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RESEARCH ARTICLE

Coronary arteries and coronary vasospasm: The Anatomical and Molecular aspects

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There are certain phenomena that can cause constriction of blood vessels in the absence of any underlying coronary disease. There are stimulants that affect muscle contraction function. The most common of these are tobacco smoke, caffeine, cocaine, exposure to severe temperatures, particularly cold more so than hot, can result in a vasospastic response. These are usually transient events of spasm in isolated segments of coronary arteries, not diffusely through the coronary arteries. They are usually transient and in some rare cases can result in myocardial infarction or even sudden death. Coronary vasospasm is currently considered to be an exaggerated contractile nonspecific response of the vascular smooth muscle in the large coronary artery to various agonists or stimulation that is established after the process of inflammation and fibro cellular proliferation. Many Patients in General Medicine, Cardiology, and Post Cardiac Surgery present with chest pain. The typical presentation of Anginas, Myocardial infarction is not always present. A lot of patients undergo a battery of invasive and non invasive tests without much yield. An entity coronary vasospasm is most often undermined. The article tries to caution General Practitioners, Cardiologists, Cardiothoracic surgeons to keep in mind the sudden appearance of this phenomenon which if not recognized and kept in mind can be fatal for the patient. The article tends to simply present the patho physiology, diagnosis, clinical associations and clinical consequences of this dangerous phenomenon.

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The term coronary artery spasm should not be applied to patients with ischemic heart disease unless there is clinical, angiographic, and physiologic evidence of its presence

Background:

In 1959, Prinzmetal et al described a syndrome of chest pain at rest secondary to myocardial ischemia associated with ST-segment elevation. Exercise tolerance was characteristically normal in these individuals, who experienced a cyclical pain pattern with most episodes occurring in the early morning hours. This syndrome, known as Prinzmetal or variant angina, is due to focal coronary artery vasospasm and may be associated with acute myocardial infarction (MI), serious ventricular arrhythmias, and sudden death.

Predisposing factors include

- Smoking,
- Lipid metabolic disorders,

- Gene expression, all of which may be interrelated issues.

Smoking appears to be a major risk factor for vasospastic angina without significant coronary narrowing.

Cocaine causes an increase in circulating catecholamines. Therefore alpha-adrenergic mediated focal or generalized coronary artery spasm has been presumed to be the likely mechanism to induce ischemia.

An imbalance of the autonomic or humoral control of the smooth muscle might serve to initiate a pathological arterial contraction. Abnormal adrenergic or cholinergic nervous function might explain vasospasm of otherwise normal coronaries.

Basic abnormality may be hyper contractility of the arterial wall associated with the atherosclerotic process itself. Results of both animal experiments and clinical studies support a role for certain cellular events in atherogenesis, including endothelial injury, presence of mitogenic factors and leukotrienes generated by platelets and macrophages, changes in histamine and serotonin receptor density of vascular smooth muscle and neovascularization of atherosclerotic plaque.

Pathophysiology

Focal coronary artery spasm typically occurs at the site of or adjacent to a fixed stenosis. A substantial number of patients have seemingly normal coronary angiogram results, although many within this subgroup have evidence of early atherosclerosis demonstrated by intravascular ultrasonographic examination or at autopsy.

Nitric oxide is a potent **endothelium-derived relaxing factor (EDRF)** responsible for maintaining the coronary arteries in a state of relative vasodilatation. Nitric oxide is synthesized from the amino acid L-arginine in a biochemical reaction catalyzed by the enzyme nitric oxide synthase. Nitric oxide is also a potent inhibitor of platelet activation, adhesion, and aggregation. Activated platelets are responsible for the release of several potent vasoconstrictors, including thromboxane A₂. Abnormalities of nitric oxide synthase and reduced bioavailability of nitric oxide may result in increased basal vascular tone, vasoconstriction, vasospasm, and in activation, adhesion, and aggregation of platelets with release of additional vasoconstrictors. The endothelium releases the powerful vasodilator and antiaggregatory substance, EDRF, both under basal conditions and upon stimulation by a wide variety of agents. Endothelial injury or dysfunction may play an important role in the spasmogenicity of the coronary artery

Elevated serum low-density lipoprotein (LDL) cholesterol, especially the oxidized form of this lipid moiety, is responsible for the decreased production of nitric oxide due to down-regulation of endogenous nitric oxide synthase and the oxidative inactivation of nitric oxide by oxygen free radicals. Since focal coronary artery spasm in Prinzmetal angina typically occurs at or adjacent to endothelium that overlies a fatty streak of early atherosclerosis or a fibrous plaque of advanced atherosclerosis, focal endothelial dysfunction seems likely. The role of endothelial vasodilator function in the genesis of coronary artery vasospasm remains controversial.

