Current concepts of Prinzmetal's variant form of angina pectoris

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Definition

Variant angina is a clinical-electrocardiographic syndrome first described by Prinzmetal et al[1] in 1959. Although others had described similar cases previously,[2–7] Prinzmetal was the first to suggest that the clinical picture in these patients formed a discrete entity.

The essential characteristics of this syndrome are (1) recurrent attacks of angina unrelated to exertion which usually occur at rest or with normal activity, (2) concomitant S-T segment elevation in EKG leads reflecting the area of myocardial ischemia, and (3) return of the electrocardiogram to its previous appearance following attacks (*Table 1*).

The pattern of chest pain is variable: it may follow an intermittent or stable course for months to years, it may present as accelerated angina over a short period, or it may appear only in the immediate preinfarction or postinfarction period.[8] The first two patterns are the ones we usually associate with the term Prinzmetal's variant angina. Perhaps the third group should be classified separately as peri-infarction Prinzmetal's angina.

The episode of angina usually lasts less than 15 minutes, but may be prolonged. It often

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Table 1. Definition of Prinzmetal's variant angina

I. Essential characteristics
A. Recurrent angina unrelated to exertion
B. S-T segment elevation during angina
C. Normalization of EKG between angina episodes
II. Common associated findings
A. Predictable daily pattern of rest pain
B. Long periods of spontaneous remission
C. Typical exertional angina
D. Positive stress test
E. Major arrhythmias during angina
F. Syncope during angina
G. Termination of variant pattern after myocardial infarction
H. Sudden death

occurs at rest, with a predictable daily pattern. The interval between pains may be minutes to years. In patients with long periods between attacks, diagnosis may be difficult due to the logistical problem of obtaining an electrocardiogram during attacks.

In addition to rest pain, typical exertional angina occurs in nearly 50% of patients, but it is usually a minor part of the clinical picture.[1, 8–10] Stress tests are also positive in nearly 50% of patients,[11, 12] showing either S-T segment elevation[13–17] or, more commonly, S-T segment depression.[11, 16, 18]

During attacks of variant angina, S-T segment elevation occurs in two or more EKG leads, and reciprocal S-T segment depression occurs in contralateral leads (*Fig. 1A and B*). With subsequent attacks, S-T segment elevation almost invariably occurs in the same EKG leads. Rarely, S-T segment elevation may occur alternately in one set of EKG leads with one attack, and in a different set of leads with other attacks.[19]

The varying degree of S-T segment elevation which occurs during angina correlates roughly with the severity of attacks in any one patient.[1] There may be barely perceptible elevation with mild attacks, and more than 5 mm elevation with severe attacks. During episodes of variant angina, 25% to 50% of patients will experience major arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or complete heart block.[1, 11, 20–22] (*Fig. 2*). This may account for

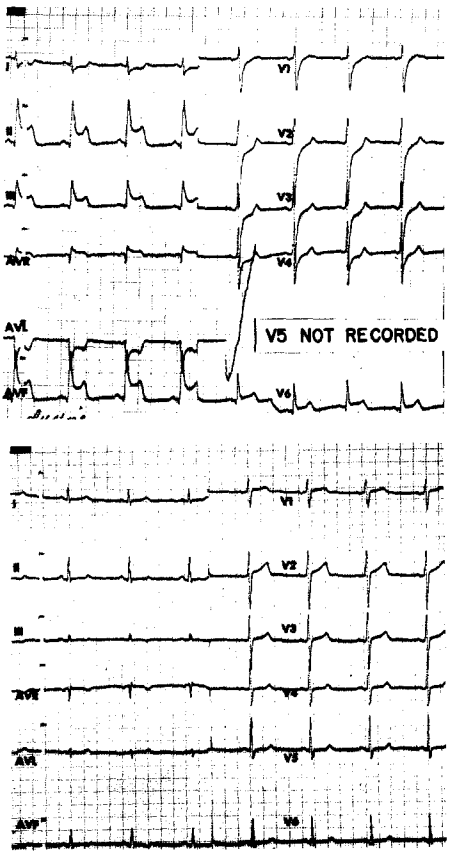

Fig. 1. A, EKG during spontaneous attack of variant angina. This demonstrates S-T segment elevation in leads II, III, AVF, and V_6 and reciprocal depression in leads AVL, I, and V_1–V_4. **B,** EKG immediately after attack of variant angina subsided. The S-T segments are isoelectric in all leads and no new Q waves have appeared.

