Angina Pectoris at Rest with Preservation of Exercise Capacity

Prinzmetal's Variant Angina

By Rex N. MacAlpin, M.D., Albert A. Kattus, M.D., and Anthony B. Alvaro, M.D.

SUMMARY

Twenty patients with Prinzmetal's variant of angina are described and the literature on the subject is reviewed. This syndrome is characterized by anginal attacks at rest with S-T segment elevation, while exercise capacity is well preserved. Coronary arteriography usually demonstrates significant, focal, obstructive disease of the major coronary artery predicted from the distribution of S-T elevation seen in the ECG during attacks. Occasionally the coronary disease is minimal or absent. The cause of attacks is believed to be transient, spastic occlusion of a major coronary artery, which was actually observed during surgery in one case. Because of this unusual pathophysiology, these patients may not make ideal candidates for isolated saphenous vein bypass surgery. Other diagnostic, therapeutic, and prognostic implications of this interesting anginal syndrome are discussed.

Additional Indexing Words:
Coronary spasm  Coronary surgery  Exercise testing  Rest angina

CLASSICAL ANGINA PECTORIS is induced by exercise and relieved by rest. When spontaneous anginal pain occurring at rest becomes a major symptom in classical angina pectoris, exercise capacity is already markedly restricted, electrocardiograms during the attacks usually show transient S-T segment depression, and severe, obstructive coronary artery disease is usually present in more than one major vessel. Over a decade ago Prinzmetal and his co-workers described a variant form of angina in which recurring attacks of pain occurred almost exclusively at rest, were rarely provoked by exercise, were associated with transient S-T segment elevation, and were related to stenosis of a single major coronary artery. They based their description on 23 cases of their own and 12 additional cases found in the literature. Since that time over 60 additional case reports have been published. The basis of this present communication is our own experience with 20 new cases studied with treadmill exercise testing and coronary arteriography.

Materials and Methods

All 20 patients were referred for diagnostic evaluation to the Division of Cardiology, UCLA School of Medicine, during the years 1960–1972. It is estimated that this group represents between 2 and 3% of new patients with angina pectoris seen by this division during those years.

Treadmill exercise tolerance tests with electrocardiographic monitoring were performed as described in a previous publication. Exercise testing was not performed in one case because of the development of left bundle-branch block at heart catheterization, and in another case because of temporal proximity to an acute myocardial infarction. Electrocardiograms during spontaneous anginal attacks were obtained fortuitously in seven cases, by long-term tape recording of a single ECG lead in seven cases, and by constant monitoring in a coronary care unit setting in three cases. An ECG during spontaneous pain was never obtained in three patients. Cardiac catheterization studies and coronary arteriography were performed in 19 patients, with left ventriculography in 11.

Long-term follow-up of these patients has been accomplished by periodic return visits to our Cardiology Clinic, by contacting the patients' personal physicians, and by contacting the patients directly via letter or telephone.
Results

Clinical Data

Some clinical and laboratory data are summarized in Table 1. The patients were 10 men and 10 women, with an average age at the onset of symptoms of slightly over 47 years. The relative equality of incidence in age and sex may be related in part to the high incidence in the women of factors predisposing to atherosclerosis; three women were diabetic and four had hypercholesterolemia. Of the six premenopausal women five had either diabetes, hypercholesterolemia, or both.

Each of the 20 patients was subject while at rest to recurring attacks of oppressive, retrosternal pain typical of angina pectoris in location, quality, and duration. The severity and frequency of symptoms were such as to suggest "preinfarction angina" and prompt hospitalization in the first 3 months of the illness in seven patients, only one of whom developed a myocardial infarction. In 18 patients there was a particular time of day when the attacks usually occurred. Sixteen patients were awakened from sleep by these attacks between midnight and 7 AM; eight of these also were subject to attacks just after having woken in the morning before getting out of bed. In 10 patients nocturnal or early morning attacks usually occurred in cycles consisting of two to four separate episodes separated by 2-20 min; at the end of the series of pains, the patient was usually free of pain for the rest of the night.

Subjectively exercise tolerance was considered to be completely normal by eight subjects and nearly normal by 11 others. Six patients who had the phenomenon of effort angina only during the first activity of the day were able to carry out normal activities during the rest of the day without symptoms. No relation of attacks could be found to cigarette smoking, gastrointestinal disease, or dreaming.

