Coronary Artery Spasm as a Cause of Angina

Running title: Kinlay; Coronary artery spasm as a cause of angina

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Journal Subject Codes: Atherosclerosis:[87] Coronary circulation, Diagnostic testing:[33] Other diagnostic testing, Vascular biology:[95] Endothelium/vascular type/nitric oxide

Key words: ergonovine, acetylcholine, Editorial, coronary microvascular function, coronary spasm, coronary spastic angina, coronary vasomotor dysfunction
Coronary vasoconstriction has moved in and out of fashion for over a century. The initial descriptions of angina considered vasomotor instability as a key mechanism\textsuperscript{1}, but pathological studies\textsuperscript{2} and the invention of coronary angiography in the middle of last century, focused attention on structural stenoses and occlusions due to atheromatous plaques. When Prinzmetal described a variant form of angina\textsuperscript{3}, which was later confirmed as coronary spasm\textsuperscript{4}, 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.

**Provocative Tests for Coronary Spasm in Variant Angina**

In the late 1970’s and early 1980’s, several groups used intravenous or intracoronary ergonovine to provoke coronary vasospasm in patients with variant angina\textsuperscript{5-9}. Ergonovine causes vasoconstriction of 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\textsuperscript{10}. Ergonovine causes this response in about 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\textsuperscript{5,6}, but even sites that are angiographically normal have atheroma by intravascular ultrasound\textsuperscript{11}.

Ergonovine has a relatively long half-life and given intravenously, often causes headaches, nausea, and hypertension. Intracoronary and intravenous administration have small risks of ventricular fibrillation, myocardial infarction, or spasm refractory to systemic nitroglycerin requiring intracoronary nitroglycerin\textsuperscript{5-7,12,13}. Acetylcholine has a much shorter half-life and is considered safer than ergonovine, although it can induce heart block or
bradycardia (requiring temporary pacing), and ventricular arrhythmias. Japanese investigators popularized the use of acetylcholine as a provocative agent for coronary spasm, which has high sensitivity and specificity in variant angina\textsuperscript{14,15}.

The causes of coronary spasm with variant angina are poorly understood. It is most often associated with cigarette smoking\textsuperscript{15-17}. There are also differences between Japanese and North American/European studies\textsuperscript{18}, with Japanese studies reporting a higher prevalence, more diffuse than focal spasm, and less obstructive and multivessel disease\textsuperscript{18}. However, these comparisons are based on 30-40 year old studies, when there were substantial differences in the prevalence of atherosclerosis and risk factors between these populations. Whether these regional differences persist with the assimilation of American-European diets and lifestyle in East Asia over the last quarter century is unknown.

**Microvascular Spasm**

Epicardial spasm is much easier to identify than microvascular spasm. Small resistance vessels are not measureable by angiography, but since they regulate blood flow, microvascular spasm is identified by a reduction in blood flow in the absence of other factors influencing flow (i.e. epicardial vasoconstriction or change in mean blood pressure)\textsuperscript{19}. Surrogates such as ECG changes or symptoms without epicardial spasm are not specific for microvascular spasm, as these are sometimes observed with the intracoronary injection of any agent, even contrast.

**Endothelial Dysfunction**

The discovery that the endothelium regulated vasomotor function\textsuperscript{20}, 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 non-obstructive stenoses compared to 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 of 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 about $10^{-6}$M. The manually delivered methods usually report a dose of up to 100µg given over 20 seconds through a diagnostic catheter, which if mixed in a 5ml syringe, amounts to about $10^{-5}$M in the coronary artery. This is important, as a high enough concentration may overcome the endothelial response to cause direct vasoconstriction, even in angiographically normal arteries.

In general, the vasoconstriction in patients without variant angina was much less and 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. In reality, vasoconstriction causing angina is probably part of a spectrum with some murky overlap. The Japanese Coronary Spasm Association and several classical studies 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.

**Prevalence of Coronary Vasoconstriction with Provocative Testing**

In this issue of *Circulation*, Ong et al 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. This updated report of 921 patient includes a mix of patients with angina, and some with prior coronary stenting or bypass, various atherosclerosis risk factors, and clinical presentations with acute and stable coronary syndromes. A third of patients had epicardial spasm by their definition, and another 24% had microvascular spasm defined as ischemic ECG changes with angina but epicardial constriction less than 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 to the nitroglycerin response versus >90% constriction compared to 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 prior report nearly half of the patients had a 20-49% stenosis\textsuperscript{29}.

Most patients had a diffuse and distal constriction pattern with only 9 (3.2\%) patients having a proximal focal epicardial constriction pattern. This is not incongruent with the reports from 30-40 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\textsuperscript{5,6}. This pattern of spasm occurred in 4\% of subjects\textsuperscript{5,6} and is virtually identical to that reported by Ong.

\textbf{Testing Vasomotor Function in Clinical Practice}

Ong’s report 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 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 HMG Co-A reductase inhibitors (statins) and risk factor modification also contribute by improving endothelial function\textsuperscript{30,31} and reducing myocardial ischemia\textsuperscript{32}. We recognize that patients with angina and non-obstructive 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 as 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 non-obstructive disease and recalcitrant symptoms or unexplained sudden cardiac death. Coronary spasm in the former may lead to more intensive vasodilator therapy and 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.

Funding Sources: This work was supported by VA Clinical Science Research and Development Awards 1/01CX000440 and 1/21CX000793.

Conflict of Interest Disclosures: Dr. Kinlay reports a research grant from VA Clinical Science Research and Development Awards.

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_Circulation_. published online February 26, 2014;
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
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