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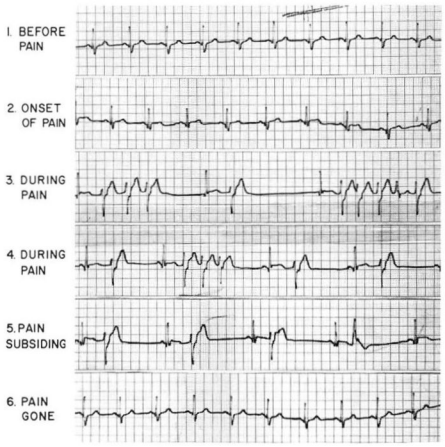

Fig. 2. Holter monitor strips demonstrating PVCs and short runs of ventricular tachycardia during an episode of variant angina. S-T segment elevation is present during angina, and the S-T segment is isoelectric when patient is free of pain.

an increased incidence of syncope and sudden death in these patients. Insertion of a pacemaker will prevent bradycardia and syncope in selected patients, but it does not prevent anginal episodes.

Acute myocardial infarction may eventually develop in patients with a stable history of variant angina, usually in the area which demonstrated S-T segment elevation during attacks of angina. After infarction, most patients do not continue to have attacks of variant angina.

Several syndromes of myocardial ischemia resembling variant angina have been described (*Table 2*). In patients with otherwise typical variant angina, episodes of mild angina may occur without S-T segment elevation and, conversely, episodes of S-T segment elevation may occur without pain.[9, 13, 15, 23–25] Some patients never experience angina, but have episodes of syncope due to a major arrhythmia, which is preceded by S-T segment elevation.[26–28] Such patients cannot properly be said to have variant angina, but the pathophysiology appears to be similar. Another group of patients has been identified who have typical exertional angina, but no angina at rest, and who develop S-T segment elevation on exercise tests.[14, 17] It is noteworthy that the mortality in these patients is much higher than in those with S-T segment depression.

Angiography in patients with major coronary artery obstructions

Prinzmetal postulated that most patients with this syndrome would have severe obstruction in the coronary artery perfusing the portion of the myocardium reflected by the S-T segment elevation during pain.[1] Coronary arteriography has confirmed this impression in most patients.[8, 9, 11, 16] Not infrequently, they have major obstructions in more than one coronary artery.

The appearance and distribution of the coronary artery obstructions in these patients are similar to those in patients with typical angina pectoris and to those with angina at rest associated with S-T segment depression.[29] One exception is that patients with variant angina rarely have been demonstrated to have isolated total obstruction with collaterals to the coronary artery perfusing the area where S-T segment elevation occurs.[16] Coronary spasm superim-

Table 2. Variations of Prinzmetal's variant angina

A. S-T segment elevation without angina
B. S-T segment elevation, arrhythmia, and syncope without angina
C. S-T segment elevation only during exertional angina

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posed on fixed severe coronary obstruction has been demonstrated angiographically during attacks of variant angina.[25, 30, 31]

Angiography in patients with no major coronary artery obstructions

Patients with no major obstructions (more than 50%) demonstrated by selective coronary arteriography constitute a small subgroup of all patients with variant angina. More than 30 such cases have been reported.[9–11, 15, 16, 19–22, 32–46] Although a few of these were said to have normal coronary arteries, most have had at least mild (up to 30%) obstructions. In this subgroup, the attacks of variant angina are probably due to severe coronary spasm superimposed on a mild obstruction.

