administered to all patients during an attack. The drug resolved the chest pain, ST-segment elevation disappeared, and arrhythmias were abolished. However, due to its short action and the tendency for attacks to occur in the early morning, the preparation is not useful in preventing attacks.

Isosorbide dinitrate (30–120 mg daily) also resolved the chest pain, and if a patient was kept on medication with doses every two hours, even during the sleeping hours, the patient seemed to remain free of symptoms. But routine administration of the drug in this way is not practical. In addition, the efficacy of the drug in patients whose attacks occur only once a month is difficult to assess. However, all patients were kept on...
either glyceryl trinitrate or isosorbide dinitrate or both.

In August, 1972, a limited supply of nifedipine, a coronary vasodilator (a 1,4-dihydropyridine derivative), became available. In 25 patients who received the preparation (40–80 mg, in four divided doses), symptoms were completely abolished. In two patients, the preparation was not effective for the chest pain associated with ST depression during exercise. 

Propranolol (60–120 mg daily) was administered to five patients without effect.

Atropine i.v. was given to five patients; only one experienced relief of pain. 

Lidocaine (1.0–2.8 g daily) was infused in two patients with a history of ventricular fibrillation but did not prevent its recurrence.

Surgical Treatment

Before nifedipine became available, neither medical treatment nor cardiac pacing was successful in preventing frequent attacks of cardiac arrhythmia. The nine patients mentioned above in whom the location of the coronary artery stenosis and the site of the ST elevation coincided underwent aortocoronary bypass surgery in an attempt to prevent a fatal cardiac arrhythmia or a myocardial infarction in the vessel distal to the stenosis (table 1). None obtained a permanent improvement and all subsequently required medical management.

Case Illustrations

Case 9

T.A. was a 57-year-old male. One morning he awoke with an anginal attack and was admitted to a local cardiac center. He was treated with propranolol, 80 mg/day, isosorbide dinitrate, 30 mg/day, and an anticoagulant. In spite of these treatments, the patient developed multiple episodes of ventricular fibrillation, preceded by chest pain accompanied by ST-segment elevation. Intravenous lidocaine was attempted without success. Only DC defibrillation terminated the life-threatening arrhythmia. The patient was transferred to the Heart Institute of Japan for surgical evaluation. Coronary angiography revealed more than

Figure 1

Representative electrocardiograms in group a, in which angina attacks occurred exclusively at rest, accompanied by ST-segment elevation.

*Bay a 1040. An antianginal drug produced by Farbenfabiken Bayer AG, Germany. The chemical structure is dimethyl 1,4-dihydro-2, 6-dimethyl-4-(o-nitrophenyl)-3, 5-pyridinedicarboxylate.
Representative electrocardiograms in group b, in which angina attacks at rest were accompanied by ST-segment elevation, and angina attacks during exercise were accompanied with ST-segment depression.

80% stenosis of the proximal portion of the left anterior descending artery.

The patient underwent successful coronary bypass and was discharged. About two months later, he was readmitted with chest pain recurring, along with elevation of the ST segment in ECG leads V1-4. A

Table 1
Data on Patients with the Variant Form of Angina Pectoris Who Underwent Aortocoronary Bypass

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Grade of coronary artery stenosis</th>
<th>ECG finding during attack</th>
<th>Patency of graft</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA</td>
<td>LAD</td>
<td>LCX</td>
<td>ST elevation (rest)</td>
<td>ST depression (exercise)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>Postop</td>
<td>Preop</td>
<td>Postop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Y.K.</td>
<td>44</td>
<td>M</td>
<td>1 4 1</td>
<td>+</td>
<td>+</td>
<td>excellent</td>
</tr>
<tr>
<td>2. T.H.</td>
<td>48</td>
<td>M</td>
<td>5 1 1</td>
<td>+</td>
<td>+</td>
<td>excellent</td>
</tr>
<tr>
<td>3. H.K.</td>
<td>54</td>
<td>M</td>
<td>4 1 1</td>
<td>+</td>
<td>+</td>
<td>excellent</td>
</tr>
<tr>
<td>4. D.I.</td>
<td>62</td>
<td>M</td>
<td>2 5 2</td>
<td>+</td>
<td>+</td>
<td>excellent</td>
</tr>
<tr>
<td>5. Y.T.</td>
<td>59</td>
<td>M</td>
<td>2 4 1</td>
<td>+</td>
<td>+</td>
<td>excellent</td>
</tr>
<tr>
<td>6. H.Y.</td>
<td>57</td>
<td>M</td>
<td>4 1 1</td>
<td>+</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>7. S.U.</td>
<td>59</td>
<td>M</td>
<td>5 1 1</td>
<td>+</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>8. T.S.</td>
<td>62</td>
<td>M</td>
<td>1 4 1</td>
<td>+</td>
<td>+</td>
<td>not performed</td>
</tr>
<tr>
<td>9. T.A.</td>
<td>57</td>
<td>M</td>
<td>1 4 1</td>
<td>+</td>
<td>+</td>
<td>excellent</td>
</tr>
</tbody>
</table>

* Died during operation.