Physical examination was noteworthy in these subjects for the lack of abnormal cardiac findings. Moderate left ventricular enlargement and the signs of mild aortic stenosis and insufficiency were present in patient W.N. Patient M.S. had left ventricular hypertrophy due to hypertensive disease. During the course of her illness patient M.H. developed a soft, late systolic murmur of mild mitral insufficiency due to papillary muscle dysfunction. Heart size and configuration on X-ray examination were normal in all patients except for W.N. who had coexistent aortic valve disease, and...
### Table 1

**ECG and Angiographic Findings**

<table>
<thead>
<tr>
<th>Pt identity: age at onset of symptoms</th>
<th>Resting ECG</th>
<th>ECG and other observations during spontaneous angina</th>
<th>Angiographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.K. 40–10–17; 63 ♀</td>
<td>Normal</td>
<td>S-T, T elevation, increased R; decreased S in leads II, III, aV_F; S-T depression and T inversion before recovery CM_1;* S-T depression and T inversion</td>
<td>80% mid-RCA stenosis with plaques in proximal RCA and LAD</td>
</tr>
<tr>
<td>M.H. 43–79–65; 55 ♀</td>
<td>Slight T inversion in leads II, III, aV_F; later normal</td>
<td>S-T, T elevation, increased R; decreased S in lead II;* no rate or pressure changes preceding ECG changes</td>
<td>57% mid-RCA stenosis; proximal RCA spasm; prolapse of posterior mitral leaflet; postop vein graft occlusion</td>
</tr>
<tr>
<td>T.D. 40–33–31; 47 ♀</td>
<td>Normal</td>
<td>S-T elevation, increased R; decreased S in leads II, III, aV_F; S-T depression and T inversion in V_T-V_3</td>
<td>85% proximal RCA stenosis</td>
</tr>
<tr>
<td>B.S. 51–56–13; 46 ♀, premenopausal</td>
<td>Normal</td>
<td>S-T, T elevation, increased R in leads II, III, aV_F; S-T depression in I, aV_L, V_1-V_6; T inversion in V_T-V_3</td>
<td>85% mid-RCA stenosis with plaques in CMFX; normal LV-gram</td>
</tr>
<tr>
<td>C.G. 41–36–41; 43 ♀, premenopausal</td>
<td>Normal</td>
<td>S-T, T elevation, increased R in leads II, III, aV_F; S-T depression in V_T-V_6; patient unaware of some attacks; no rate or pressure changes preceding ECG changes</td>
<td>85% mid-RCA stenosis; occlusion of right ventricular branch with distal collateral filling; normal LV-gram; postop RCA occlusion</td>
</tr>
<tr>
<td>Mi.Ha. 35–58–94; 65 ♀</td>
<td>Possible inferior infarction</td>
<td>S-T, T elevation, increased R in leads II, III, aV_F; S-T depression in I, aV_L, V_T-V_3; hypotension during first week; patient unaware of some attacks</td>
<td>—</td>
</tr>
<tr>
<td>W.R. 20–36–51; 53 ♀, later normal</td>
<td>Symmetrical T inversion in leads I, V_1-V_6; later normal</td>
<td>S-T depression in leads II, V_T-V_3; T inversion appeared in II and V_6, and deepened in I, V_T-V_3</td>
<td>90% LMCA stenosis with moderate plaques in RCA; LMCA patent 4 years after endarterectomy</td>
</tr>
<tr>
<td>C.W. 37–70–44; 43 ♀, premenopausal</td>
<td>Low T in leads V_T-V_6</td>
<td>—</td>
<td>85% LMCA stenosis; proximal RCA stenosis also present 5 years later</td>
</tr>
<tr>
<td>E.R. 21–39–57; 42 ♀, premenopausal</td>
<td>Normal</td>
<td>—</td>
<td>70% proximal CMX stenosis; 50% proximal LAD stenosis; lesions unchanged 11 years later</td>
</tr>
<tr>
<td>R.C. 40–10–17; 42 ♀</td>
<td>Normal</td>
<td>S-T, T elevation: increase in R in CM_1,*</td>
<td>50% LAD stenosis with mild plaques in LMCA and RCA; normal LV-gram</td>
</tr>
<tr>
<td>C.K. 35–61–98; 38 ♀</td>
<td>Normal</td>
<td>S-T depression in CM_1,*</td>
<td>80% LAD stenosis; unchanged on repeat studies 1 and 5 years later</td>
</tr>
<tr>
<td>W.N. 24–68–78; 47 ♀</td>
<td>LVH with symmetrical T inversion in V_T-V_3 which was recent</td>
<td>S-T elevation V_T-V_3; inverted T became upright V_T-V_3</td>
<td>80% LAD stenosis</td>
</tr>
<tr>
<td>I.K. 38–02–75; 34 ♀</td>
<td>Normal at first; S-T elevation V_T-V_3; inverted T became upright V_T-V_3; U-wave inversion in V_T-V_4</td>
<td>Slight S-T elevation; inverted T became upright V_T-V_3; U-wave inversion in V_T-V_4</td>
<td>90% LAD stenosis</td>
</tr>
<tr>
<td>T.C. 52–46–46; 43 ♀</td>
<td>T inversion in V_T-V_3 when symptoms severe; later normal</td>
<td>T became taller V_T-V_3; S-T depression in leads II, III, aV_F</td>
<td>80% LAD stenosis proximally; normal LV-gram; postop vein graft occluded and LAD unchanged</td>
</tr>
</tbody>
</table>