In at least 20 such patients, reversible, severe coronary spasm with S-T segment elevation and chest pain has been demonstrated during angiography.[15, 25, 32, 34–36, 42, 44, 46, 47] In most of these, the spasm occurred in the right coronary artery. The location of the spasm may vary from one section of the artery to another on subsequent injections. Coronary spasm may extend several centimeters along an artery, or it may produce a short, discrete, annular constriction. It may involve more than one artery. Spasm of a coronary artery may produce an appearance which is angiographically identical to a fixed organic obstruction. The major difference between these two types of coronary artery narrowing is that the degree of spasm tends to vary with subsequent injections, whereas the degree of fixed obstruction remains stable. The spasm generally responds rapidly to nitroglycerin. If nitroglycerin is given to such patients prior to coronary arteriography, it may prevent the occurrence of spasm during catheterization. Therefore, we do not recommend its routine use before coronary arteriography in patients in whom we suspect coronary spasm plays a significant role.

"Malignant" coronary spasm, which is associated with S-T segment changes and angina, should be differentiated from "benign" or "catheter-induced" spasm not associated with chest pain or EKG changes. The term benign coronary spasm is preferred to the term catheter-induced spasm for two reasons: (1) this type of spasm may occur before the catheter is introduced into a coronary artery, and (2) malignant spasm with angina and S-T segment changes may be induced by catheter manipulation in a coronary artery. Benign coronary spasm occurs in about 1% of all patients undergoing coronary arteriography, and is of no clinical significance, as far as we know, except that occasionally it may be mistaken for a fixed organic coronary artery obstruction.[48, 49]

Rarely coronary spasm may be induced by withdrawal of nitrates after prolonged occupational exposure. Angina and myocardial infarction have been reported in workers who are chronically exposed to nitrates in the manufacture of explosives. Severe coronary spasm with normal coronary arteries has been documented occasionally in such patients.[50, 51]

Since weeks may pass between spontaneous attacks of variant angina, provocative tests for inducing malignant coronary spasm at the time of coronary angiography can be helpful in confirming the diagnosis. Either epinephrine or methacholine

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chloride may induce coronary spasm and attacks of variant angina; atropine has been said to prevent and abolish such attacks.[47, 52] Yasue et al[52] were able to precipitate attacks of angina and coronary spasm with methacholine chloride in 3 of 10 patients with variant angina.

A more sensitive provocative test has been recently developed at the Cleveland Clinic Hospital. On the recommendation of Proudfit, of our group, ergonovine maleate was first administered in December 1972, as a provocative agent for patients with variant angina and no major coronary obstructions.[46] In our experience since then, this drug has reproduced attacks of angina and S-T segment elevation in 10 of 13 patients with a history of variant angina and no major coronary obstructions, and provoked severe coronary spasm in 12 of 13 (*Fig. 3A–D*). Ergonovine maleate is highly specific for this group of patients: it did not induce severe coronary spasm or angina in more than 50 patients who did not have the Prinzmetal syndrome. This provocative test is not recommended for patients with variant angina who have fixed, severe coronary artery obstructions because of the possibility of inducing myocardial infarction. The use of any provocative agent for in-

