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EDITORIAL COMMENT

Provoking Coronary Vasospasm for Diagnosis of Variant Angina

Outdated Trick of the Trade or a Resurgent Diagnostic Modality?*

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In 1959, Prinzmetal et al. (1,2) reported on 32 patients with a form of angina pectoris that was not generally precipitated by increased cardiac workload, as described by Heberden (3). During an attack of this variant type of angina, Prinzmetal et al. noted that ST segments were transiently and often markedly elevated, did not resolve with rest, and occurred in a cyclic fashion with a predilection for the early morning hours. This seminal report proposed "temporary increased tonus of a large narrowed coronary artery" as a possible cause of these attacks (1,2).

Variant angina (VA) is now known to be caused by vasospasm of an epicardial artery, typically, but not invariably, in segments with insignificant atherosclerosis (4,5). Even when an epicardial artery appears to be angiographically normal, atherosclerotic plaques can be demonstrated within a centimeter of the spastic site by intravascular ultrasonography (6,7). In some patients, VA may involve more than 1 artery and may occur either simultaneously or fluctuate between different epicardial vessels. Proposed etiologies include abnormalities in nitric oxide signaling and smooth muscle hypertrophy or hypersensitivity, among others (8–10).

Irrespective of the presence or severity of obstructive atherosclerotic disease, coronary spasm often results in myocardial ischemia and causes anginal symptoms. Transmural ischemia of a large area of the myocardium can result in ventricular arrhythmias and heart failure, and prolonged attacks may lead to thrombus formation and infarction (11,12). Several physiological stimuli can provoke coronary vasospasm including exercise, mental stress, hyperventilation, and cold exposure. However, these are unreliable stressors for diagnostic purposes (13,14). In the context of preserved exercise tolerance and normal stress imaging, the presence of ST-segment deviation recorded during an attack that occurs at rest and resolves with nitrate administration readily identifies patients with VA. Ambulatory monitoring and provocative testing are often necessary to confirm the diagnosis (15).

Although VA is uncommon compared with other coronary syndromes, its true incidence and prevalence remain unknown. In some patients, symptoms may be exertional due to exercise-provoked vasospasm, there may be systemic vasospastic diathesis, or the vasomotor instability may resolve over time after an acute coronary syndrome (16–18). Pharmacological provocation, with intracoronary acetylcholine or with intravenous or intracoronary ergonovine has been used to diagnose vasospasm and has a sensitivity of ~90% in patients with VA compared with a ~4% to 5% rate of vasospasm observed in patients referred for diagnostic angiography (19). The sensitivity and specificity of intracoronary ergonovine are higher than intravenous ergonovine and similar to that of acetylcholine (19).

The vasoconstrictor response to ergonovine is mediated by endothelium-independent contraction of vascular smooth muscle and typically involves proximal coronary segments (20). Acetylcholine stimulates nitric oxide production by endothelial

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cells while simultaneously exerting direct contractile effects on vascular smooth muscle cells. When endothelial cell activity is preserved, the vasodilator response predominates and usually overwhelms any constrictive effects (21). However, with endothelial dysfunction, the contractile effects of acetylcholine remain unopposed, and vasoconstriction ensues (15,22,23).

The optimal provocation procedure in terms of safety and diagnostic utility has yet to be defined. Controversies surround the choice and doses of the provocative agent (ergonovine vs. acetylcholine), infusion route (intracoronary vs. intravenous), and the defining criteria of coronary spasm. Most studies have used the precipitation of greater than 90% focal or diffuse coronary narrowing during provocative testing, together with the development of angina and ischemic electrocardiographic changes for the diagnosis of VA, whereas other reports have used narrowing greater than 75% as diagnostic (19,20). There is also controversy regarding whether diffuse coronary constriction, diagnostic of endothelial dysfunction when provoked by intracoronary acetylcholine, should even be considered diagnostic of VA and whether this should only be diagnosed when there is focal epicardial spasm (22). More recently, the term microvascular spasm has been used when provocation with intracoronary acetylcholine results in the clinical syndrome of angina, ischemic electrocardiographic changes, and/or reduction in coronary blood flow, but with little or no epicardial vasoconstriction (24–26).

