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STATE-OF-THE-ART PAPER

# Provocative Testing for Coronary Reactivity and Spasm

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**Coronary spasm is an important and often overlooked etiology of chest pain. Although coronary spasm, or Prinzmetal's angina, has been thought of as benign, contemporary studies have shown serious associated adverse outcomes, including acute coronary syndrome, arrhythmia, and death. Definitive diagnosis of coronary spasm can at times be difficult, given the transience of symptoms. Numerous agents have been historically described for provocative testing. We provide a review of published data for the role of provocation testing in the diagnosis of coronary spasm.** (J Am Coll Cardiol 2014;63:103–9) © 2014 by the American College of Cardiology Foundation

Coronary spasm (CS) is an important etiology of angina that often goes undiagnosed. Although older published data suggest that the prognosis for patients with coronary spasm is relatively benign (1), contemporary reports indicate that CS has been associated with ischemia, acute coronary syndrome, arrhythmia, and sudden cardiac arrest (SCA) (2–4), with a worse prognosis reported in those with even trivial coronary stenosis (5). Diagnosis can be difficult, given the transience of CS, and might require more sophisticated provocative diagnostic approaches. In current U.S. practice, it seems provocation testing in the cardiac catheterization laboratory is performed less frequently, although quantitative data are not available. Numerous agents have been described for spasm provocation testing including ergonovine (ER), acetylcholine (ACH), neuropeptide Y, and dopamine (6–9); however, a relatively larger body of evidence supports ER and ACH for clinical practice. We herein review provocative testing for the diagnosis of CS.

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## Pharmacology

The pharmacological agents most often used clinically in provocation testing for the diagnosis of CS are ER (6,10–20) and ACH (1,8,21–23). Ergonovine acts on smooth muscle mainly via activation of serotonergic (5-HT2) receptors to produce vasoconstriction (24). Activation of the endothelium in response to ER also causes release of inhibitory prostanoid substances; those with endothelial dysfunction might have more pronounced contraction (24). Ergonovine is predominantly metabolized by the liver and serves as a major substrate of CYP3A4 hepatic enzymes. Adverse reactions to ergot alkaloids are diverse and include angina, ischemia, myocardial infarction (MI), arrhythmia, nausea, allergic reaction, and ergotism (18,25).

ACH acts on the endothelium and smooth muscle via muscarinic receptors. In healthy endothelium, ACH activation results in vasodilation. However, in the setting of endothelial dysfunction, endothelial cells insufficiently produce nitric oxide, a potent smooth muscle relaxant (26) resulting in blood vessel contraction rather than vasodilation. Adverse reactions to ACH include hypotension, bradycardia, dyspnea, and flushing (27). When using intracoronary (IC) ACH, the risk of bradyarrhythmia is often circumvented with temporary ventricular pacing. Serious reactions include ventricular tachycardia, shock, and cardiac tamponade (28).

Both ACH and ER are not U.S. Food and Drug Administration-approved for the indication of coronary vasospasm diagnosis. Various testing protocols using IC and intravenous (IV) administration have been described (Table 1). Importantly, induction of spasm with IV ER can produce multivessel spasm and hemodynamic instability, making arteriograms difficult to obtain. Furthermore, IC nitroglycerin might be required to relieve spasm. For these reasons, Hackett et al. (6) demonstrated that induction of

**Abbreviations and Acronyms**

ACH = acetylcholine
CFR = coronary flow reserve
CS = coronary spasm
ER = ergonovine
IC = intracoronary
IV = intravenous
MI = myocardial infarction
SCA = sudden cardiac arrest

CS with IC ER might be safer than IV administration. Additionally, IC (ER or ACH) administration allows provocation of the right and left coronaries separately. Furthermore, although IV ER provocation testing has good sensitivity (100% with angina as part of the diagnostic criteria, and 94% with ST-segment elevation) (17), reports show frequency of provoked CS with IC ER to be 2.2 to 2.6 times higher than IV testing (23). Specificity of IV and IC ER provocation testing are similarly high, >90% (6,11). Despite high sensitivity, false negatives have been reported (29); thus, a negative test cannot always exclude CS.