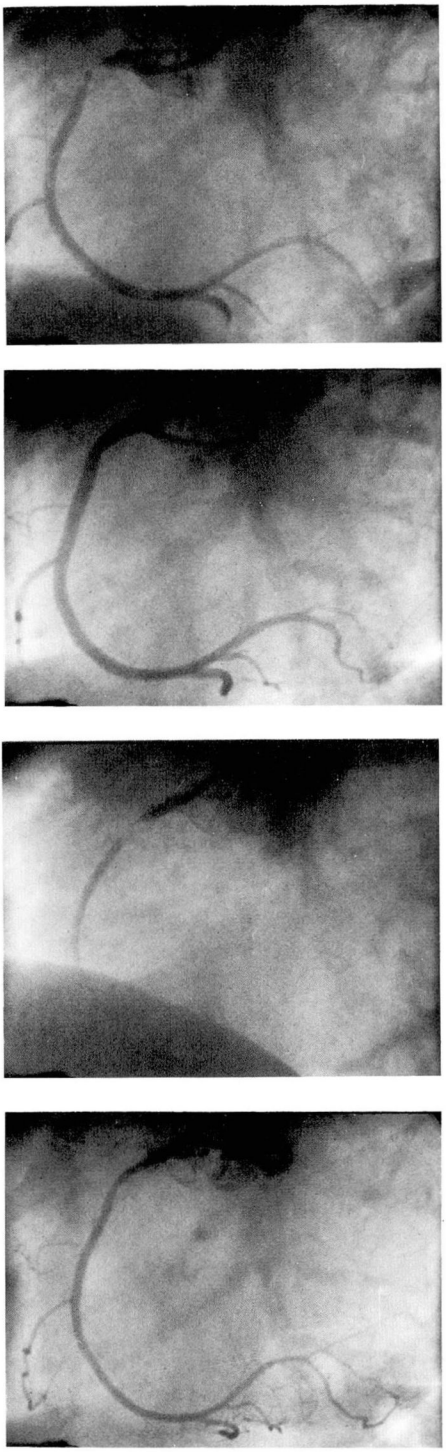

Fig. 3 A to D.

Fig. 3. Sequence of angiographic changes in RCA in LAO projection. **A,** Spontaneous spasm with 95% obstruction in proximal one third; angina and S-T segment elevation in leads II, III, and AVF. **B,** After nitroglycerin, only slight narrowing in proximal one third; no chest pain; EKG normal. **C,** Spasm with 95% obstruction in proximal one third induced by ergonovine maleate; angina and S-T segment elevation in leads II, III, and AVF. **D,** After second nitroglycerin, mild diffuse narrowing throughout; no chest pain; EKG normal.

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ducing attacks of Prinzmetal's variant angina is potentially dangerous and is recommended only for use by cardiologists, preferably in a cardiac laboratory with the necessary equipment and personnel to manage any complications.

Natural history of Prinzmetal's variant angina

Because of the scarcity of patients with variant angina, it is necessary to combine the experience of several centers to assess the clinical course of this syndrome. In one such study by Bentivoglio et al,[53] 90 cases were collected from the literature. Myocardial infarction developed in 22 patients within months after the onset of symptoms, and 13 others died suddenly. This comprises a combined incidence of major cardiac events of 39%. At this time, not enough patients have been catheterized and followed for a sufficient length of time to be certain of the natural history of variant angina in relation to the presence and severity of coronary artery obstructions. But, as a group, patients with the Prinzmetal syndrome comprise a high risk subset in the group of patients with ischemic heart disease.

Patients with episodes of variant angina appearing in the immediate postinfarction period have a higher incidence of reinfarction and death than other patients with myocardial infarction.[54] Patients with the syndrome of exercise-induced S-T segment elevation, but without the typical clinical picture of Prinzmetal's angina, also have a poor prognosis. Of the 10 patients followed for more than 1 year by Fortuin and Friesinger,[17] four died within 2 years, and a nonfatal myocardial infarction developed in a fifth patient.

Physiology of Prinzmetal's variant angina

Prinzmetal's variant angina appears to be associated with more severe myocardial ischemia than typical exertional angina. In experimental studies on dogs, S-T segment elevation occurred 25 to 35 seconds after complete occlusion of a coronary artery, and this was observed in the central, severely ischemic area, whereas S-T segment depression occurred in the more peripheral and less severely ischemic myocardium. As the severe ischemia in the central area was lessened by release of the occlusion, S-T segment elevation was replaced by S-T segment depression before returning to normal.[55]

To determine whether episodes of variant angina are associated with an increase in cardiac work, Guazzi et al[23] recorded continuous EKGs and intraarterial pressures in four patients with variant angina. During 38 anginal episodes in these patients, no change in blood pressure or pulse preceded the S-T segment changes and angina. A similar study by Maseri et al[25] confirms these results. Since an increase in pulse or blood pressure or both is the major determinant of an increase in cardiac work, these findings make it highly unlikely that episodes of variant angina are secondary to an increase in cardiac work. They are consistent with the theory that acute changes in diameter of the coronary artery, such as may be caused by spasm, are responsible for the physiologic events in Prinzmetal's variant angina (*Fig. 4*).

