Variant Angina Pectoris

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INTRODUCTION

The first clear description of variant angina pectoris was given by Prinzmetal et al. in 1959.[1] They reported patients who presented with chest pain at rest and transient ST-segment elevation in the ECG. The most common pathogenic mechanism in variant angina pectoris is coronary artery spasm, and can occur in both angiographically normal or diseased vessels.

PATHOPHYSIOLOGY

Current evidence suggests that coronary spasm is likely to result from a local nonspecific coronary hyper-reactivity to constrictor stimuli.[2] An alteration of signal transduction in vascular smooth muscle cells has been reported to be responsible of the local coronary hyperreactivity seen in coronary vasospasm. Phosphorylation of regulatory subunits of myosin light chain (rMLC), which increases affinity of myosin for actin, is determined by the balance between the MLC kinase (MLCK) and the MLC phospohatase (MLCPh). Rho-kinase, activated by the upstream GTPase RhoA, reduces MLCPh activity and thus augments smooth muscle contraction at a given calcium concentration ('calcium sensitization').[3] It has been shown that Rho-kinase is upregulated at the spastic site and mediate hypercontractility to vasoactive substances.[4]

It is unlikely that endothelial dysfunction alone is responsible for coronary spasm in patients with variant angina. However, decreased NO production and/or bioavailability could potentially shift the balance in favor of RhoA and Rho-kinase activation and enhanced vascular contractility.[5]

CLINICAL PRESENTATION

Patients with variant angina experience typical angina at rest associated with transient ST-segment elevation in the ECG and tends to occur mainly at night or in the early morning hours. Coronary spasm may develop during exercise in approximately 30% of patients. Although coronary spasm tends to resolve spontaneously, prolonged vasospastic episodes may lead to myocardial infarction, arrhythmias and sudden cardiac death.[6,7]

Coronary spasm is often a focal process that affects only one segment of an artery. However, coronary spasm is a generalized process that results in diffuse coronary artery narrowing. Multivessel spasm has been reported to occur in approximately 9% of cases, and is more common in patients with angiographically normal or non-hemodinamically significant coronaries.[8] Normal or midly abnormal coronary arteriograms have been reported in approximately 40% of patients with vasospastic angina.

DIAGNOSTIC TECHNIQUES

Provocation testing

The ergonovine test is perhaps the most sensitive and specific provocation testing for variant angina.[9] Ergonovine has been administered safely under ECG and echocardiographic monitoring. However, safety of ergonovine administration outside the cath-lab has been questioned on the basis that it may be difficult to reverse spasm using intravenous nitrates as opposed to intracoronary nitrates. Intracoronary acetylcholine (Ach) is also useful for provocative testing and this test has been reported to be sensitive and relatively safe.[10] The hyperventilation test has a sensitivity and specificity of 62% and 100%, respectively. Patients with a positive hyperventilation test had more frequent anginal attacks, multivessel spasm and high degree AV block or ventricular tachycardia during attacks.[11]

The clinical role of provocation testing for coronary spasm is controversial. Non-invasive provocation testing such as ergonovine stress echo may be useful to rule out spasm in patients with intermediate clinical suspicion of variant angina, and invasive testing should be limited to patients with refractory vasospastic angina in order to identify a target for coronary stenting.[12]

MANAGEMENT

Medical therapy

Acute attacks

Coronary spasm can be a life-threatening condition and acute episodes should be treated promptly. Sublingual nitrate preparations usually relieve the chest pain and the ECG changes within minutes. Admission to hospital is usually required for ECG monitoring and clinical stabilization by the administration of intravenous nitroglycerin. In the catheterization laboratory, intracoronary nitrate preparations can be used to relieve spasm.

Long-term therapy

Long-term therapy is aimed at preventing coronary spasm and associated myocardial ischemia, whether painful or silent, and also at reducing cardiac events (i.e. unstable angina, myocardial infarction and death). Therapy should be kept at a high dose at least during the initial 3-6 months as serious cardiac events in patients with variant angina may occur within this peridod. Withdrawal from antianginal agents may be considered in patients who do not have serious arrhythmias or syncopal episodes during attacks and after a prolonged asymptomatic period of approximately 12–18 months. In every case, careful assessment of disease activity, i.e. Holter monitoring or provocation testing, is necessary before discontinuing therapy.

Calcium channel blockers (nifedipine, diltiazem and verapamil) and nitrates (and combinations of these) are effective long-term therapy. Calcium channel blockers are now considered to be the agents of choice for the therapy of vasospastic angina. Newer sustained-release or long-acting formulations of calcium channel blockers are also effective.[13] High doses are usually required during the first 3–4 months of treatment. The dose can be individually titrated to minimize side effects and to avoid hypotension.

