Variant Angina of Prinzmetal with Normal Coronary Arteriograms

A Variant of the Variant

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SUMMARY

Variant angina of Prinzmetal has been generally presumed to be caused by a significant focal obstruction in a single major coronary artery which should be an ideal lesion for aortocoronary saphenous vein bypass graft. Recognition of this clinical syndrome would then be of particular diagnostic and therapeutic importance if such a consistent association can be demonstrated. Of five patients with variant angina studied in our cardiac catheterization laboratories, four had normal coronary arteriograms. Two important conclusions may be derived from this study. First, identical ECG changes may be observed both in the presence and absence of pain and thus the incidence and severity of the variant angina could be underestimated. Second, until a larger series of patients with variant angina is studied by coronary arteriography, one must exercise reservation in assuming that all patients with the clinical syndrome are operative candidates for saphenous vein bypass surgery.

Additional Indexing Words:
Aortocoronary saphenous vein bypass
Exercise electrocardiogram
Oxygen-hemoglobin dissociation
Atrial pacing
Papillary muscle dysfunction
Coronary artery spasm

RECENT reports1-3 seem to suggest that the presence of variant angina of Prinzmetal4,5 indicates a severe focal obstruction of a major coronary artery. If this assumption proves to be correct, it has important therapeutic implications, as the clinical syndrome may thus be relied upon to identify a surgically bypassable coronary arterial lesion. Of five patients with variant angina studied in our cardiac catheterization laboratories, however, only one was shown to have significant focal obstructive coronary artery disease on coronary arteriogram. The other four, rather to our surprise, had no demonstrable coronary artery disease. It is the purpose of this communication to present these four patients with variant angina and normal coronary arteriograms, to describe some of the clinical observations, and to discuss the pathophysiology of the variant angina in the light of our findings.

Case Reports

Case 1

Patient O.T., a 60-year-old white man, complained of substernal pain and cold sweats every morning for 2 weeks duration. It was not related to exertion and always relieved by nitroglycerin. On the day of admission he was awakened early in the morning by severe substernal pain which radiated to the left shoulder, and fainted briefly 2 hours later. Past health was good except for mild hypertension discovered over 1 year ago.

Physical examination revealed a blood pressure of 140/80 mm Hg and a pulse of 82. The first heart sound was accentuated, preceded by an atrial gallop, and followed by a faint early systolic murmur. His electrocardiogram showed slight depression of the S-T segment in leads I, II, III, aV6, and V6. Coincident with the pain the patient developed a loud early systolic ejection murmur and the atrial gallop became elongated (fig. 2). The pain decreased in intensity 60 sec later and was almost gone 90 sec later; also, the apical systolic murmur practically vanished (fig. 2). The same pain recurred every morning;
coincident with each attack, which lasted a few minutes, the same ECG changes were noted. On several occasions the identical ECG changes were observed even though the patient did not experience chest pain. A Master’s two-step test produced marked S-T elevation and chest pain; both diminished soon after cessation of exercise. Selective cinecoronary arteriography revealed normal left and right coronary arteries (fig. 3A). Left ventricular end-diastolic pressure was normal; ventriculogram revealed normal myocardial contractility. His oxygen-hemoglobin dissociation curves were normal.

On the morning of the fifth day after admission the patient experienced a fainting spell. Electrocardiogram taken at this time revealed sinus standstill with ventricular ectopic beats followed by sinus bradycardia. Transfemoral venous demand ventricular pacing was instituted. The endocardial pacing catheter was removed 3 days later since the patient continued to be in sinus rhythm. Twenty-one hours later the patient developed ventricular fibrillation and died. At autopsy both coronary arteries and their branches were patent throughout and contained no thrombi or emboli; there was no evidence of myocardial infarction.