Since the severity of fixed coronary obstructions is highly variable in patients with variant angina, it appears that the relative contribution of fixed

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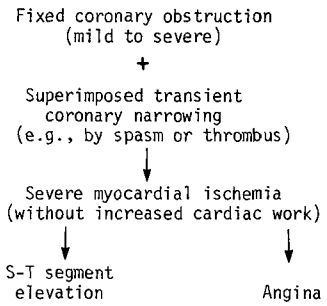

Fig. 4. Physiologic sequence in Prinzmetal's variant angina.

obstruction and of spasm-induced obstruction may vary from one patient to another, but that the combination of the two is operative in most patients (*Fig. 5*).

Assuming that the combination of fixed obstruction and superimposed spasm underlies all or most cases of Prinzmetal's variant angina, the mechanism which precipitates the spasm is not understood. It is not yet certain whether the severe coronary spasm in patients with mild coronary obstructions is triggered by the autonomic nervous system, humoral factors, increased sensitivity of the coronary artery to vasoconstrictive stimuli, or by a combination of these.[33, 45, 52, 56] It may be that the physiologic mechanism which triggers coronary spasm in patients with mild, fixed coronary obstructions is different from that in patients with severe, fixed obstructions.

The physiologic events in patients with Prinzmetal's variant angina are in marked contrast to those in patients with exertional angina and in patients with angina at rest associated with S-T segment depression: in these latter two groups, an increase in blood pressure or pulse or both usually precedes the onset of EKG changes and angina (*Fig. 6*).

Medical treatment of Prinzmetal's variant angina

It is difficult to evaluate the effect of treatment in patients with Prinzmetal's variant angina. Spontaneous variations in frequency of angina are the rule in these patients, especially in the subgroup with no major coronary obstructions. Periods of daily attacks for months may alternate with periods of months, or even years, when no attacks occur. In patients with fixed coronary artery obstructions, many authors have reported favorable responses to the common modes of therapy, including vasodilators and propranolol.[57] In almost all patients, nitroglycerin will rapidly

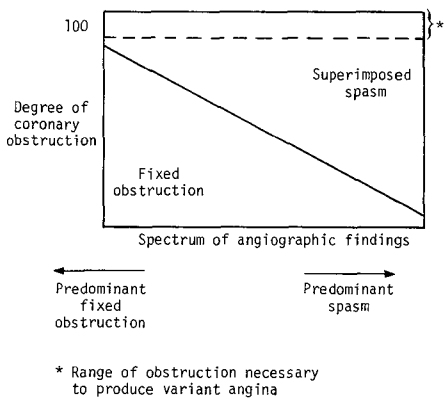

Fig. 5. Angiographic findings in Prinzmetal's variant angina.

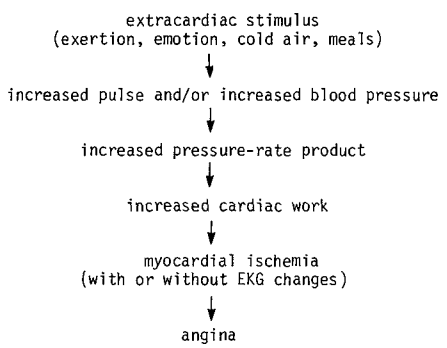

Fig. 6. Physiological sequence in typical angina pectoris.

