Coronary Artery Spasm
A 2009 Update

Shlomo Stern, MD; Antoni Bayes de Luna, MD

Case presentation: A 37-year-old man was admitted in the early morning hours to the emergency department after experiencing excruciating chest pain. The patient was a heavy smoker who gave a history of several previous similar but less intense episodes of pain during the past 2 years; most of them also during the early morning hours. One of his earlier attacks was associated with sensing his heart “bouncing.” In addition, he had experienced several episodes of “palpitations” without pain. On admission, ECG showed a 2 to 3 mm ST elevation which returned to baseline quickly, concomitant with his pain subsiding. Cardiac biomarkers were normal but C-reactive protein was elevated. Twenty-four hours later, a treadmill test showed good exercise capacity and no ST changes even at target heart rate. The clinical and ECG pictures pointed to the diagnosis of a vasospastic-type Prinzmetal angina, and the patient responded well to calcium blockers and long-term nitroglycerin therapy and remained symptom-free throughout a 2-year follow-up.

Ways to Diagnose Coronary Artery Spasm

Severe chest pain, usually without physical effort and with a concurrent ECG showing transient ST elevation, is the key for the diagnosis of coronary artery spasm (CAS) (Figure 1). Diagnosis of the silent variety of CAS is possible if the vasospastic attack occurs under medical observation or during ambulatory ECG monitoring, but long-term surveillance may be needed to establish the diagnosis. Exercise testing may also be helpful, although approximately equal numbers of patients show ST depression, ST elevation, or no change whatsoever during the exercise. Further pharmacological testing, such as provocation with intravenous ergonovine, should be used only under special conditions and with extreme care (Table 1).

New Observations on the Pathophysiology of CAS

Vagal withdrawal is most often the mechanism leading to spontaneous spasm, but a change in sympathetic activity may also have a role in CAS. Endothelial dysfunction through abnormalities of nitric oxide (NO) synthase and its reduced bioavailability and hypercontractility of vascular smooth muscle in spastic arteries are major factors in the development of CAS. However, Egashira and coworkers demonstrated that NO was not decreased at the spastic sites of the coronary arteries; they pointed to additional mechanisms, such as enhanced phospholipase C enzyme activity inducing focal smooth muscle cell hyperactivity in variant angina patients.

In a Japanese population, the genetic risk and gene environment in both genders with CAS was stressed by Murase and coworkers, whereas in women polymorphism analysis of the endothelial NO synthase gene was shown to be associated with coronary spasm. Type A behavior pattern and severe anxiety and panic disorders were described as factors even without significant coronary stenosis. Signs of chronic low-grade inflammation, such as an increased monocyte count and even minor elevations of serum high sensitive C-reactive protein levels were shown to be significantly associated with CAS. In a Japanese population, Takaoka found that the classic risk factors, with the exception of cigarette smoking, were poorly associated with CAS (Table 2).

Coronary Spasm, Myocardial Infarction, and Ventricular Arrhythmias

CAS was shown to play an important role in the pathogenesis of myocardial infarction, with or without significant coronary stenosis. In these latter pa-
tients, the infarctions are normally relatively small, suggesting that coronary reperfusion occurred in the early stage of the infarction.

Ventricular fibrillation, tachycardia, and complete atrioventricular block were repeatedly observed during ischemic episodes caused by spasm, even if the attack was painless. Transient sympathovagal imbalance, detected during Holter monitoring by a marked decrease in heart rate variability in the period immediately preceding the onset of the ST shift, was suggested as the trigger for sudden death during ischemia.

Therapies, Established and New

Calcium-channel blockers seem to be the established therapy for CAS, and the decrease in frequency of variant angina is attributed to the widespread use of these drugs. Long-acting nitrates were also found to be efficient, and their vasodilatory effect may be additive to calcium antagonists. Response to β-blockade varies: in some, particularly in those with associated fixed lesions, a reduction in the frequency of exertion-induced angina is observed, but in others these drugs may be detrimental. Magnesium deficiency is a possible factor contributing to CAS, and Teragawa and coworkers suggested that its long-term supplementation might also have a preventive effect.

After an early report on the beneficial effect of cholesterol-lowering therapy on endothelial function and, consequently, a reduced coronary vasconstrictor response to acetylcholine, suppression of acetylcholine-induced CAS through the addition of a statin (fluvastatin) to conventional calcium-channel blocker therapy was reported; the purported mechanism is inhibition of the RhoA-associated kinase pathway.

Medically intractable life-threatening Prinzmetal was treated successfully with internal mammary artery grafting in 2 patients, despite angiographically normal coronary arteries. Coronary angioplasty performed in CAS patients produced results similar to those without variant angina. Life-threatening ventricular arrhythmias in CAS were the reason for automatic defibrillator implantation (Table 3).

