**CARDIOLOGY CASEBOOK**

A regular feature of the *American Journal of Critical Care*, Cardiology Casebook is intended to enhance practitioners’ knowledge and critical thinking. Stylized case studies are accompanied by self-assessment quizzes. We welcome letters to the editors regarding this feature.

**PRINZMETAL’S ANGINA**

By Kathryn Buchanan Keller, RN, PhD, and Louis Lemberg, MD. From Florida Atlantic University Christine E. Lynn College of Nursing, Boca Raton, Florida (KBK) and the Division of Cardiology, Department of Medicine, University of Miami School of Medicine, Miami, Fla (LL).

A 75-year-old female, retired private duty nurse, has been complaining for the past 10 days of unprovoked classical attacks of angina 2 to 3 a day usually in the mornings. The angina occurs at rest and may last 5 to 10 minutes. On careful questioning she admitted to similar attacks during the previous 2 years, which were disregarded because they were infrequent (every 4 to 6 weeks) and shorter in duration. However, the attacks were also unprovoked and unrelated to any specific activity, emotional upset, or food intake. Family history revealed her father and mother died at age 72 and 78, respectively, of causes unknown, and her only sibling, a brother, died at age 74 of an acute myocardial infarction. Past medical history revealed symptomatic osteoarthritis of her large extremity joints. Periodically she obtained relief with two 325 mg aspirin tablets 3 to 4 times daily and lately had a greater dependency on aspirin. In addition, she was taking a multivitamin daily.

On physical examination, the patient was normal in weight 56 kg (125 lb), 1 m 65 (5 ft 5 in) in height and moderately active. Blood pressure was 120/75 mm Hg in the right arm, and pulse was 76/min and regular. The lungs were normal on auscultation. The heart rate was 76/min; S1 and S2 were normal. A grade II aortic systolic murmur was heard over the second right intercostal interspace, consistent with aortic valve sclerosis. The point of maximal cardiac impulse was in the fifth intercostal interspace at the midclavicular line. Peripheral vascular examination was unremarkable. A complete blood count and urinalysis were normal. Blood chemistries revealed normal liver and renal function. A lipid profile revealed:

- cholesterol 1.19 mmol/L (46 mg/dL)
- low-density lipoprotein cholesterol 2.46 mmol/L (95 mg/dL)
- very-low-density lipoprotein cholesterol 0.31 mmol/L (12 mg/dL)
- triglycerides 1.35 mmol/L (120 mg/dL)
- high-density lipoprotein cholesterol 1.19 mmol/L (46 mg/dL)

A high-sensitivity C-reactive protein was normal. A resting electrocardiogram (ECG) revealed a cardiac rate of 72/min, regular sinus rhythm, and was considered within normal limits (Figure 1). Since the patient was asymptomatic and by history her new symptoms were unrelated to anything specific and were in fact unprovoked, a 48-hour Holter ECG monitor was applied in an effort to document any ECG changes that may appear associated with her symptoms. A review of the Holter monitoring recording a few days later revealed 2 episodes of unprovoked angina accompanied by marked ST-segment elevation in the monitored leads that lasted 7 minutes. Occasional ventricular premature beats were noted during the attacks. The ST segments returned to normal after 8 to 9 minutes in both episodes (Figure 2).

**QUESTIONS**

1. Which one of the following is the diagnosis in this case?
   a. atherosclerotic heart disease
   b. congenital anomalous angina of the left coronary artery from the right or non-coronary aortic sinus of valsalva
   c. myocardial bridges
   d. Prinzmetal’s variant angina (PVA)
   e. hypoplastic coronary arteries

2. Which of the following statement(s) is/are correct?
   a. the occurrence of coronary spasm is referred to as PVA
   b. coronary vessel spasm is always associated with ST-segment elevation
   c. PVA is a rare clinical phenomenon and has a benign course
Figure 1 Routine resting electrocardiogram is within normal limits.