*CM: cardiac muscle; LVH: left ventricular hypertrophy; CMFX: coronary artery bypass graft surgery; LV-gram: left ventriculogram; RCA: right coronary artery; CM: cardiac muscle.*
for Mi.Ha., C.L., and M.S., all of whom had mild left ventricular enlargement.

**ECG Studies**

The ECG at rest in the absence of attacks was usually normal. Transient T-wave inversion, persisting for days to months in ECG leads reflecting the distribution of the coronary artery disease, were present during a period of very frequent anginal attacks in five patients. Serum enzymes were persistently normal during these periods. Patient Mi.Ha. had the ECG findings of a recent, inferior myocardial infarction.

In 10 cases, the ECG before pain was basically normal and the following changes were observed (figs. 1 and 2): upwardly concave elevation of the S-T segment often associated with increase in T-wave amplitude and sometimes peaking of the T wave; increase in amplitude of the R wave and decrease in amplitude or disappearance of the S wave; slurring of the S-T junction when the degree of S-T elevation was great. When the degree of S-T elevation became very pronounced, there could be merging of the R wave with the S-T and T waves into a wide complex suggesting a monophasic action potential (fig. 3). In an occasional patient, during recovery, the previously elevated S-T segment became transiently depressed below the baseline along with T-wave inversion (fig. 4). During attacks the S-T segment elevation increased to a maximum over a few minutes, remained constant for 1–4 min, and then receded. In four patients episodes of S-T segment deviation without awareness of discomfort were documented interspersed between qualitatively identical episodes associated with pain.

In four patients the baseline ECG had abnormal T-wave inversion which was associated with S-T depression in two of them; here the sequence of events during attacks included reversion of the T wave to upright with the S-T segment usually becoming slightly elevated (fig. 5). This resulted in “normalization” of the ECG during the attacks. In

**Abbreviations:** CMF = left circumflex coronary artery; LAD = left anterior descending coronary artery; LBBB = left bundle-branch block; LMCA = left main coronary artery; LV-gram = left ventriculogram; LVH = left ventricular hypertrophy; postop = postoperatively; R = R wave; RCA = right coronary artery; S = S wave; S-T = S-T segment; T = T wave; V<sub>1</sub>-V<sub>6</sub> = bipolar chest lead with positive electrode at V<sub>1</sub> and negative electrode over manubrium of sternum; CMF = left circumflex coronary artery; LAD = left anterior descending coronary artery; LBBB = left bundle-branch block; LMCA = left main coronary artery; LV-gram = left ventriculogram; LVH = left ventricular hypertrophy; postop = postoperatively; R = R wave; RCA = right coronary artery; S = S wave; S-T = S-T segment; T = T wave; V<sub>1</sub>-V<sub>6</sub> = bipolar chest lead with positive electrode at V<sub>1</sub> and negative electrode at V<sub>6</sub>.