Cineangiographic findings were classified, based on the state of the maximum stenotic site, into grade 1 (0–25% stenosis); grade 2 (25–50% stenosis); grade 3 (50–75% stenosis); grade 4 (75–90% stenosis); grade 5 (more than 90% stenosis); and grade 6 (total obstruction).

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repeat angiogram revealed good patency of the graft. He was put on nifedipine therapy and has experienced no further attacks.

Case 2
T.H., a 48-year-old male, was admitted to the hospital with a history of frequent anginal chest pain intermittently in the early morning for five years. Frequency of chest pain increased to over 15 times a day. During chest pain, the ECG showed ST elevation in leads II, III, and aV_{l}, followed by complete atrioventricular block and Adams-Stokes syndrome. The patient was initially treated with isosorbide dinitrate, 120 mg/day, and propranolol, without success. Coronary angiography revealed more than 90% stenosis at the midportion of the right coronary artery. The patient underwent aortocoronary bypass. Three days postoperatively, he developed anginal pain with ST-segment elevation in leads II, III, and aV_{l}. One year later, he was readmitted because of frequent anginal attacks. His coronary angiogram revealed good patency of the graft. In 1973, he was started on nifedipine therapy and the symptoms completely disappeared.

Clinical Course
None of the 35 patients has developed myocardial infarction. One death was due to complete atrioventricular block during surgery, and the other death was due to ventricular fibrillation. The rest of the patients responded favorably to nifedipine, although symptoms improved spontaneously in some patients.

Discussion
Prinzmetal and his coworkers\(^1\)\(^-\)\(^4\) presented the first description typical of chest pain associated with ST elevation. These researchers concluded, on the basis of autopsy studies, that the symptoms were due to stenosis of one of the major coronary arteries. The work of many other investigators supported an association between the symptoms and the stenosis of a coronary artery.

In contrast, in variant angina, only nine cases (25.7%) in our study showed good correlation between ST elevation and the angiographic findings. From our study and those of others,\(^7\)\(^-\)\(^11\) it has become clear that some patients have normal coronary angiograms. There have also been reports of aortocoronary bypass grafts performed on patients with this syndrome. In our study, although the graft was proven to have good patency after the operation, attacks continued postoperatively.\(^11\)\(^,\)\(^12\) These data confirm that an atherosclerotic stenosis or occlusion of a major coronary artery is not always involved in this disease.

Attacks of Prinzmetal's variant angina have frequently been attributed to functional stenosis (spasm).\(^10\)\(^,\)\(^13\) However, in our laboratory, in the six cases (out of 400 studies done) in which functional spasm of more than 75% of the proximal right coronary occurred, no chest pain or ST-segment elevation accompanied the spasm. In addition, coronary spasm has been noted in about 1% of all selective coronary angiograms performed, without significant accompanying chest pain.\(^6\)\(^,\)\(^14\)\(^,\)\(^15\)

Prinzmetal\(^1\) originally treated five patients with nylidrin with good results. While Ueda et al.\(^16\) reported one patient who responded favorably with atropine, we found we could induce pain in patients with variant angina with pilocarpine (0.13 mg/kg) in only six of 20 patients.

Prinzmetal and his coworkers\(^5\) tried to explain the phenomenon of ST elevation experimentally by ligating the major coronary artery. They found that permeability of myocardial cell membranes increased with egress of intracellular K\(^+\) into extracellular space and ingress of extracellular Na\(^+\) into intracellular space, thus causing reduction of the stationary membrane potential, reduction of Q-T interval, apparent increase of R wave amplitude, and increase of ST-segment elevation. Acetylcholine and catecholamine are known to accelerate permeability of a cellular membrane to K\(^+\) and Na\(^+\) ions.\(^17\)

Thus, we speculate that neurohumoral control may play the greater part in causing the symptoms. Nowlin et al.\(^18\) and Murao\(^2\) suggested that the anginal attack occurs at the time of rapid eye movement (REM) period of sleep. The authors\(^19\) injected 2 ml of 5 \times 10^{-6}\) M acetylcholine into the coronary arteries of experimental dogs, directly, for 1–2 min. ST-segment elevation, accompanied by an increase of R wave amplitude associated with the epicardial ECG recorded near the

Figure 3
Experimental data showing acetylcholine injected into the left anterior descending artery directly for 1–2 min. ST-segment elevation accompanied by increase of R wave amplitude in the epicardial ECG (A and B) was found. A) epicardial ECG tracing of anterior left ventricle. B) epicardial ECG tracing of anterior right ventricle. C) epicardial ECG tracing of posterior left ventricle.

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coronary artery on the side of the injection, was found (fig. 3). Sinus arrest, sinoatrial block, and atrioven- 
tricular block were also associated with ST-segment 
elevation. Short runs of tachycardia and ventricular 
fibrillation were sometimes observed when acetyl-
choline injection was stopped. These changes varied 
from experiment to experiment and were similar to 
the variability of the ECG during variant angina in 
man.

Our results suggest that further study of the effects 
of the autonomic nervous system on the heart may ul-
timately clarify the pathogenesis of variant angina.

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