Figure 2 The clock times are given in hours, minutes and seconds. Arrows point to the ST-segment elevations. Note the regression of "J" point elevation. Ventricular premature beats appear just before ventricular repolarization returns to normal. The subject’s diary indicated that the acute electrocardiographic changes appeared at the time of the angina.
d. PV A may initiate serious cardiac arrhythmias that can lead to sudden cardiac death (SCD)
e. PV A is unprovoked angina caused by coronary vasospasm occurring at rest, producing ST-segment elevations

3. Which of the following statement(s) is/are correct?
a. patients with PVA typically have the same risk factors as patients with coronary artery disease
b. cigarette smoking is a risk factor for PVA
c. PVA can be triggered by the use of cocaine
d. PVA can be associated with Raynaud’s phenomenon
e. autonomic dysfunction has been implicated in the etiology of PVA
f. angina attacks may vary with the menstrual cycle

4. The diagnosis of PVA is verified by which of the following procedures?
a. echocardiography
b. magnetic resonance imaging of coronary arteries
c. 24-hour Holter ECG monitoring
d. event recorder
e. ergonovine stimulation
f. loop recorder

5. Which of the following is not/are not helpful in the diagnosis of PVA?
a. 24-hour Holter ECG monitoring
b. thallium-201 ECG exercise stress test
c. coronary angiography
d. ergonovine stimulation
e. event recorder

6. Which of the following medications should be used in the treatment of patients with PVA?
a. nitrates
b. calcium channel blockers
c. α-adrenoreceptor blockers
d. β-blockers
e. aspirin

ANSWERS
1. d. PVA
2. d. PVA may initiate serious cardiac arrhythmias that can lead to SCD

Myron Prinzmetal first described a “variant” form of angina in his classic 1959 publication in the *American Journal of Medicine.* The term “variant” angina or PVA is a distinct clinical entity characterized by episodes of chest pain occurring at rest, associated with ST-segment elevation and caused by coronary vasospasm. Coronary vasospasm, however, is not synonymous with PVA, since the clinical spectrum of vasospasm also includes angina associated with ST depression and exertional angina. Variant angina represents only 1 aspect of a continuous spectrum of acute myocardial ischemia caused by coronary vasospasm. PV A, once thought to be infrequent, is currently recognized more often and is a significant determinant of cardiac morbidity and mortality. Continuous 24-hour Holter ECG monitoring of patients with PVA revealed serious cardiac arrhythmias in approximately 50% of cases. These included complex ventricular ectopic beats, ventricular tachycardia, ventricular fibrillation, asystole, and second- and third-degree atrioventricular block. There was no relationship between the severity of coronary artery disease and the occurrence of these serious arrhythmias. In PVA, these arrhythmias are generally associated with marked ST-segment elevation of 4 mm or more. Bradycarrhythmias are associated with acute ST elevations in the inferior leads, whereas ventricular arrhythmias can be seen with acute ST elevations in the anterior leads. There is a high risk for SCD when ventricular arrhythmias occur during acute ST elevations; the ventricular arrhythmias during resolution of the ST elevations (accelerated idioventricular beats) are benign and a sign of reperfusion. In a study of 114 patients with variant angina followed for 26 months, SCD occurred in 42% of those who experienced serious arrhythmias during their anginal episodes compared with an incidence of 6% in those without serious arrhythmias. Multivessel spasm increases the risk of SCD.
The classical clinical manifestation of PVA is chest pain at rest associated with ST-segment elevation. PVA tends to occur in younger females who, except for cigarette smoking, may not exhibit the usual clinical cardiac risk factors. The anginal attacks in PVA tend to have a circadian rhythm and generally occur in the early morning hours. These attacks can be triggered by alcohol, drinking iced drinks, rapid eye movement sleep, ergonovine, atrial pacing, cocaine, nicotine, acetylcholine, and hyperventilation. PVA has been associated with other vasospastic disorders such as migraine headaches and Raynaud’s phenomena.

The pathogenesis of coronary spasm is not well understood. Factors implicated include the activation of the autonomic nervous system (α-adrenergic receptors) and endothelial dysfunction. Vasospasm can be precipitated by acetylcholine and meta-choline and prevented by atropine and α-receptor blockers, eg, prazosin or clonidine; these factors implicate involvement of the parasympathetic nervous system and α-adrenergic vascular receptors. Autonomic nervous system involvement is further supported by the observation that surgical sympathetic denervation has been effective in treating patients who are refractory to medical treatment. The role of endothelial dysfunction in PVA has been reported in a prospective study of premenopausal women with variant angina in which endothelial dysfunction and the frequency of anginal attacks varied with the menstrual cycle and estradiol levels. Anginal episodes were most frequent with the lowest estradiol levels and least frequent with the highest levels. Other studies have shown that the coronary artery that is vasospastic in PVA reveals diffuse intimal thickening. This may be a response to repeated spasms.