*Only leads monitored during an attack of rest angina.*
three patients only S-T depression was seen in the leads monitored during an attack of pain.

The lead distribution in which S-T segment elevation appeared usually, but not always, represented the area of distribution of the major coronary artery in which angiograms subsequently

Figure 2

The ECG is shown before (above) and during (below) angina pectoris occurring at rest in patient C.G.

Figure 3

The first and second rows show the ECG of patient Mi.Ha. during and after a spontaneous anginal attack. The bottom strip of lead II demonstrates complete atrioventricular block with a slow junctional rhythm during another episode of angina pectoris.
ANGINA OF PRINZMETAL

Figure 4

This ECG lead CM sub 5 of patient M.K. was taken from a continuous tape recording made during a spontaneous attack of angina pectoris.

demonstrated significant disease. S-T segment elevation occurred in leads II, III, and aVF with disease of the right coronary artery and was associated with reciprocal S-T segment depression in I, aVL, and anterior precordial leads (figs. 2 and 3). S-T segment elevation in leads I, aVL, the anterior and sometimes also lateral precordial leads, along with reciprocal S-T depression in the inferior leads, was associated with disease in the anterior descending coronary artery. Patient M.S. had S-T elevation in leads suggesting involvement of her "preponderant" right coronary artery whereas her major arteriographic abnormality was in her circumflex coronary artery. Patient T.G. had S-T segment elevation in inferior and lateral leads in the absence of significant coronary disease by arteriography.

Monitoring with a single ECG lead, as is usually done with long-term tape recording of the ECG and with coronary care unit observation, was occasionally misleading. S-T segment elevation was seen in leads similar to V5 and V6 when attacks were due to right coronary artery disease if the right coronary artery was dominant and supplied blood to areas of the left ventricular apex (fig. 4). On the other hand, anterior and lateral precordial leads showed only reciprocal S-T depression in attacks due to right coronary artery disease where S-T elevation was limited to leads II, III, and aVF (figs. 2 and 3).

Arrhythmias at the height of an attack were observed in five patients. Patient T.D. had two episodes of ventricular tachycardia, one of which led into ventricular fibrillation requiring emergency defibrillation. Patient D.W. had recurrent episodes of ventricular tachycardia and syncope associated with attacks of pain; the arrhythmia was prevented with oral procainamide, but angina without arrhythmia continued. Patient M.H. demonstrated occasional periods of 2:1 atrioventricular block and junctional rhythm. Patient Mi.H. manifested frequent episodes of atrioventricular block varying between first degree and complete. During complete block she had a very slow junctional pacemaker (fig. 3) with lightheadedness or syncope. She also had some premature ventricular beats. Patient T.G. frequently had long runs of supraventricular tachycardia with his angina attacks.

In observations on four subjects no significant changes were noted in heart rate and blood pressure leading into the attacks, although minor changes often occurred after the patient began experiencing pain. Observations of heart rate during the onset of ECG changes were available in eight additional patients and in only one of these
did a significant increase in rate precede the S-T segment shift.

**Exercise Testing**

Treadmill exercise testing produced maximum heart rates of 150/min or greater in 13 patients, and this represented over 85% of predicted maximal heart rate for their ages. In three of the five patients with lower heart rates exercise tolerance was excellent, and angina could be produced in only two of these with moderately strenuous activity. The lowest exercise capacities found were in M.K., one of our oldest patients, who was severely deconditioned by 10 weeks of bed rest, and in D.W. who may have stopped for psychological rather than physiological reasons. Anginal pain was produced by exercise in six patients but ischemic S-T segment depression was produced in only three of these.

In three subjects S-T segment elevation, peaking of the T wave, and diminution of the S wave occurred during or just after exercise testing at one time in the course of their illness. This was of particular interest in patient I.K. where this occurred on the first effort only, and a marked warm-up phenomenon, not due to attenuation of heart rate or blood pressure, was observed on the second effort (fig. 6).

**Catheterization and Angiographic Studies**

Left ventricular end-diastolic pressure at rest was normal in 11 of the 13 cases where it was recorded; it was markedly elevated in the patient with coexistent mild aortic valve disease, and slightly high in a patient with hypertensive heart disease. Left ventricular cineangiocardiology revealed no abnormalities in nine patients; in one it showed mild systolic prolapse of the posterior mitral leaflet with minimal regurgitation, and in another minimal mitral regurgitation was also seen.