Treatment with α-receptor blockers may be of some benefit, especially in patients with an incomplete response to calcium channel blockers and nitrates.

β-blockers, aspirin and coronary spasm

β-blockade as sole therapy may be deleterious in vasospastic angina patients, particularly in those who have normal coronary arteries or mild coronary atherosclerosis. β-blockade may also be useful in the few patients who develop spasm in association with a marked sympathetic response or migraine. Even so, treatment with beta-blockade alone should probably be contraindicated in patients with coronary spasm, especially nonselective β-blockers.

Aspirin should be used with caution since it is an inhibitor of prostacyclin production.

Coronary revascularization and brachytherapy

Percutaneous coronary revascularization may be heplful if hemodinamically significant fixed-obstructive coronary disease is present. Stenting may be also clinically effective for highly symptomatic patients with uncontrolled anginal attacks associated with mild to moderate obstructive coronary disease, in whom a localized vasospastic coronary artery segment can be clearly identified,[14] given the fact that the majority of patients with positive provocation testing and recurrent symptoms seem to have consistency in the location of coronary spasm.[15] However, spasm may reoccur at sites distinct from the treated segment, including multivessel spasm.

Both percutaneous and surgical coronary revascularization are not indicated in patients with isolated coronary spasm without hemodinamically significant atheromatous coronary stenoses. However, succesful results with coronary-artery-bypass grafting have been recently reported in two patients with life-threatening refractory vasospastic angina with normal coronary arteries. Concerns have been raised however raised over the long-term IMA graft patency due to competitive flow.[16]

Despite the immediate increase of vasoconstriction and spasm induced by high-dose intravascular β-irradiation brachytherapy, a loss of vasomotion several weeks after the application of the intracoronary irradiation may occur, suggesting the potential benefit of this technique in patients with refractory and highly symptomatic variant angina.[17]

Implantable cardioverter defibrillator (ICDs) therapy

Arrhythmias are a frequent finding during vasospastic acute attacks, i.e. AV block and life-threatening ventricular arrhythmias. In most cases of variant angina presenting with syncope, appropriate treatment with vasodilators prevent further episodes of vasospasm thus making unnecessary the use of ICD therapy. However, ICDs should be contemplated as a therapeutic option in refractory vasospatic angina patients with syncope and/or serious ventricular arrhythmias and multivessel spasm, despite the absence of severe fixed-obstructive coronary artery stenoses.[18]

General measures

Trigger mechanisms: Several factors have been associated with the recurrence of coronary vasospasm, i.e. smoking, cocaine addiction, high alcohol intake, hypomagnesemia, use of serotonin-uptake inhibitors and hyperventilation. Exposure to cold and emotional stress have been also associated with recurrent vasospastic attacks.[19]

Pharmacological agents: Coronary spasm has been also associated with antimigraine agents, chemotherapy, anesthetics, and antibiotics. Ephedrine, ergonovine, ergotamine, sumatriptan, bromocriptine, 5-fluoruracil, propofol, and amoxicillin have been linked to cases of severe vasospasm. Selective serotonin type 1 (5-HT-1B/D) agonists both oral and subcutaneous 5-HT-1B/D such as sumatriptan have been also implicated in spasm-induced myocardial infarction and its use is patients with variant angina may be problematic.[20-23]

Illicit drugs: Coronary spasm-related infarctions in the younger are associated with drug abuse, cocaine being the most frequent cause. However, most of the commonly used illicit substances may cause vasospasm when used alone or in combination.[24] Vasodilator therapy may be life-saving in the treatment of patients with cocaine-induced coronary spasm whereas thrombolytic drugs and propranolol have been reported to have deleterious effects in these cases.[25]

Recent developments

Fasudil, a Rho-kinase inhibitor, has been reported to inhibit both serotonin-induced coronary hypercontraction and enhanced MLC phosphorylations in the spastic coronary segment.[26] Fasudil was also effective in selectively preventing acetylcholine-induced coronary artery spasm in patients with vasospastic angina.[27] Fasudil may be a more suitable choice for patients with vasospastic angina than calcium channel blockers because of its selective spasmolytic effect.

PROGNOSIS

Prognosis is good in patients with variant angina and normal coronary arteriograms who respond to treatment with calcium channel blockers or nitrates. The incidence of acute myocardial infarction, malignant arrhythmias and sudden death is extremely low in this patient cohort. In a large series of 277 patients with a median follow-up of 7.5 years, recurrent angina was common (39%), but cardiac death and myocardial infarction were relatively infrequent and occurred in 3.5% and 6.5% of patients, respectively.[28]

Long-term follow-up studies have shown that episodes of variant angina may persist despite treatment with calcium channel blockers and nitrates. Persistent symptoms are associated with continuing to smoke, insufficient dosage of antianginal agents and continuing exposure to triggers of spasm.

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