| Differences Between Prinzmetal's Variant Angina and a Variant of the Variant Angina |
|---------------------------------|---------------------------------|-----------------|
| Parameter                      | Prinzmetal's variant angina     | Variant of the variant |
| S-T-elevation on ECG           | During angina                   | With/without angina |
| Papillary muscle dysfunction   | ?                               | +                |
| Exercise ECG                   | -                               | S-T elevation    |
| Atrial pacing                  | ?                               | S-T elevation    |
| Coronary artery disease        | +                               | -                |
| Coronary spasm                 | ?                               | +                |
| Relief by nitroglycerin        | +                               | +                |
| Dysrhythmias                   | Frequent                        | Less frequent    |
| Myocardial infarction          | +                               | -                |
| Hemoglobin-oxygen dissociation curves | ?                         | Normal          |

Figure 1

ECG changes in case 1, before angina (top), during angina (middle), and 4 min after nitroglycerin (bottom).
Case 2

Patient A.T., a 40-year-old white man, had anterior chest pain occurring at rest and occasionally at night for 3 years duration. The pain frequently radiated to the neck and down the left arm and was relieved by nitroglycerin. Two years ago the patient underwent surgical repair of a hiatal hernia without any improvement in his anginal attacks. His electrocardiogram on admission showed slight S-T-segment depression in leads V₅-V₆ but was otherwise unremarkable. Exercise electrocardiogram was normal. Electrocardiograms taken during the attacks of pain showed S-T-segment elevations in leads II, III, and aVF which lasted less than 1 min. Physical examination was essentially negative.

Cinecoronary arteriography revealed both coronary arteries to be free of luminal narrowing (fig. 3B). Within 1 min following the third injection of the right coronary artery, which showed a severe constriction in its distal third (fig. 4), the patient suddenly complained of anterior chest pain with radiation into the left arm. At the same time marked S-T-segment elevation was noted in lead aVF (fig. 5). Ninety seconds after sublingual isosorbide dinitrate (Isordil) administration the pain subsided and the displaced S-T segment returned to the isoelectric line. Repeat injection of the right coronary artery at this time revealed the distal constriction to have disappeared. Left ventricular end-diastolic pressure was normal and left ventriculogram revealed neither mitral regurgitation nor disorder of myocardial contractility.

The patient continued to experience pain at rest and during the night, although some improvement was noted following combined propranolol (40 mg/day) and isosorbide dinitrate (40 mg/day) administration. Repeat cinecoronary arteriography performed 5 years later revealed normal left and right coronary arteries. Atrial pacing and treadmill exercise test performed at this time failed to induce either chest pain or S-T-segment changes.

He had normal oxygen-hemoglobin dissociation curves over a full range of partial oxygen pressures, and a normal hemoglobin-electrophoretic pattern.

Case 3

Patient A.J., a 48-year-old Negro man, complained of oppressive anterior chest pain, either at rest or during the night and lasting 10-15 min, for 1 year duration. He had numerous hospital admissions for these painful attacks, each time associated with transient S-T-segment elevations, usually in lead II (fig. 6A). Both the chest pain and S-T elevations responded promptly to sublingual nitroglycerin administration (fig. 6B). Physical examination was negative. His oxygen-hemoglobin dissociation curves and hemoglobin electrophoretic patterns were normal.

During right heart catheterization performed percutaneously through the right femoral vein, the catheter transversed a patent foramen ovale and entered the left atrium. During an attempt to pass the transseptal catheter from the left atrium into the left ventricle, the tip entered the left upper pulmonary vein where it