The results of coronary arteriography are described in table 1. Significant abnormalities were
noted in 18 of the 19 patients whose coronary arteries were studied. In 15 the only significantly obstructive disease was a single stenotic lesion in a single major coronary artery. Minor areas of irregularity in the lumina of other vessels were common. Patient G.R. was unique in that he had three-vessel obstructive disease with complete occlusion of his distal circumflex coronary artery. In patient T.G. no obstructive coronary disease was present.

Angiographic filling and washout rates of the contrast medium in the involved coronary arteries were normal in all patients. Filling of the vascular bed by collateral circulation did not occur except distal to a complete obstruction of a coronary branch, and this was present in only two patients.

Pharmacologic stress of the heart with isoproterenol was carried out in three patients; in none could angina be precipitated.

**Effects of Medical Therapy**

The efficacy of any therapeutic intervention was difficult to evaluate since spontaneous variations in the frequency of attacks were the rule in this group of patients. Periods of weeks or months when multiple attacks occurred daily commonly alternated with periods of weeks, months, and even years when there were no attacks at all. Eleven patients insisted that nitroglycerin ameliorated and abbreviated their attacks. Four patients maintained that nitroglycerin was not helpful at all. Sublingual isosorbide dinitrate and erythrityl tetranitrate were effective in some patients in reducing the frequency of clinical attacks. Propranolol, nylidrin, and dipyridamole were tried in too few patients for efficacy to be established or excluded. Chronic anticoagulation with warfarin was prescribed in 12 patients but did not affect symptoms; the effect of such treatment on prognosis is unknown. Eleven patients were put on a program of gradually increasing walking exercise.\(^\text{39}\) This type of therapy appeared to accelerate improvement in symptoms in some patients; it was not harmful to any patient.

**Results of Surgical Treatment**

Nine patients had some form of surgical procedure in an attempt to improve the myocardial blood
supply. Endarterectomy of the left main coronary artery lesion was done on patient W.R. and resulted in permanent relief of angina pectoris, with angiographically proven patency of the endarterectomized area 42 months later.

In patient C.G. the right coronary artery stenosis was relieved by opening the vessel at that point and roofing over the lumen with a piece of saphenous vein. Total thrombotic occlusion of the right main coronary artery must have occurred immediately postoperatively resulting in an inferior myocardial infarction. Repeat coronary arteriography 1 year postoperatively documented occlusion of the right coronary artery at the surgical site with filling of the distal right coronary bed by newly developed left-to-right coronary collateral channels. The patient was cured of her rest angina but was left with moderate exertional angina which persists 58 months postoperatively.

In patient C.W. a left internal mammary implantation into the myocardium was performed. No improvement in her condition resulted. Three years later she had aortocoronary saphenous vein grafts to her right coronary artery and left anterior descending coronary artery at another institution (a new right coronary lesion had been discovered on a repeat arteriogram); no permanent improvement in symptoms resulted.

In six other patients saphenous vein grafts were placed between the aorta and a coronary artery, bypassing significant obstructions; a single coronary artery was bypassed in five of these (M.H., B.S., E.R., C.L., W.G.) and two vessels were bypassed in G.R. The surgical findings tended to corroborate the angiographic pictures showing distal coronary arteries which were quite satisfactory for bypass grafting (except in patient G.R.). Attacks of anginal pain at rest recurred within 4 weeks after surgery in five of these six patients (M.H., E.R., C.L., W.G., and G.R.). Occlusion of the graft was proven angiographically in patients M.H., E.R., and C.L. In patient W.G., the graft was shown angiographically to be patent and functioning well, but the circumflex coronary artery was occluded just proximal to the insertion of the graft; the first marginal branch of this circumflex vessel was being perfused antegrade through the proximal stenosis. The patient's previously positive treadmill test with angina was completely negative, without pain or S-T segment abnormalities postoperatively, even though he continued to have attacks of pain and S-T segment elevation at rest 16 months postoperatively.

Patient B.S. was the only patient to be "cured" of her symptoms by vein bypass graft surgery, and she remains free of symptoms 27 months postoperatively.