4. c. 24-hour Holter ECG monitoring
e. ergonovine stimulation
f. loop recorder

A 24- or 48-hour Holter recording can be very definitive in the diagnosis, but is dependent on attacks of PVA. A loop recorder is an effective diagnostic tool. The ECG recordings are stored at either a 7, 14, 21, or 42 minute event. Stored data can be retrieved at any time. Loop recorders can operate for 1 year before battery failure.

The most sensitive test for coronary artery spasm is coronary stimulation by ergonovine, which has a greater than 90% sensitivity and specificity for the diagnosis of PVA. This test is recommended when recurrent episodes of ischemic chest pain occur at rest without the classic ECG manifestations of PVA (ie, ST-segment elevation) and normal or minimally abnormal coronary angiograms.

5. b. thallium-201 ECG exercise stress test
c. coronary angiography
e. event recorder

Exercise stress testing is of little use in the diagnosis of PVA because the basic pathophysiology in PVA is a decrease in oxygen supply as a result of vasospasm: this is in sharp contrast to the increase in demand with exercise that occurs in the pathophysiology of occlusive coronary artery disease. Coronary angiography in PVA often demonstrates normal coronary vessels or minimal coronary artery disease (in the elderly). An event recorder is patient reliant, and as a result the recording may lack the onset or resolution of the ECG recording during the angina in PVA. An event recorder is therefore not recommended for the diagnosis of PVA.

6. a. nitrates
   b. calcium channel blockers
c. α-adrenoreceptor blockers

The nitrates and/or the calcium channel blockers (nifedipine, diltiazem, or verapamil) are the mainstay of treatment for PVA. Calcium channel blockers and nitrates prevent vasoconstriction and promote vasodilation. Prazosine is a selected α-adrenoreceptor blocker and is an alternative therapy in PVA. Long-term survival is excellent. β-Blockers can exacerbate vasospasm in coronary vasospastic states and propranolol is known to prolong the attacks of PVA. β-Adrenergic blockade of vasodilatory β-adrenergic receptors convert the effects of sympathetic stimulation into a pure α-adrenergic vasoconstrictor response. Thus the use of non-selective β-blockers should be avoided. Aspirin in small doses (81 mg to 325 mg) block thromboxin A₂, a powerful vasoconstrictor, allowing the full vasodilating and platelet-inhibiting effects of prostacyclin. Aspirin in large doses inhibits prostacyclin production. Excessive aspirin intake (325 mg tablets 4-8 daily) can aggravate coronary artery vasospasm in PVA by blocking cyclooxygenase, which results in suppression of prostaglandin production.

SUMMARY

Prinzmetal’s angina, often referred to as “variant” angina, is a temporary increase in coronary vascular
tone (vasospasm) causing a marked, but transient reduction in luminal diameter. This coronary vasospastic state is usually focal at a single site and can occur in either a normal or diseased vessel. Patients are predominantly younger women who may not have the classical cardiovascular risk factors (except for cigarette use). PVA has been associated with vasospastic disorders such as Raynaud’s phenomenon and migraine headaches. Arrhythmias are common and may be life threatening especially when the effects of vasospasm are seen in those ECG leads that reflect the potential variations of the epicardial surface of the left ventricle. Endothelial dysfunction has been considered as primarily responsible for PVA. The diagnosis is made by observing transient ST-segment elevation during the attack of angina. Since PVA is not a “demand”-induced symptom, but rather a supply (vasospastic) abnormality, exercise treadmill stress testing is of no value in the diagnosis of PVA. The most sensitive and specific test for PVA is the administration of ergonovine intravenously. Fifty micrograms at 5-minute intervals is given until a positive result or a maximum dose of 400 µg has been administered. When positive, the symptoms and associated ST-segment elevation should be present. Nitroglycerin rapidly reverses the effects of ergonovine if refractory spasm occurs.

Medical therapy classically employs vasodilator drugs, which include nitrates and calcium channel blockers. The prognosis is good when there is no significant coronary artery stenosis. Treatment of associated coronary atherosclerosis in elderly patients with PVA is advised. When PVA is associated with coronary atherosclerosis, the prognosis is determined by the severity of the underlying disease. β-Blockers and large doses of aspirin are contraindicated in PVA.

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REFERENCES

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Kathryn Buchanan Keller and Louis Lemberg

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