Figure 2

In case 1 the systolic murmur (SM) became louder during angina, at the same time the atrial gallop (AG) also became elongated. Both the systolic murmur and the atrial gallop shortened 60 sec later and were barely audible 90 sec later when angina subsided. Car = carotid pulse; MAᵥ₀ = mitral area medium frequency phonocardiogram; MAᵥ₉₀ = mitral area high frequency phonocardiogram; ACG = apexcardiogram.
became wedged. The catheter was quickly withdrawn into the left atrium and advanced into the left ventricle, where the end-diastolic pressure was recorded to be 3 mm Hg. At this time the patient experienced severe anterior chest pain identical to his spontaneous episodes of chest pain. The pain radiated down the left arm and was associated with cold sweats. While the simultaneously recorded ECG displayed S-T-segment elevations in leads II, III, and aVF with reciprocal depressions in leads I and aVL, the left ventricular end-diastolic pressure rose to 15 mm Hg (fig. 7, top). Following sublingual nitroglycerin administration the pain subsided and the S-T segments and left ventricular end-diastolic pressure returned to normal levels (fig. 7, bottom). Selective coronary arteriography performed 10 min later revealed normal left and right coronary arteries (fig. 3C). Left ventriculogram revealed normal ventricular contractility. Atrial pacing at 150 beats/min produced anterior chest pain and S-T-segment elevations in leads II and V₅. The patient was subsequently discharged on isosorbide dinitrate (80 mg/day) with great improvement in his angina. In spite of the

**Figure 3**

Normal coronary arteriograms in case 1 (A), case 2 (B), case 3 (C), and case 4 (D). RCA_LAO = right coronary artery in left anterior oblique view; LCA_LAO = left coronary artery in left anterior oblique view; LCA_RAO = left coronary artery in right anterior oblique view.
occasional attacks of severe chest pain at rest several times yearly, he is able to accomplish heavy physical labor without discomfort.

Case 4

Patient T.J., a 43-year-old Negro man, was known to be hypertensive for 10 years. Anterior chest pain was first noticed 6 months ago and appeared usually at rest. When examined during these painful attacks, an atrial gallop and an early-to-midsystolic ejection murmur were heard. On several occasions during hospitalization, S-T segments became elevated on the cardiac monitor during these painful attacks and returned to isoelectric line as the pain subsided, either following sublingual nitroglycerin or spontaneously. Serial serum enzyme values failed to disclose evidence of myocardial infarction. Exercise ECG test failed to provoke pain or disclose S-T-segment changes.

During left ventricular catheterization the patient developed severe chest pain and diaphoresis. Both the S-T segment in lead II and left ventricular end-diastolic pressure became elevated during pain but returned to baseline levels following sublingual nitroglycerin administration (fig. 8). During opacification of the right coronary artery the patient again developed chest pain and S-T-segment elevation, and the arteriogram of the right coronary artery disclosed focal constriction in its proximal third (fig. 9). Following sublingual nitroglycerin administration the pain and the S-T elevation subsided. Both coronary arteries now appeared normal (fig. 3D). Repeat coronary arteriograms, done a few days later to obtain additional views, confirmed the normalcy of both coronary arteries. Atrial pacing up to 165 beats/min did not produce pain or S-T-segment elevation. The patient continued to have anterior chest pain at rest with relief by sublingual nitroglycerin administration.

He had normal oxygen-hemoglobin dissociation curves over a full range of partial oxygen pressures and normal hemoglobin electrophoretic patterns.

Discussion

Since Heberden's classic description of angina pectoris over 200 years ago, the hallmark of its diagnosis has always been that the discomfort is typically related to exertion, and classical angina has long been known to be associated with S-T depression on electrocardiogram. Yet, as early as
the 1930s, rare cases have been reported of patients exhibiting currents of injury in one or more leads during angina.² Twenty-three such patients, in addition to 12 cases found in the literature, were reported by Prinzmetal et al.¹, ⁶ who clearly delineated a new anginal syndrome and called it variant angina. The discomfort was typical of effort angina in quality, location, radiation, transient duration, and prompt relief afforded by nitroglycerin. It was not precipitated by exertion or emotional upset; rather, it recurred when the patient was at rest or relatively inactive. The attack often consisted of a series of pains occurring in a cyclic and regular pattern. The attacks often recurred at the same time each 24 hours. ECGs were normal in the absence of chest pain or between attacks. During the attack the S-T segments were elevated transiently, often to a striking height, with reciprocal S-T depressions in standard leads. During peak S-T-segment elevation ventricular tachycardia and atrioventricular block were frequent.²⁻⁵, ⁸, ⁹ An exercise ECG test did not elicit pain or S-T changes. Incidence of myocardial infarction was quite high. If myocardial infarction resulted, the ECG changes were located in the area predicted by the S-T-segment elevation during episodes of pain. After infarction, the variant pattern of angina usually ceased.