Interesting observations were made in patient M.H. at the time of her coronary surgery. On dissecting out the right coronary artery, the 4 cm length which had been exposed went into intense spasm; the vessel became small, hard, and cordlike so that the area of disease could not be identified by palpation; the left ventricle became cyanotic, the blood pressure fell to 70/60, and ischemic S-T depression developed in lead II. Administration of nitroglycerin sublingually was followed within 1 min by relaxation and dilation of the right coronary artery, a rise in arterial pressure to 108/70, and regression of myocardial cyanosis and ECG changes. At this time the area of stenosis could be easily separated by palpation from the normally soft vessel above and below. A saphenous vein graft was placed between the ascending aorta and the distal right coronary artery where the latter vessel was 2.5–3 mm in diameter. During the first few days after surgery elevation of S-T segments and loss of R-wave amplitude in leads II, III, and aV_{F} suggested a postoperative inferior myocardial infarction. She continued to have attacks of angina at rest which were mild and gradually disappeared over the next 6 months. As of 25 months postoperatively she was without symptoms and had a good exercise capacity with a negative treadmill test to heart rate 160/min, even though her vein graft was proven to be occluded.

**Course in Patients Not Having Surgery**

Follow-up information is available in 19 patients. Of these, 10 have been observed for over 5 years since the onset of their symptoms, and an additional four have been watched for over 4 years. Four subjects have been followed for only 1½–4 years. At the time of this writing, the only mortality was in T.G., who died suddenly 7 months after the onset of symptoms.

Ten of these 19 patients did not have surgery for myocardial revascularization; this included seven patients followed for more than 5 years. The tendency in this medically treated group was for stability or gradual symptomatic improvement with time without any acute coronary events. (T.G., who died, is an exception to this generalization.) Seven patients have become completely free of anginal attacks at rest, and five of these do not have exertional angina either. In one such patient...
myocardial infarction “cured” his angina but left him limited by marked dyspnea on exertion. Two patients continue to have mild attacks of angina at rest 2 years after the onset of symptoms.

Patients treated surgically tended to have more severe and intractable symptoms and more severe coronary stenotic lesions than those treated medically.

Discussion

Pathophysiology

The pathophysiology of classical angina pectoris is currently explained on the basis of the production of subendocardial ischemia when myocardial oxygen supply-demand relationships are transiently unbalanced by some type of stress in the presence of fixed obstruction of major coronary arteries.42, 43 This is inadequate to explain the manifestations of the variant form of angina which we believe are due to spasm of a major coronary artery with transient, complete occlusion of that vessel.

Coronary spasm does exist in humans.44 Severe coronary spasm in association with anginal attacks has been demonstrated arteriographically in some patients with classical angina pectoris,45, 46 and in others with variant angina.27, 47 Attacks of angina and sudden death with normal coronary angiograms in some munitions workers after sudden withdrawal from chronic, heavy nitroglycerin exposure are almost certainly due to coronary spasm.48

The degree of coronary artery obstruction in variant angina is variable rather than fixed. Usually neither symptoms nor signs of myocardial ischemia can be reproduced by strenuous physical or emotional stress, during which marked increases in myocardial oxygen need occur; it must be presumed that at these times coronary artery obstruction is not severe enough to prevent an adequate increase in coronary flow. Arteriograms done in the absence of angina demonstrate in many patients coronary lesions that do not appear severe enough to impair flow; in other patients permanent obstructive disease may be completely absent;26, 29, 34, 37, 38, 47 and in almost all patients the degree of obstruction is insufficient to cause development of coronary collateral circulation or impair the speed of run off in the distal coronary bed. On the other hand the attacks of variant angina occur at a time of rest when myocardial need for oxygen is low, and they are usually not preceded by nor associated with significant changes in factors influencing myocardial oxygen need.55 Finally, when variant angina occurs, the ECG changes in the QRS, S-T, and T waves are identical to those produced experimentally in animals by temporary, complete occlusion of a coronary artery50–52 and are usually in a direction opposite to those seen in classical angina.44

Direct observation of coronary artery obstruction by spasm during surgery in patient M.H. allows insight into the mechanism involved in variant angina. The intense spasm was not localized to one area of the coronary artery, but included a segment of vessel at least 4 cm long. This is a possible explanation for the disappointing results we have had treating this condition with saphenous vein bypass grafts; the insertion of the grafts may well have been into areas of coronary arteries susceptible to spastic occlusion during spontaneous anginal attacks.