Experimental evidence from porcine models of this disorder suggests that spasm is caused primarily by vascular smooth muscle cell hypercontraction and not by local endothelial vasodilatory dysfunction. The molecular mechanism(s) of this smooth muscle cell abnormality remains unclear.

Low levels of intracellular magnesium and increased retained magnesium after an intravenous load in patients with this disorder suggest that magnesium metabolism is abnormal in patients with coronary artery vasospasm. This may occur with vitamin E as well.

Hyperinsulinemia and insulin resistance are probable risk factors for variant angina, although the pathogenic mechanisms of these apparent associations have not been defined.

The role of the autonomic nervous system in the pathogenesis of variant angina is controversial. Withdrawal of parasympathetic activity before the onset of angina has been suggested, but Japanese investigators actually found an increase in parasympathetic and sympathetic activity. Whether this discrepancy is due to methodological flaws or to racial vasomotor heterogeneity in vasomotor angina is unclear.

Imaging Studies

Thallium scintigraphy has been used to localize the myocardial perfusion defect to an area perfused by a coronary artery in which spasm can be demonstrated by angiography. This was a valuable research tool and helped define the syndromes of coronary artery vasospasm; however, the routine clinical utility of this test is uncertain.

Coronary angiography is the criterion standard for the diagnosis of variant angina when coupled with the clinical syndrome of angina pectoris at rest with transient ST-segment elevation. Focal spasm of the proximal portion of a major coronary artery not preceded by an increase in heart rate or blood pressure that is followed by chest pain, ST-segment elevation, and ventricular dysfunction is pathognomonic.

Most patients with variant angina and documented coronary artery vasospasm have some angiographic evidence of atherosclerotic coronary artery disease, although evidence is mild in many patients. Spasm typically occurs within 1 cm of an angiographically apparent obstruction. If minimal or no angiographic evidence of coronary artery disease is found in a patient who has recently had angina at rest with transient ST-segment elevation, variant angina is the likely diagnosis, and further testing is unnecessary. In some patients, it may be necessary to perform provocative testing to induce coronary artery spasm.

Ergonovine maleate is an ergot alkaloid that stimulates both alpha-adrenergic and serotonergic receptors and thus exerts a direct constrictive effect on vascular smooth muscle. Coronary arteries, which constrict spontaneously, appear to be abnormally sensitive to this agent. The response of normal coronary arteries to Ergonovine maleate is a mild, diffuse spasm.

Of the provocative test agents shown to induce coronary artery spasm in susceptible patients, **Ergonovine maleate, methylergonovine maleate, acetylcholine, or hyperventilation** are the most useful. Ergonovine maleate for injection is no longer available, and the availability of methylergonovine is limited. The intravenous administration of incremental doses of methylergonovine starting at 0.05 mg to a maximum of 0.40 mg is both sensitive and specific, and there is an inverse relationship between the dose required to provoke spasm in the laboratory and the frequency or spontaneous episodes experienced by the patient.

To ensure a valid test, nitrates and calcium antagonists must be withdrawn for at least 48 hours before testing. Women are more sensitive than men to methylergonovine. The intracoronary route of administration of methylergonovine for provocation of spasm is relatively safe, sensitive, and specific, but rarely used today. This route is preferable in hypertensive patients and affords the opportunity to evaluate the left and right coronary circulations separately. Small dosing increments of 5-10 mcg are used, with a total dose not to exceed 50 mcg and with intracoronary nitroglycerine available.

Absolute contraindications to methylergonovine include pregnancy, severe hypertension, severe left ventricular dysfunction, moderate-to-severe aortic stenosis, high-grade left main coronary stenosis, and significant stenoses in epicardial coronary vessels. Relative contraindications include uncontrolled or unstable angina, uncontrolled ventricular arrhythmia, recent MI, and advanced coronary disease. Alternatively, intracoronary acetylcholine can be used as a provocative test for spasm, and its effectiveness is comparable to methylergonovine. In patients with more than 1 episode of variant angina per day, the hyperventilation provocative test is nearly as effective as methylergonovine in causing vasospasm. In patients with less frequent attacks, hyperventilation is less sensitive.

Electrocardiography: Transient ST-segment elevation is the characteristic finding in patients with variant angina. If the patient is fortunate, this is detected during the initial evaluation of a patient with chest pain. Until the diagnosis is firmly established, a 12-lead electrocardiograph should be performed during each and every episode of chest pain. As previously noted, ST-segment elevation and depression and T-wave inversion or pseudo normalization may follow episodes of ST-elevation.

Medical Care

Patients with angina pectoris at rest are routinely admitted to a hospital for observation, evaluation, and initiation of medical therapy. This should include a 12-lead electrocardiograph (which should be repeated with each episode of chest pain), telemetry monitoring for the initial 24-48 hours, and serial cardiac enzyme assays.