Coronary Spasm Under Special Circumstances

In teenagers and young adults, the use of illicit substances, primarily cocaine, is an important cause of drug-induced myocardial infarction secondary to coronary spasm, with important therapeutic and prognostic implications. A 2008 American Heart Association Scientific Statement summarized the accumulated data on cocaine users’ cardiac complications, arising mainly

Table 1. Diagnostic Options in CAS

<table>
<thead>
<tr>
<th>Test</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram</td>
<td></td>
</tr>
<tr>
<td>Holter monitoring</td>
<td>If silent episodes or arrhythmias are suspected</td>
</tr>
<tr>
<td>Exercise testing</td>
<td>Results equivocal</td>
</tr>
<tr>
<td>Coronary arteriography</td>
<td>For possible associated lesions</td>
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</tbody>
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Table 2. The Coronary Arteries of Patients With Spasm

<table>
<thead>
<tr>
<th>Test</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor tone</td>
<td>Increased</td>
</tr>
<tr>
<td>Smooth muscle contraction</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Vagal activity</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Sympathetic activity</td>
<td>Reduced?</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>Increased</td>
</tr>
<tr>
<td>Nitric oxide release</td>
<td>Decreased?</td>
</tr>
<tr>
<td>Phospholipase C activity</td>
<td>Enhanced</td>
</tr>
</tbody>
</table>

Table 3. Therapeutic Options in CAS

<table>
<thead>
<tr>
<th>Option</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation of smoking</td>
<td>Obligatory</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>The most commonly used drugs</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>Alone, or in combination with calcium antagonists</td>
</tr>
<tr>
<td>Magnesium IV</td>
<td>for acute therapy</td>
</tr>
<tr>
<td>Statins</td>
<td>In addition to calcium antagonists</td>
</tr>
<tr>
<td>Coronary bypass</td>
<td>If life-threatening arrhythmias are documented</td>
</tr>
<tr>
<td>Percutaneous interventions</td>
<td></td>
</tr>
<tr>
<td>Automatic defibrillator</td>
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from the coronary vasoconstriction induced by this agent; phenolamine was found to be effective against cocaine-associated ischemia. Users of commercial weight-loss products should be warned against the use of ephedra-based products, but even bitter orange, advertised as being “ephedra-free,” was reported to induce variant angina.\textsuperscript{15} CAS is associated also with marijuana, alcohol, butane, amphetamine, and several over-the-counter, chemotherapeutic, antiinflammatory, and antibiotic medications.\textsuperscript{16} Perioperative CAS is prevalent in elderly male patients with coronary risk factors; instability of the autonomic nervous system and vascular hyperactivity in these patients are supposed to be the underlying autonomic mechanism of the spasm.\textsuperscript{17} CAS is reported to occur in 1\% to 5\% of percutaneous coronary interventions and can be induced even solely by guide wire insertion. Cardiogenic shock caused by severe coronary artery spasm immediately after stenting is frequently but not always resolved by local injection of nitroglycerin.\textsuperscript{18,19}

Ethnic Differences in Frequency of CAS
The racial differences in the incidence of CAS between Japanese and whites, pointed out earlier,\textsuperscript{20} have been confirmed recently by Sasayama.\textsuperscript{21} If the far greater number of recent investigations from the Far East than from the Western world is a true measure of the frequency of CAS, this gap has become even wider today. In the study by Ong and coworkers\textsuperscript{22} in a white (German) population with acute coronary syndrome without a culprit lesion, 49\% had a positive acetycholine test, whereas 16\% of French\textsuperscript{23} and 79\% of similar Japanese patients developed CAS after intracoronary acetylcholine.\textsuperscript{24} In the Western world the marked reduction in cigarette smoking, a major element for CAS, and the wide-spread use of calcium antagonist therapy could be factors if the incidence of CAS is truly decreasing.

Conclusions
Even if the frequency of spastic angina seems to be on the decrease in the Western world, acute chest pain episodes in a relatively young patient, especially if they occur during the early morning hours, should raise the suspicion of a vasospastic (variant-type) angina. The key for its diagnosis is episodic ST elevation concomitant with the pain. Ambulatory ECG monitoring, exercise testing, or both may provide a clue for the diagnosis, and coronary arteriography may or may not demonstrate associated fixed coronary obstruction. Calcium antagonists are extremely effective in treating and preventing coronary spasm, with or without the additive vasodilatory effect of nitroglycerin, and may provide long-lasting relief for the patient. Up-to-date therapies include coronary stenting or bypass surgery if fixed coronary occlusions are demonstrated; the association of potentially lethal ischemia-induced ventricular arrhythmias may justify the use of an implantable defibrillator.

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Disclosures
None.

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