The manner in which recurrent attacks of coronary spasm are generated is obscure. In only occasional instances do stimuli outside the heart seem to be responsible for initiating attacks.17, 24, 25, 29, 35, 54 Spasm of coronary arteries cannot often be produced artificially by any stimulus other than a tactile one such as occurs with the catheter tip during selective coronary arteriography. Considerable vasomotion of large coronary arteries does occur.44, 55 It is possible that the atherosclerotic lesion itself might act as the tactile stimulus when normal vasomotion of the large coronary artery causes the vessel diameter to reach a certain size. It is suggested that during rest and sleep the tone of the large coronary artery is highest and its diameter smallest, a state perhaps most conducive to the development of spasm. During exercise, when dilation of the artery would be expected to occur, the tendency for spasm would be minimized and counteracted by neurohumoral vasodilator influences.

Etiology and Pathology

The etiology of variant angina was atherosclerotic coronary artery disease in all those cases studied at postmortem examination.3, 9, 19, 26, 29, 31, 35 Our experience and that of others29, 35, 38 indicates that the lesions, when seen arteriographically, looked like atherosclerotic disease, but were unusual in their tendency to be localized in a given patient to one part of one major coronary artery. The equality of incidence in men and women in our group of patients was not repeated in the literature on this subject where men outnumbered women by a 5 : 1 ratio. The location of disease primarily in the right
coronary artery distribution in women in our patients was also not representative of the experience of others in whose reports could be found no significant differences between men and women in this regard.

Variant angina pectoris can develop in patients who already have more conventional forms of atherosclerotic coronary disease. Cases have developed during the course of chronic, classical effort angina.\(^22\) Cases were not rare in which typical myocardial infarction in one area of the heart had occurred 4 months–14 years prior to the onset of variant angina involving the coronary supply to a different area of the myocardium.\(^1, 3, 13, 14, 22, 30, 38\) It is expected that such subjects would tend to show multiple areas of coronary disease rather than the focal disease so common where variant angina develops de novo.

### Clinical Manifestations

Transient impairment of left ventricular function may occur during attacks of variant angina as has been shown by the sophisticated monitoring studies of Guazzi and his co-workers.\(^49\) This has usually not been severe enough to be detected clinically except for gallop rhythms.\(^17, 37\)

Arrhythmias and conduction disturbances during the attacks have been observed in about 40% of variant angina patients reported in the literature. Premature ventricular beats were most common and occurred equally in patients with left and right coronary involvement as did ventricular tachycardia. High-grade atroventricular block was next most common, occurred exclusively in subjects with involvement in what is usually the right coronary artery distribution, and accounted for syncopal episodes in a high proportion of patients so affected; it prompted implantation of permanent artificial pacemaking systems in two patients despite the fact that atroventricular conduction was normal between anginal attacks.\(^29, 34\) Transient block of portions of the left bundle branch were observed during attacks of angina in two patients whose disease involved the left coronary artery distribution.\(^14\) Sudden death unassociated with acute myocardial infarction was almost exclusively seen in patients with disease in the left coronary artery distribution, primarily in the left anterior descending coronary artery. Ventricular arrhythmias were documented during prior anginal attacks in most of these sudden deaths.

### Diagnosis

The diagnosis of variant angina pectoris is usually suspected from the history. Confirmation of the diagnosis is obtained by finding a transient S-T segment displacement (usually elevation) in the ECG during a spontaneous attack of angina and by documentation of a good exercise capacity. Since many patients with variant angina demonstrate a marked warm-up phenomenon,\(^49\) the chance of obtaining significant S-T segment changes during exercise testing may be improved by performing the test early in the morning before the patient has been physically active, and by beginning at a high work intensity. Ischemic S-T segment depression can be produced by high-intensity exercise in some patients since most have some degree of permanent coronary obstruction. In certain patients with variant angina, typical attacks of localized S-T segment elevation have occurred during or shortly after exercise testing.\(^18, 28, 34, 35, 37, 58\) This has also been noted in some patients with classical angina pectoris.\(^38, 59\)

### Management

There is no ideal drug for this condition. Of the vasodilators, nitroglycerin provides relief most reliably. In more difficult cases a number of other drugs can be tried. Excellent results have been obtained with propranolol by some investigators\(^21, 60\) although our own experience with this drug gave equivocal results. Prinzmetal himself had good results with nyldrin.\(^5\)

Close observation of patients is indicated during the first 3 months of their symptoms, the period when serious complications are most apt to occur. When significant arrhythmias are present, prophylactic antiarrhythmic therapy with quinidine, procainamide, or propranolol may be advisable since most of the sudden, unexpected deaths have been reported in such subjects.