On the basis of postmortem examinations and animal experimentation, Prinzmetal considered this pattern of angina to be due to a temporary occlusion of a large coronary artery with a seriously compromised lumen. Even a modest increase in the tone of such a vessel, he reasoned, could lead to complete, though temporary, obstruction. Selective coronary arteriographic studies have now been reported in several studies¹⁻³ which seemed to confirm Prinzmetal's conclusions. MacAlpin¹, ² studied 12 patients with the variant angina syndrome and found in all a focal stenotic lesion of a major coronary artery in the area predicted on the basis of the ECG S-T-segment elevation pattern during pain. Silverman and Flamm⁹ described five patients with variant angina, four of whom had severe stenosis of a single major coronary artery.

The four patients reported here conform to the clinical syndrome described by Prinzmetal; yet selective coronary arteriograms were normal. Several clinical features in our patients are at variance with Prinzmetal's variant angina (table 1). In Prinzmetal's variant angina characteristic S-T-segment elevation was observed only during the anginal attack, whereas in two of our four patients, identical ECG alterations were observed both in the presence and the absence of pain. Had the ECG

![ Electrocardiograms in case 2, showing the usual S-T-segment depression and T-wave inversion in lead aVF during right coronary artery injection (A); marked S-T elevation associated with angina 1 min later (B); and return of S-T segment to normal after sublingual isosorbide dinitrate with relief of angina (C). BA = brachial arterial pressure.](http://circ.ahajournals.org/doi/10.1161/01.CIR.44.3.481)
been recorded only during painful attacks, because of the frequent occurrence of episodes of typical ECG alterations unaccompanied by pain, the severity of the angina could be underestimated.\textsuperscript{10} Papillary muscle dysfunction, a common accompaniment of coronary artery disease,\textsuperscript{11} was noted in two of the four patients during the attack. Exercise, which produces either no change in the S-T segment or S-T depression in variant angina, induced S-T elevation in one of our patients. In another patient atrial pacing resulted in S-T elevation. Although coronary artery spasm was postulated by Prinzmetal, it was actually demonstrated in two of our four patients.

Spasm of a major coronary artery has been postulated from time to time as a mechanism whereby angina and sudden death might result without atherosclerotic coronary disease being demonstrable either by coronary arteriography or at autopsy. Sphincterlike muscles have been described at the orifice of the right coronary artery.\textsuperscript{12} Their contraction could markedly compromise blood flow to widespread areas of myocardium supplied by this vessel, leading to S-T-segment elevations and acute heart block. Spasm of the left coronary artery, if severe and sustained, has also been reported to lead to acute myocardial infarction.\textsuperscript{13} Evidence of spasm of the right coronary artery was adduced arteriographically in two of our four patients during the attack of pain and S-T elevation, and deduced in a third patient in whom the presence of a cardiac catheter wedged in the pulmonary vein apparently precipitated angina and S-T-segment elevation in the area supplied by the right coronary artery. The phenomenon of coronary spasm offers a logical explanation for attacks of angina that occur at rest and unassociated with tachycardia, elevation of the blood pressure, or other evidence of decreased coronary blood flow or increased cardiac work. The sudden occurrence and prompt subsidence of the episodes, the quick relief afforded by vasodilator drugs, the lack of evidence in reported studies that nitroglycerin relieves cardiac pain by augmenting coronary flow or

