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Prinzmetal's Variant Angina

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Summary: Although the prevalence of variant angina pectoris is unknown, it appears to be substantially less common than typical, exertional angina and unstable angina at rest. The patient with variant angina typically complains of a pressure-like, squeezing retrosternal chest discomfort of several minutes duration. The diagnosis is secured by the occurrence of transient ST-segment elevation in association with chest pain, both of which resolve spontaneously or with nitroglycerin. After the diagnosis is made, the patient usually becomes symptom-free on calcium-channel blockers with or without long-acting nitrates. Although the long-term survival of these patients is excellent, an occasional individual with variant angina sustains a complication, most often myocardial infarction, a life-threatening arrhythmia, or sudden cardiac death.

Key words: Prinzmetal's angina, variant angina, vasospasm, vasoconstriction

Introduction

In 1959, Prinzmetal *et al.*[1] described 32 subjects with what they called "variant" angina pectoris. They chose the term "variant" because these patients complained of chest pain at rest not usually precipitated by physical exertion or emotional excitement. An electrocardiogram obtained during chest pain showed ST-segment elevation. Both chest pain and ST-segment elevation promptly resolved with sublingual nitroglycerin. During a prolonged period of observation, some of these patients went on to have myocardial infarction and/or sudden death. At postmortem examination, the few who died were found to have atherosclerotic coronary artery disease. Armed with this information, Prinzmetal *et al.*[1] hypothesized that variant angina was caused by transient increases in coronary arterial tone (i.e., vasospasm) at the site of an atherosclerotic plaque, leading to repetitive episodes of transmural myocardial ischemia.

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Clinical Characteristics

The patient with variant angina pectoris typically complains of a pressure-like, squeezing retrosternal chest discomfort of several minutes duration. Classically, episodes of chest pain are especially frequent in the early morning hours. As noted, the episodes of chest pain occur at rest and, on occasion, may resolve with exercise, so that some subjects with variant angina have a well-preserved exercise capacity.[2] However, others (probably those with particularly severe underlying fixed atherosclerotic coronary artery disease) complain of chest pain at rest and with exertion. In comparison with subjects with typical exertional angina, those with variant angina are somewhat younger (average age, 48 years) and are more likely to be female.[3] Although the exact prevalence of variant angina pectoris is unknown, it is substantially less common than typical, exertional angina and unstable angina at rest.

Pathophysiology

Although Prinzmetal *et al.*[1] hypothesized that variant angina was caused by coronary arterial spasm, their hypothesis was validated only when selective coronary angiography was developed and performed in patients with the clinical syndrome. These angiographic assessments demonstrated that transient coronary arterial spasm could occur in arteries with or without significant atherosclerotic coronary artery disease.[4] On the one extreme, vasospasm may occur in a severely diseased coronary artery (the mechanism originally hypothesized by Prinzmetal *et al.*[1]). On the other extreme, the involved segment of coronary artery may appear to be normal angiograph-

ically. Even these apparently nondiseased coronary arterial segments, however, often have evidence—by intravascular ultrasound, for example—of minimal atherosclerosis.[5] In either situation, the coronary arterial segment in which vasospasm occurs has dysfunctional endothelium, which allows the underlying smooth muscle of the arterial media to be exposed to abnormally high concentrations of a variety of vasoconstrictors, such as catecholamines, thromboxane A_2, serotonin, histamine, endothelin, and arginine vasopressin, to name only a few.[6] In individual patients with variant angina pectoris, each of these substances has been shown to induce intense coronary arterial vasoconstriction with concomitant chest pain and ST-segment elevation. At the same time, however, all subjects with the clinical syndrome do not respond to the same substance, leading to the conclusion that variant angina does not appear to be induced by a single agent. Finally, an imbalance between certain endothelium-derived relaxing factors (i.e., prostacyclin, nitric oxide, endothelium-derived hyperpolarizing factor) and contracting factors (i.e., endothelin, angiotensin II) may lead to vasospasm.[7]

As noted, patients with variant angina manifest enhanced reactivity to a variety of vasoconstrictive and vasodilatory substances at the site of coronary vasospasm.[8–11] More recent studies,[9, 10] however, have suggested that these subjects have a more generalized abnormal response to vasoactive stimuli. Okumura *et al.*[9] have shown that patients with variant angina appear to have a diffuse abnormality of vasomotor tone, such that the reactivity of the entire coronary vasculature to vasoconstricting and vasodilating substances is exaggerated. At present, the precise mechanism underlying such a generalized vasomotor abnormality is unknown, but some investigators have hypothesized that these subjects have a generalized alteration in nitric oxide production and/or release.

Contributing Factors

The precise cause of coronary vasospasm has not been defined. The well-accepted risk factors for atherosclerosis, such as hypertension, diabetes mellitus, and hypercholesterolemia, do not occur with increased frequency in subjects with variant angina.[12, 13] In contrast, the incidence of cigarette smoking among patients with variant angina is high.[12–14] In an occasional subject, cocaine use, chronic ethanol ingestion with associated hypomagnesemia, insulin resistance syndrome, and vitamin E deficiency may contribute to the disease.[15–17] Although variant angina occurs frequently in certain geographic locations, such as Japan, Italy, and Canada, there is no evidence that it is transmitted genetically.[18]

Diagnosis

The diagnosis of variant angina pectoris is made when the patient has angina in association with transient ST-segment elevation, both of which resolve spontaneously or with nitroglycerin. Although angiographic evidence of intense coronary vasoconstriction is not required for one to make the diagnosis, such angiographic findings may serve to corroborate the clinical/electrocardiographic diagnosis. An occasional patient has multivessel vasospasm or fluctuation of its location within one coronary artery, but the vast majority have repetitive vasoconstriction of a specific segment of only one epicardial coronary artery.[19, 20] In some reports, vasospasm has been shown to occur more commonly in the right coronary artery than in the left anterior descending or left circumflex coronary arteries.[3, 21]