Surgical treatment should be reserved for patients having incapacitating symptoms refractory to medical therapy. Even though many of these patients angiographically seem to be ideal candidates for isolated saphenous vein bypass grafting because of the focal nature of their coronary disease and their excellent ventricular function, our own experience and the unusual pathophysiology involved suggest otherwise. If it remains patent, a bypass graft might relieve associated exertional angina which is present in some patients. In the patient with a focal area of stenotic disease, it might be worthwhile to perform a direct attack on that part of the vessel such as its attempted denervation by extensive adventitial stripping. (It is possible
that such dissection of the vessel that did occur at surgery was responsible for amelioration of symptoms which followed surgery in some of our patients.) If severe stenosis exists, this denervation procedure could be coupled with insertion of a vein bypass graft, or by excision of the stenotic area and insertion of an interposition graft.

**Prognosis**

The prognosis of the patient with variant angina pectoris is probably not as bad as has been suggested by others. Sudden death in the absence of acute myocardial infarction, presumably due to arrhythmia, has been reported in about 15% of cases, and half of these occurred in the first 3 months of symptoms. Acute myocardial infarction in the area predicted by the distribution of S-T segment elevation during angina has been reported in about 25% of cases, and again over half of these were within the first 3 months of symptoms. Only 20% of those having myocardial infarction died; of the remainder most had no further attacks of their angina. some were left with only classical angina, and a few continued to have variant angina as before.

In the great majority of patients with variant angina, whose course was not interrupted by death, there was a tendency for symptoms to become less with time; some patients gradually had their attacks of rest angina replaced with classical exertional angina, and other patients eventually became completely asymptomatic.

**References**

1. **Rougheaden JW:** Circulatory changes associated with spontaneous angina pectoris. Amer J Med 41: 947, 1966
2. **Coren LS, Elliott WC, Klein MD, Gorlin R:** Coronary heart disease: Clinical, cinearteriographic and metabolic correlations. Amer J Cardiol 17: 153, 1966
6. **Sanazaro PJ:** Transient electrocardiographic changes simulating acute myocardial infarction. Amer Heart J 51: 149, 1956
7. **Cubbay ER:** Prinzmetal’s variant angina. Canad Med Ass J 83: 164, 1960
8. **Puddu V, Similia D:** Contributo clinico alla conoscenza dell’angina tipo Prinzmetal. Atti III Congresso Uropeo di Cardiologia, 1960, p 139
11. **Costini M:** Sulla cosiddetta “variant form” di angina pectoris. Cuore Cir 45: 229, 1961
18. **Robinson JS:** Prinzmetal’s variant angina pectoris. Amer Heart J 70: 797, 1965
20. **Bottini RE:** A variant form of angina pectoris with recurrent transient complete heart block. Amer J Cardiol 17: 443, 1966
22. **Schwartz LS, Schwegel JB, Schwartz SP:** Adams-Stokes syndrome during angina pectoris associated with coronary artery disease. Amer J Cardiol 17: 426, 1966
42. Robinson BF: Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. Circulation 35: 1073, 1967
53. Wilson FN, Johnston FD: Occurrence in angina pectoris of electrocardiographic changes similar in magnitude and kind to those produced by myocardial infarction. Amer Heart J 22: 64, 1941
54. Moschowitz E: Tobacco angina pectoris. JAMA 90: 733, 1928
Angina Pectoris at Rest with Preservation of Exercise Capacity: Prinzmetal's Variant Angina

REX N. MACALPIN, ALBERT A. KATTUS and ANTHONY B. ALVARO

Circulation. 1973;47:946-958
doi: 10.1161/01.CIR.47.5.946

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/47/5/946

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/