Figure 6

Electrocardiogram in case 3, showing S-T elevation in lead II during angina (A) and return of S-T segment to isoelectric line with relief of pain following nitroglycerin (B).
VARIANT ANGINA OF PRINZMETAL

During Angina: I
After Nitroglycerin

Figure 7
Electrocardiograms in case 3 showing S-T elevation in leads II, III, and aVF, and reciprocal S-T depressions in leads I and aVL, during angina with simultaneous elevation of left ventricular end-diastolic pressure (LVEDP) to 15 mm Hg (top) and return of S-T segments and LVEDP to normal levels following relief of angina by nitroglycerin (bottom). Horizontal lines for pressure calibration are 25 mm Hg apart, and vertical time lines 0.2 sec apart.

Correcting myocardial hypoxia, and the dramatic appearance of vessel dilation on coronary arteriogram following nitroglycerin all support the theory of coronary spasm. It is possible that spasm could result from the direct effect of epinephrine or other circulating humoral substances on smooth muscles of the arteries or that it could be induced by vasomotor reflex impulses. Such impulses could account, in part at least, for the provocation of anginal attacks by chilling of the hands, cigarette smoking, pulmonary embolism, and various gastrointestinal disorders. One case of variant angina has been described with the associated ECG changes reproducible by ingestion of iced water. A study of the myocardial arterioles in patients with angina pectoris has disclosed more large arterioles, greater thickening of their walls, and greater muscularity than in hearts from control subjects. Yet, spasm of the coronary arteries has not been consistently associated with the occurrence of anginal pain in patients with either diseased or normal vessels. Furthermore, when it occurs during coronary arteriography, it is more often than not asymptomatic and unassociated with ECG changes.

The advent of aortocoronary saphenous vein bypass operation for the treatment of coronary atherosclerotic heart disease casts a new light and a different emphasis on the syndrome of variant angina. An ideal candidate for this type of myocardial revascularization would have occlusive disease limited to one segment of a major coronary artery. If the pathophysiology of variant angina, as originally postulated by Prinzmetal and recently
supported by other workers, is a single severe focal obstruction of a major coronary artery, this association has obvious diagnostic, prognostic, and therapeutic implications, as the clinical syndrome may be relied upon to identify a surgically correctable lesion. On the other hand, the finding in four of five patients in this study and in three recent case reports of variant angina, of normal coronary arteriograms casts doubt on the consistency of such an association. Until a larger series of patients with variant angina is studied by selective coronary arteriography, continuous ECG recording, exercise ECG, and atrial pacing tests, caution is needed to avoid making a clinical presumption that all patients with Prinzmetal’s variant angina are ideal operative candidates for saphenous vein bypass surgery.

Acknowledgment
The authors wish to express their appreciation to Miss Helga Imle and Mrs. Sandy Hall for their able assistance in the preparation of this manuscript.

References

Electrocardiographic changes associated with angina during left ventricular catheterization in case 4. Just before the onset of angina the left ventricular end-diastolic pressure (LVEDP) was 12 mm Hg (left). During angina S-T segment became elevated in lead II with simultaneous elevation of LVEDP to 20 mm Hg (middle). After relief of pain by nitroglycerin the elevated S-T segment and LVEDP both returned to normal (right). The vertical time lines on the lower two-fifths of the tracings are 0.04 sec apart.

Figure 8
VARIANT ANGINA OF PRINZMETAL

Figure 9
Right coronary cinearteriogram of case 4, showing spasm (arrow) in the proximal third of the right coronary artery during angina. That the spasm was not catheter-induced was shown by the shallow penetration of the catheter tip as evidenced by the free reflux of contrast substance into the right aortic sinus of Valsalva.

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Variant Angina of Prinzmetal with Normal Coronary Arteriograms: A Variant of the Variant
TSUNG O. CHENG, TALI BASHOUR, GEORGE A. KELSER, JR., LOWELL WEISS and JAMES BACOS

Circulation. 1973;47:476-485
doi: 10.1161/01.CIR.47.3.476

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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