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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.

have been identified (44) that are thought to be related to CS.

Provocation Testing

Invasive. A positive response to ACH or ER spasm provocation testing is defined as transient occlusion (>90% narrowing) of a coronary artery with signs and symptoms of myocardial ischemia (angina/ST-segment changes) (45).

The incidence of positive testing depends on the population. Bertrand et al. (11) conducted a large French cohort study with 1,089 patients who underwent ER provocation testing during routine coronary angiography for suspected ischemia. They found that 12.3% of patients developed CS. Provoked spasm was most common in patients with rest angina (38%) and recent MI (20%) and less in those with exertional symptoms (4.3%) and atypical angina (1.2%). Notably, 59% of vasospasm episodes occurred on pre-existing fixed stenoses. Harding et al. (12) conducted a large North American study evaluating 3,447 patients with nonobstructive coronary disease (<50% stenosis) and without previously documented Prinzmetal's angina. These investigators reported 4% positive invasive ER testing. In comparison with the study by Bertrand et al. (11), lower doses of ER were used. After multivariate analysis, degree of coronary disease on angiography and smoking were statistically significant predictors of spasm (12).

Yasue et al. (21) evaluated the sensitivity of IC ACH in provoking CS. All 27 patients studied had CS on the basis of rest angina symptoms with associated ST-segment changes. Injection of ACH into the suspected coronary artery induced spasm in 30 of 32 (94%) arteries in 25 of 27 (93%) patients. One-half of the coronary arteries tested not suspected to be responsible for the attacks showed 25% to 75% luminal narrowing, without chest pain or ST-segment changes, suggesting that the testing had good sensitivity and specificity (21). Okumura et al. (22) examined the effect of IC ACH testing in 70 patients with variant angina and 93 patients without variant or rest angina and reported 90% sensitivity and 99% specificity. In a larger study, Sueda et al. (23) explored the incidence of spasm with IC ACH testing in 685 patients undergoing angiography and found CS in 221 patients (32.3%). More provoked spasm was seen in patients with rest angina (83 of 125, 66.9%), similar to ER provocation studies, and least in those with atypical angina (4 of 83, 4.8%). Spasm was also more common in patients with prior MI and atherosclerosis, although those with advanced atherosclerosis were excluded (23).

Ergonovine testing is often compared with or used in combination with ACH. Sueda et al. (13) performed IC administration of both ACH and ER in the same 171 patients, all of whom had <50% stenosis. They found no significant differences in provoked spasm between the 2 agents (ACH: 33% vs. ER: 32%, p = NS). Notably, ACH

Table 2 Practice Guidelines for Coronary Spasm Provocation Testing

Guidelines (Ref. #)	Classification	Level of Evidence	Recommendations
2006 European Society of Cardiology stable angina guidelines (55)	IIa	B	IC provocation testing known anatomy, nonobstructive CAD
2008 Japanese Circulation Society vasospastic angina guidelines (45)	I	—	IC provocation testing during angiography in patients with suspected variant angina without a diagnosis by noninvasive measures (ECG, Holter, exercise, hyperventilation) recommended protocol provided in Table 1
2011 ACCF/AHA unstable angina/non-STEMI guidelines (54)	IIb	C	Provocation testing indicated known coronary anatomy failed empiric treatment life-threatening disease and verification of spasm is necessary
2011 ACCF/AHA/SCAI percutaneous coronary intervention guidelines (56)	—	—	None
2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS stable ischemic heart disease guidelines (57)	—	—	None
2012 ACCF/AHA unstable angina/non-STEMI guidelines (58)	—	—	None

AATS = American Association for Thoracic Surgery; ACCF = American College of Cardiology Foundation; ACP = American College of Physicians; AHA = American Heart Association; CAD = coronary artery disease; ECG = electrocardiogram; IC = intracoronary; MI = myocardial infarction; PCNA = Preventive Cardiovascular Nurses Association; SCAI = Society for Cardiovascular Angiography and Interventions; STEMI = ST-segment elevation myocardial infarction; STS = Society of Thoracic Surgeons.

provoked more diffuse and distal spasm, whereas ER induced more focal spasm. No serious or irreversible complications were observed. In a subsequent study in 2004, the same Japanese investigators retrospectively analyzed 1,508 selective spasm provocation tests (873 ACH, 635 ER) (14). They found no difference between the agents in patients with ischemic heart disease but found significantly higher provoked spasm with ACH than ER in patients with no coronary artery disease (11.0% vs. 6.4%, $p < 0.05$). Additionally, multiple spasm as well as spasm not associated with focal stenosis was provoked more with ACH. More complications were seen with ACH compared with ER (1.4% vs. 0.2%); however, none were serious (death, MI) or irreversible.

Sueda et al. (15) also investigated the usefulness of combined provocation testing with ACH and ER. Three sequential provocation tests were performed with ACH, then ER, followed by a combination test using sequential IC injections of both agents, eliminating patients with positive spasm between tests. In this study, significantly more spasm was induced in patients with rest angina and ischemia (98% with provoked spasm) compared with patients with atypical angina and no ischemia (8% with provoked spasm). Ischemia was defined as electrocardiogram changes or abnormal scintigraphy during exercise. In those with rest angina, ACH provoked spasm in 55%, ER provoked spasm in 33%, and the combination test provoked spasm in 92% of the remaining patients. No major complications were reported.

