Coronary Artery Spasm as a Cause of Angina

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Coronary vasoconstriction has moved in and out of fashion for more than a century. The initial descriptions of angina considered vasomotor instability as a key mechanism, but pathologic studies and the invention of coronary angiography in the middle of the last century focused attention on structural stenoses and occlusions attributed to atheromatous plaques. When Prinzmetal et al described a variant form of angina, which was later confirmed as a coronary spasm, vasomotor instability returned to the limelight. Variant angina is characterized by symptoms at rest (not exertion) with ST elevation on ECG (not depression). It usually occurs in the early hours of the morning during depressed vagal tone and is associated with occlusion or near occlusion (>90% stenosis) of a focal proximal coronary segment on angiography.

Proven tests for Coronary Spasm in Variant Angina

In the late 1970s and early 1980s, several groups used intravenous or intracoronary ergonovine to provoke coronary vasoconstriction of the vascular smooth muscle, which is usually mild in patients without variant angina. In variant angina, ergonovine causes severe focal epicardial spasm with ST elevation and typical angina symptoms. Ergonovine causes this response in ≈4% of patients referred for angiography for a variety of indications but in >80% of patients with variant angina. Spasm most often occurs at sites of mild-to-moderate atheromatous stenoses, but even sites that are angiographically normal have atheroma by intravascular ultrasound.

Microvascular Spasm

Epicardial spasm is much easier to identify than microvascular spasm. Small resistance vessels are not measurable by angiography, but because they regulate blood flow, microvascular spasm is identified by a reduction in blood flow in the absence of other factors influencing flow (ie, epicardial vasoconstriction or change in mean blood pressure). Surrogates such as ECG changes or symptoms without epicardial spasm are not specific for microvascular spasm, because these are sometimes observed with the intracoronary injection of any agent, even contrast.

Endothelial Dysfunction

The discovery that the endothelium regulated vasomotor function generated an explosion of interest in endothelial dysfunction as a mechanism contributing to angina and the progression of atherosclerosis. Acetylcholine could reveal the functional status of the endothelium because of its dual action on muscarinic receptors on the endothelium and vascular smooth muscle. In healthy endothelium, acetylcholine stimulated the production of nitric oxide, a potent vasodilator, but it also had an opposing direct vasoconstrictor effect on vascular smooth muscle. Within a specified dose-response curve, the vasodilator response of acetylcholine in healthy arteries overwhelmed the direct vasoconstrictor action. In arteries lacking endothelium, or where endothelium was dysfunctional, the net effect was vasoconstriction.

The initial human studies in patients without variant angina used infusion catheters to direct acetylcholine into a major coronary artery and showed vasoconstriction of arteries, particularly at sites of nonobstructive stenoses compared with arteries with little angiographic disease. Even in patients with smooth coronary arteries, the presence of recognized risk factors for atherosclerosis associated with endothelial dysfunction.

Other investigators used manually delivered doses of acetylcholine delivered into coronary artery ostia by a catheter.
Differences in the various protocols and whether investigators were reporting the concentration in the syringe or the estimated concentration in the coronary artery led to some confusion as to the dose of acetylcholine between studies. The initial selective infusion catheter method used a steady-state maximum concentration of acetylcholine in a coronary artery of ≈10^{-6} mol/L. The manually delivered methods usually report a dose of ≤100 μg given over 20 seconds through a diagnostic catheter, which, if mixed in a 5-mL syringe, amounts to ≈10^{-5} mol/L in the coronary artery. This is important, because a high enough concentration may overcome the endothelial response to cause direct vasoconstriction, even in angiographically normal arteries.24,25

In general, the vasoconstriction in patients without variant angina was much less and was more diffuse than that observed in patients with true coronary spasm and variant angina. However, in the presence of mild stenoses or disease, a modest vasoconstrictor response reflecting endothelial dysfunction could contribute to myocardial ischemia.26

In reality, vasoconstriction causing angina is probably part of a spectrum with some murky overlap. The Japanese Coronary Spasm Association27 and several classic studies5,6,18,24 define coronary spasm as a >90% stenosis or occlusion with acetylcholine or ergonovine. Variant angina requires this definition of spasm plus chest pain with ST elevation. Vasoconstriction without the clinical syndrome or with lesser and more diffuse degrees of constriction arguably indicate endothelial dysfunction and, if this occurs with angina, could be called vasospastic angina.18

Prevalence of Coronary Vasoconstriction With Provocative Testing

In this issue of Circulation, Ong et al28 describe their experience with acetylcholine testing in patients with unobstructed coronary arteries defined as no angiographic disease or <50% stenosis. It extends their work from an earlier report in 304 patients without variant angina.29 This updated report of 921 patients includes a mix of patients with angina and some with previous coronary stenting or bypass, various atherosclerosis risk factors, and clinical presentations with acute and stable coronary syndromes.29 A third of patients had microvascular spasm by their definition, and another 24% had microvascular spasm defined as ischemic ECG changes with angina but epicardial constriction <75%. Thus, microvascular spasm was inferred but was not directly measured by changes in flow.

Given the history of provocative testing described above, it is not surprising that they should find focal and diffuse patterns of vasoconstriction to acetylcholine. Factors contributing to their high prevalence of spasm include the high concentrations of acetylcholine used in their protocol (manual injection of 200 μg), the lesser degree of constriction required for their definition of spasm (>75% compared with the nitroglycerin response versus >90% constriction compared with the baseline angiography), and a patient mix that included advanced or acute coronary disease. The presence of modest coronary stenoses was not reported, but in their previous report nearly half of the patients had a 20% to 49% stenosis.29

Most patients had a diffuse and distal constriction pattern, with only 9 patients (3.2%) having a proximal focal epicardial constriction pattern. This is not incongruent with the reports from 30 to 40 years ago. The older studies ignored diffuse vasoconstriction and were only interested in a focal, proximal, near occlusive response considered the hallmark of variant angina.3,6 This pattern of spasm occurred in 4% of subjects5,6 and is virtually identical to that reported by Ong et al.28

Testing Vasomotor Function in Clinical Practice

The report by Ong et al28 does remind us of the importance of vasomotor dysfunction as a contributor to myocardial ischemia. Although the risks of the procedure were small, they are potentially higher in patients with left main disease, multivessel disease, severe left ventricular dysfunction, or incipient heart failure. In these patients, acetylcholine delivered into the left main artery could prove catastrophic if it precipitated severe multivessel vasoconstriction.

True variant angina seems to be a rare fish in the sea of coronary syndromes. The ubiquitous use of calcium channel blockers and long-acting nitrates could explain the paucity of vasospastic angina. The greater use of statins and risk factor modification also contribute by improving endothelial function30,31 and reducing myocardial ischemia.32 We recognize that patients with angina and nonobstructive coronary disease should receive risk factor modification because it decreases any vasomotor component of angina and the progression of structural disease. Patients with obstructive coronary disease will almost always be offered revascularization by percutaneous coronary intervention or bypass surgery.

If this is the standard, the need for routine provocative testing is uncertain, because it is unlikely to change clinical practice in most patients with coronary artery disease. Its value probably lies in a smaller group of patients with nonobstructive disease and recalcitrant symptoms or unexplained sudden cardiac death. Coronary spasm in the former may lead to more intensive vasodilator therapy and in the latter an implantable cardioverter defibrillator. Testing for vasomotor function should be used cautiously in patients at higher risk of adverse events (above), and operators should have interventional equipment and skills to treat severe vasospasm with intracoronary vasodilators and obstructive disease with percutaneous coronary intervention.

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Disclosures

None.

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