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abort attacks of angina. In patients with no major coronary obstruction, the effect of medical treatment varies. Most authors report improvement with isosorbide dinitrate, but it is often ineffective. Propranolol is less effective in these patients, and it may even increase their symptoms.[8, 52] Initial experience with nifedipine, which is not yet commercially available in the United States, appears promising.[45]

Because of the small number of patients with variant angina in any one institution, most reports of medical treatment are anecdotal and involve few patients. Despite medical treatment, the morbidity and mortality in patients with this syndrome is high.

Surgical treatment of Prinzmetal's variant angina

The surgical treatment of variant angina in patients with severe, fixed coronary obstructions must be considered separately from surgical treatment in patients with no major coronary obstructions because the results are so different.

There is still some controversy concerning the use of coronary bypass surgery for patients with variant angina and severe, fixed coronary obstructions. Patients who have the poorest symptomatic results after surgery usually have occluded bypass grafts or persistent, severe coronary obstructions which have not been bypassed.[9, 11, 37] If a patent bypass graft with no anastomotic narrowing and with good runoff is placed in the severely (more than 70%) obstructed coronary artery supplying the area of myocardial ischemia in a patient with Prinzmetal's variant angina, relief of the Prinzmetal syndrome is virtually invariable.[12, 16, 24, 53, 58] The experience with bypass surgery for severe, fixed obstructions in patients with variant angina in Japan appears to be totally at variance with the experience in the United States. One author reports that none of the nine patients so treated had relief of symptoms, even though postoperative coronary angiography in some patients demonstrated patent bypass grafts.[45] Since the patency rate of saphenous vein grafts at the Cleveland Clinic is usually more than 80%, and that of internal mammary artery grafts approaches 95%, our current practice is to consider bypass surgery in any patient with variant angina and severe, fixed coronary artery obstructions.

Bypass surgery has been applied in a small number of patients with variant angina secondary to malignant coronary spasm.[39–41, 59] As opposed to those patients with variant angina and severe, fixed obstructions, most patients with variant angina associated with normal or mildly to moderately narrowed coronary arteries continue to have symptoms despite successful bypass surgery. This may be because spasm occurs distal to the graft or in other nongrafted vessels. The indication for bypass graft surgery in patients with variant angina due to malignant spasm in the absence of significant fixed coronary obstruction remains uncertain at this time.

Pathologic findings in patients with Prinzmetal's variant angina

The coronary arteries of patients with variant angina do not demonstrate distinctive pathologic changes, such as abnormal innervation or increased muscle thickness in the arte-

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rial wall. They have typical atherosclerotic obstructions similar to those found in patients with exertional angina or myocardial infarction. Autopsies in patients with variant angina and angiographically mild coronary artery obstructions have demonstrated a variety of findings in the coronary arteries: some arteries were reported as normal, and others showed a spectrum from mild to 75% narrowing.[10, 15, 20, 36] The reason for the discrepancy between the angiographic finding of mild obstruction and the autopsy finding of severe obstruction is not obvious at this time. It is possible that a severe obstruction was not detected during angiography. Or, it may be that at autopsy the severity of a fixed, moderate obstruction was overestimated because the coronary artery collapsed in the postmortem state, making the lumen appear smaller. At least mild coronary atherosclerosis is almost invariably found at autopsy in any patient with the syndrome of variant angina, even if the vessels were interpreted as angiographically normal.

Summary

The syndrome of Prinzmetal's variant angina consists of recurrent attacks of angina unrelated to exertion and accompanied by reversible S-T segment elevation. Variant angina is associated with a high risk of sudden death and myocardial infarction. Coronary spasm plays a major role in inducing attacks. Ergonovine maleate has been used as a provocative test for patients with no major coronary obstructions. Medical therapy is moderately effective in relieving symptoms. Coronary bypass surgery should be considered for any patient with severe, fixed obstructions, but is usually ineffective in patients with mild obstructions associated with malignant coronary spasm. The pathogenesis of the coronary spasm in these patients is poorly understood.

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