Provocative testing with ergonovine and acetylcholine is relatively safe (27). Adverse effects are usually benign such as headache and nausea, but provocation can potentially result in life-threatening sequelae including ventricular arrhythmias, complete heart block, refractory coronary spasm, and myocardial infarction. Testing for coronary spasm should therefore be performed with caution by well-trained operators equipped for delivery of percutaneous therapeutics, especially in patients with obstructive coronary artery disease.

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In this issue of *JACC: Cardiovascular Interventions*, Shin et al. (28) report findings from a multicenter registry of Korean patients who were free of obstructive coronary artery disease and were evaluated for VA using intracoronary ergonovine. Based on their coronary vasomotor response, more than 2,000 patients were classified into positive (>90% stenosis), intermediate (50% to 90%) and negative (<50%) groups for vasospasm that constituted 21%, 46%, and 32% of study patients, respectively. The majority of positive patients had diffuse rather than focal coronary spasm, experienced more severe and recurrent attacks of angina, had higher rates of hospitalization for angina, and higher levels of circulating C-reactive protein levels compared with their counterparts. Patients in the positive group were more often male, had the highest rate of smoking, and appeared to have a higher rate of adverse events including cardiac death, acute coronary syndromes, and ventricular arrhythmia during a 2-year follow-up. However, the incomplete or absent follow-up in patients in the intermediate and negative spasm groups makes the relatively low adverse event rate in the spasm-positive group difficult to interpret.

The report by Shin et al. (28) nevertheless provides contemporary data necessary to advance the field of coronary vasoreactivity and provocative testing and highlights a true collaborative effort among multiple institutions in South Korea. Strengths include its large population size and implementation of a clearly defined protocol in centers with established expertise. Longer follow-up of all study patients will be required to ascertain whether morbidity and mortality are influenced by the type of ergonovine response, particularly in the intermediate responders, the most common form of test result observed.

Although earlier reports have suggested that VA occurs more frequently in Asians, recent larger studies in European patients suggest that the frequency of vasomotor abnormalities during provocative testing in patients without obstructive coronary artery disease may be similar to that in Asians (29,30). For example, in a series of 900 consecutive patients without obstructive coronary artery disease, intracoronary acetylcholine provoked significant spasm (greater than 75% narrowing) in one-third of study patients. Microvascular spasm, defined by the presence of angina and ischemic electrocardiographic shifts in the absence of significant epicardial vasoconstriction, occurred in nearly one-fourth of patients. Unlike the Asian experience, both epicardial and microvascular spasm occurred more frequently in women, and smoking frequency was not greater in those with microvascular spasm (29).

The field of coronary provocative testing remains challenging for the practicing physician. Ergonovine may not yield information similar to that of acetylcholine testing, although there is a clear overlap between these agents. It is likely that the substrate, treatment, and prognosis of patients with focal epicardial spasm (classic VA), diffuse epicardial spasm, and microvascular spasm are dramatically different. For example, patients with epicardial

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spasm respond to calcium antagonists and nitrates and may need to be taken off beta-antagonists, whereas those with more diffuse epicardial or microvascular spasm are likely best treated by agents that improve endothelial function such as statins, angiotensin antagonists, and arginine (23,31).

The most common finding with provocative testing is an intermediate response that is neither diagnostic of spasm nor entirely normal. The lack of long-term follow-up of these patients makes interpretation of these findings problematic. In the United States, ergonovine is not readily available, although ergometrine may offer an alternative. Acetylcholine testing is performed at a few centers only; nevertheless, provocative testing implemented in patients with persistent anginal symptoms but nonobstructive coronary disease can often be diagnostic and is reassuring for patients and often results in a more defined therapeutic strategy.

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