In the patient in whom the diagnosis of variant angina pectoris is elusive, various provocative maneuvers can be employed in an attempt to induce an episode of chest pain with ST-segment elevation, including intravenous ergonovine maleate, intracoronary acetylcholine, intense hyperventilation (often coupled with the intravenous infusion of an alkaline tris buffer solution), and exposure to cold (the so-called "cold pressor" maneuver).[22–25] Since an occasional subject with variant angina develops advanced atrioventricular block or a ventricular tachyarrhythmia during vasospasm, the chosen provocative maneuver should be performed in a carefully controlled setting, such as a catheterization laboratory or intensive care unit, where adequate resuscitative equipment and support personnel are readily available should the need for them arise. The sensitivity of any of these provocative maneuvers is related directly to the level of disease activity at the time of provocation.[26] Thus, the patient with only an occasional episode of chest pain (i.e., $\leq$1 episode per week) may not respond to any of the maneuvers; in contrast, the patient with frequent angina (i.e., $\geq$ 1 episode per day) is much more likely to manifest a positive response.

Natural History and Prognosis

Following initial presentation and diagnosis, most subjects with variant angina become symptom-free on calcium-channel blockers with or without long-acting nitrates.[27–32] After an angina-free period of at least 6 months, many individuals continue to be symptom-free even when medical therapy is discontinued; in these subjects, the disease is said to have "burned out."[33] Less often, patients may have periods of remission and exacerbation of disease activity.[34] The overall 5-year survival is 89 to 97%.[33] The long-term prognosis of the patient with variant angina is determined by the extent of underlying fixed atherosclerotic coronary artery disease; that is, the prognosis of the patient with variant angina and, for example, double-vessel coronary artery disease is similar to the patient with typical, exertional angina and double-vessel disease.[34, 35] Additional adverse prognostic factors include the presence of multivessel coronary vasospasm, left ventricular systolic dysfunction, continued cigarette smoking, and the avoidance of treatment with calcium-channel blockers.[36] During long-term follow-up, many patients with persistent vasospastic activity manifest a progression of coronary atherosclerosis; in contrast, many whose disease has become quiescent manifest a regression of atherosclerosis.[21] The mech-

anism by which repetitive vasospasm causes a progression of atherosclerosis is unknown.

Complications

An occasional subject with variant angina pectoris sustains a complication, most often myocardial infarction, high-degree atrioventricular block, a life-threatening ventricular tachyarrhythmia, or sudden cardiac death.[37–39] Most of these adverse events occur within 3 months of the initial diagnosis, at a time when the disease is likely still to be active. Myocardial infarction most often results from sustained vasospasm with or without coronary arterial thrombosis. High-degree atrioventricular block may occur during vasospasm of the coronary artery supplying blood to the atrioventricular node (i.e., the right coronary artery in 90% of patients and the left circumflex artery in the remaining 10%). Most (> 85%) episodes of chest pain and ST-segment elevation are not associated with ventricular ectopic activity, but an occasional episode is accompanied by frequent ventricular premature beats or even runs of ventricular tachycardia.[38–40] It is interesting that the propensity for ventricular ectopic activity does not appear to be related to the magnitude or duration of ST-segment elevation.[40]

Therapy

Medical

The cornerstone of therapy for the patient with variant angina pectoris is calcium-channel blockers, alone or in combination with long-acting nitrates.[27–32] Calcium-channel blockers inhibit the entry of calcium ions into smooth muscle cells, leading to smooth muscle cell relaxation. In long-term, placebo-controlled, double-blind, and randomized trials, several calcium-channel blockers have been shown to be highly efficacious in reducing the incidence of chest pain, sublingual nitroglycerin use, and episodes of transient ST-segment deviation (assessed with ambulatory electrocardiographic monitoring).[27–32, 34] The usual dosages of calcium-channel blockers are similar to those used for the treatment of systemic arterial hypertension (i.e., verapamil, 240–480 mg daily; diltiazem, 120–360 mg daily; nifedipine, 60–120 mg daily). The various calcium-channel blockers appear to have similar efficacy in patients with variant angina, and all are relatively well tolerated. Therefore, the choice of a specific agent depends on individual patient and physician preference.

The response of the subject with variant angina to one calcium-channel blocker, or lack thereof, does not predict the response to others. Therefore, if a specific calcium-channel blocker is ineffective in alleviating chest pain in the patient with variant angina, another calcium-channel blocker should be prescribed. If angina continues despite treatment with several different calcium-channel blockers at maximal tolerated doses, long-acting nitrates, such as oral isosorbide dinitrate, should be added. Beta adrenergic blockers are best avoided in the subject with variant angina pectoris, since—in some subjects at least—they cause unopposed alpha adrenergically mediated coronary vasoconstriction, with a resultant worsening of symptoms.[41]

Nonmedical

In the patient with variant angina refractory to medical therapy who has significant fixed atherosclerotic coronary artery disease, transluminal coronary angioplasty or bypass grafting are sometimes required for pain relief, but their efficacy is inferior to the results that are obtained in patients with typical, exertional angina.[41–43] In this patient population, the incidence of restenosis following balloon angioplasty is distressingly high. No data are available concerning the efficacy of intracoronary stents in this patient population. Subjects with variant angina who undergo bypass grafting are at increased risk of graft thrombosis, with resultant myocardial infarction.[41]

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