Thallium scintigraphy and coronary angiography may be required for diagnostic, prognostic, and therapeutic reasons. Ambulatory electrocardiography and Holter monitoring may increase the sensitivity of the aforementioned in-hospital evaluation if the diagnosis of variant angina remains elusive.

Medical therapy initially should include intravenous or sublingual nitroglycerin and an oral calcium channel antagonist. Long-acting oral nitrates are appropriate for the prevention of recurrent episodes and may be used in combination with the calcium channel antagonist for long-term prophylaxis.

Surgical Care

Percutaneous coronary revascularization and coronary artery bypass surgery may be helpful in patients with a mixed presentation, including both rest and limiting exertional angina with suitable proximal coronary artery stenoses.

Effects:

Abnormal levels of serum cardiac troponin I (cTnI) are occasionally found in patients presenting with acute coronary syndromes but having insignificant coronary artery disease. Before one concludes that an abnormal cTnI level is a false-positive result, the possibility of coronary vasospasm should be considered. This study investigated whether coronary vasospasm could be a reason for elevated cTnI in this patient population.¹

Coronary vasospasm can be a possible cause of myocardial infarction. A conclusion derived from the study of "preinfarction" angina. To investigate the pathogenesis of myocardial infarction was undertaken a systematic study of patients with angina at rest, a syndrome known to evolve frequently into infarction. Among 187 consecutive patients, 37 had infarction, all in the area that showed electrocardiographic changes during angina. In all 76 patients who underwent hemodynamic monitoring, 201thallium myocardial scintigraphy or angiography during angina, a vasospastic origin of the attacks was documented. In six patients with infarction shortly after these studies and in two in whom the infarction developed during hemodynamic monitoring or during angiography the onset of infarction was indistinguishable from the onset of anginal attacks. One patient in whom spasm was observed at the onset of infarction died six hours later; at post-mortem examination, a fresh laminar thrombus was found at the site of the spasm. After infarction, complete thrombotic occlusion of the branch shown to undergo vasospasm was documented in two patients by angiography

Cause of myocardial infarction: It has been seen that although not often but in some situations, coronary spasm in intense cases can lead to a situation similar to myocardial infarction.²

However it needs a significant degree of spasm and that too persisting for a long period of time to produce a significant infarction

Cause of postoperative ischemia : Native coronary artery spasm is a rare, but important cause of postoperative ischemia and infarction. Suspicious electrocardiographic changes warrant consideration of transesophageal echocardiography to detect unexpected wall motion abnormalities. The consideration of Post operative ischemia should rank high on most of the patients undergoing any form of cardiac surgery as post operative spasm can be associated with multiple procedures performed in cardiac patients.

Development of fixed atherosclerotic coronary obstructions : Recurring coronary artery spasm may lead to the development of fixed atherosclerotic coronary obstructions.³

However further investigation is needed to substantiate this fact and presently research focused on this aspect is underway in leading cardiology centres of United Kingdom as well as United States.

Development of Arrhythmias

Silent myocardial ischemia due to coronary-artery spasm can initiate potentially fatal arrhythmias in patients without flow-limiting structural coronary-artery lesions. The role of silent ischemia, reperfusion, or both in the initiation of fatal arrhythmias in larger groups of patients with advanced coronary-artery lesions remains to be defined.⁴

Precipitation of Cardiomyopathies

Genetic defects in the plasma membrane-associated sarcoglycan complex produce cardiomyopathy characterized by focal degeneration. The infarct-like pattern of cardiac degeneration has led to the hypothesis that coronary artery vasospasm underlies cardiomyopathy in this disorder⁵

Associations of Coronary vasospasm:

Rebound vasospasm after coronary revascularization in association with calcium antagonist withdrawal. Four patients experienced life-threatening coronary vasospasm following discontinuation of calcium channel blocking medication at the time of coronary revascularization. The last dose of the calcium blocker in each instance was administered between 8 and 18 hours before operation. Two of the patients were receiving diltiazem (60 mg four times a day) and 2, nifedipine (20 mg four times a day).⁶

Migraine and Angina Pectoris by Coronary Artery Spasm⁷

Many patients with migraine simultaneously can present with Coronary spasm. However some studies lately have declined the strength of this association while as other school of thought considers this as a part of general vasospastic condition.

Cardiac complications are well known after Aneurysmal subarachnoid hemorrhage. Three of four patients developed symptomatic vasospasm, and two required balloon angioplasty. Three patients achieved good outcomes. The eldest died from severe vasospasm that was unresponsive to angioplasty. Reversible cardiac failure associated with subarachnoid hemorrhage may be due the neurogenic stunned myocardium. Frequent symptomatic vasospasm occurs, possibly related to poor cardiac output and the inability to optimize hyperdynamic hypervolemic therapy⁸

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