## Pathogenesis of CS

The role of CS in variant angina, or Prinzmetal's angina, is well documented (30). Patients have spontaneous angina episodes associated with reversible constriction of a focal segment or segments of coronary artery leading to restriction of coronary blood flow and myocardial ischemia. These episodes are often associated with ST-segment elevation (31). Spasm can involve the epicardial coronary vessels, but coronary microvascular spasm can also occur and might be associated with cardiac syndrome X (32).

The pathogenesis of CS is likely multifactorial and heterogeneous among different populations. Coronary vascular smooth muscle hyper-reactivity (33) has been described and is thought to be a consequence of loss of balance between vascular myosin light chain kinase and phosphatase activity, leading to a predominance of myosin light chain phosphorylation and resultant excessive vascular smooth muscle contraction (34). Endothelial cell dysfunction also contributes, as these cells act as paracrine regulators of vascular tone and respond to changes in shear stress, myogenic constriction, and vasoactive substances by releasing various vasorelaxant substances (35,36). Prior work has demonstrated that ACH-induced dilation is lost in the presence of atherosclerosis in the coronaries of human transplanted hearts (37).

Interestingly, differing pathophysiology has been proposed for focal and diffuse vasospasm. Atherosclerotic lesions have been identified at the site of focal spasm with intravascular ultrasound (38). Akasaka et al. (10) compared coronary flow reserve (CFR) of patients with focal versus diffuse spasm and found that patients with ER-induced diffuse spasm had significantly reduced CFR compared with control (normal coronaries, no spasm). In contrast, those with focal ER-induced spasm maintained normal CFR. They suggested that focal spasm might be related to localized epithelial dysfunction of the epicardial coronaries without significant effect on coronary microvascular function.

Variant angina episodes occur most from midnight to early morning when vagal tone is highest. Increased vagal tone and hyper-reactivity to sympathetic stimulation have been described in the mechanism, with some even reporting surgical sympathetic denervation as a therapeutic option for medically refractory patients (39).

Environmental factors such as smoking (1,40), metabolic abnormalities (41), and alcohol consumption (1) might also be pathogenic contributors. Racial variations in incidence have been reported (42), with a higher prevalence found in Japanese than Western individuals (11,23,43), suggesting genetic differences in addition to differences in environmental exposures. Several single nucleotide polymorphisms

**Table 1 Provocation Testing Dosing Protocols**

| First Author (Ref. #) | Ergot Derivative | Acetylcholine |
|---|---|---|
| Invasive | | |
| Akasaka et al. (10) | ER 100 μg IV (up to 200 μg) | N/A |
| Bertrand et al. (11) | Methergine 400 μg IV | N/A |
| Hackett et al. (6) | ER 6–50 μg IC | N/A |
| Harding et al. (12) | ER 50–150 μg IV | N/A |
| Japanese Circulation Society (45) | ER 20–60 μg (LCA, IC); ER 20–60 μg (RCA, IC) | 20–100 μg (LCA, IC); 20–50 μg (RCA, IC) |
| Okumura et al. (8,22) | 200 μg IV | 20–100 μg (LCA, IC); 20–50 μg (RCA, IC) |
| Song et al. (19) | ER 1–30 μg IC | 10–100 μg IC |
| Sueda et al. (13–16,23) | ER 40 μg (RCA, IC); 64 μg (LCA, IC) | 20–100 μg (LCA, IC); 20–80 μg (RCA, IC) |
| Takagi et al. (18) | ER 20–60 μg (LCA, IC); ER 20–60 μg (RCA, IC) | 20–100 μg (LCA, IC); 20–50 μg (RCA, IC) |
| Waters et al. (17) | ER 12.5–400 μg IV | N/A |
| Yasue et al. (21) | N/A | Suspected vessel: 10–100 μg IC; contralateral artery: 20–100 μg (LCA, IC); 20–50 μg (RCA, IC) |
| Noninvasive | | |
| Song et al. (20) | ER 25–50 μg IV (up to 350 μg total) | N/A |

ER = ergonovine maleate; IC = intracoronary; IV = intravenous; LCA = left coronary artery; NSS = normal saline solution; RCA = right coronary artery.