Sueda et al. (16). additionally studied whether the CS induced by provocation testing correlated with the angina-provoking artery responsible for the sites of ST-segment elevation during ischemic attacks. They evaluated 42 patients, predominantly men, with variant angina and history of a recent ST-segment elevation myocardial infarction attributed to spasm. The correlation with the ACH test was 78.6% for all patients and 80.0% for all sites of ST-segment elevation. By adding the ER test after the ACH test, the correlation increased to 95.2% for all patients and 95.6% for all sites of ST-segment elevation.

A particularly important population in which diagnostic testing for CS might be critical are survivors of SCA who have no apparent cardiac disease. Studies demonstrate that CS might trigger lethal arrhythmias and lead to SCA (3,46).

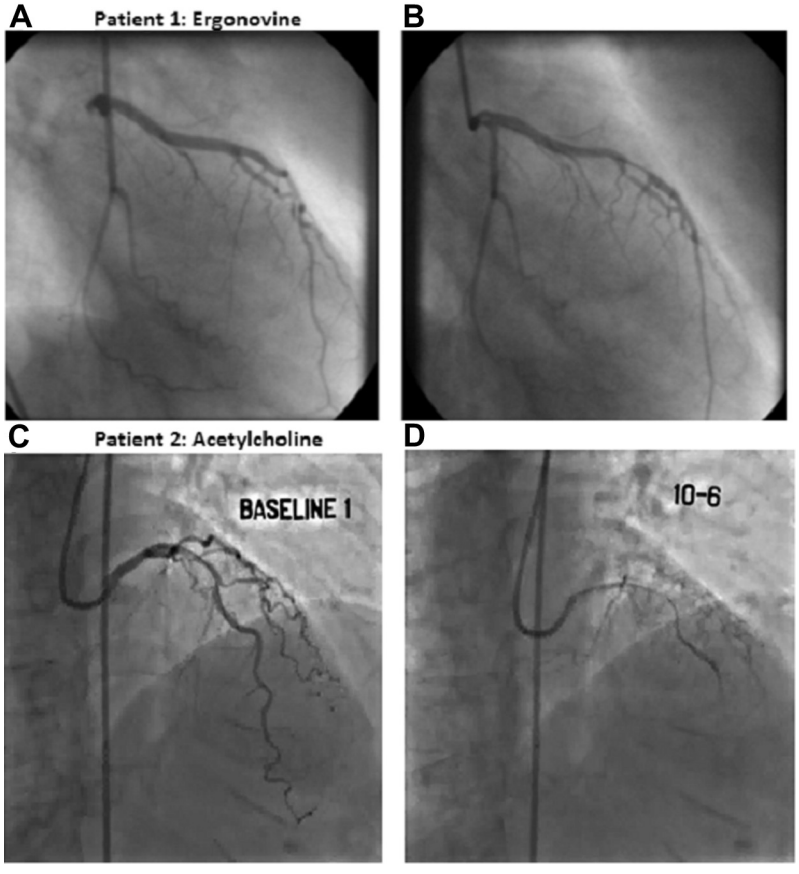

Figure 1 **Coronary Spasm**

Angiogram before **(A)** and after **(B)** administration of 200 μg intravenous ergonovine showing focal spasm of the left anterior descending artery. Reprinted with permission from Adlam et al. (59). Angiogram before **(C)** and after **(D)** intracoronary infusion of acetylcholine at a concentration of 0.182 μg/ml (2 ml over 3 min) showing diffuse spasm of the left anterior descending artery.

Igarashi et al. (47) studied 14 survivors of SCA without apparent heart disease. Overall, 4 were found to have angina with ST-segment elevation during observation; 5 of the remaining 9 had positive ER provocation testing. Survivors who underwent subsequent diagnostic spasm provocation testing and appropriate therapy seem to have a good prognosis. Chevalier et al. (48) followed 7 survivors of SCA (with absence of known heart disease) who underwent ER provocation testing that was positive. Treatment with a calcium channel blocker was initiated at a dose determined by titration until a negative provocation test resulted. All were habitual smokers. In 58 months of follow-up, only the patient who did not abstain from tobacco had a recurrent event, highlighting treatment efficacy and importance of risk management (48). Studies indicate that severe multivessel spasm, daytime ST-segment changes, and younger age are predictors of SCA (3). Additionally, Togashi et al. (4) have reported differing circadian variance in patients with SCA and syncope triggered by CS relative to patients with typical CS (nocturnal symptoms, angina only), suggesting possible differences in pathogenesis and need for provocation testing even in those without typical variant angina.

Noninvasive. Noninvasive, nonpharmacological evaluation for the diagnosis of CS includes standard 12-lead electrocardiogram (during attack), Holter monitoring (45), exercise testing (49), and hyperventilation testing (50). Waters et al. (17) reported better sensitivity with pharmacological testing (IV ER) compared with noninvasive, nonpharmacological measures in patients with untreated variant angina. The ER testing induced angina in all 34 patients and ST-segment elevation in 32 (94%), exercise testing induced angina in 17 (50%) and ST-segment elevation in 10 (29%), and cold pressor testing provoked angina in 5 (15%) and ST-segment elevation in 3 (9%) (17). Conversely, Okumura et al. (8) reported 93% sensitivity with exercise myocardial scintigraphy and echocardiography during the hyperventilation provocation test in predicting IC ACH spasm. Sueda et al. (51) assessed the usefulness of a combined hyperventilation and exercise test and reported 64.9% sensitivity and 100% specificity.

There is a relative paucity of published data with regard to the safety of bedside ER provocation testing for CS. Protocols using continuous monitoring of wall motion by echocardiography to detect spasm-induced ischemia in

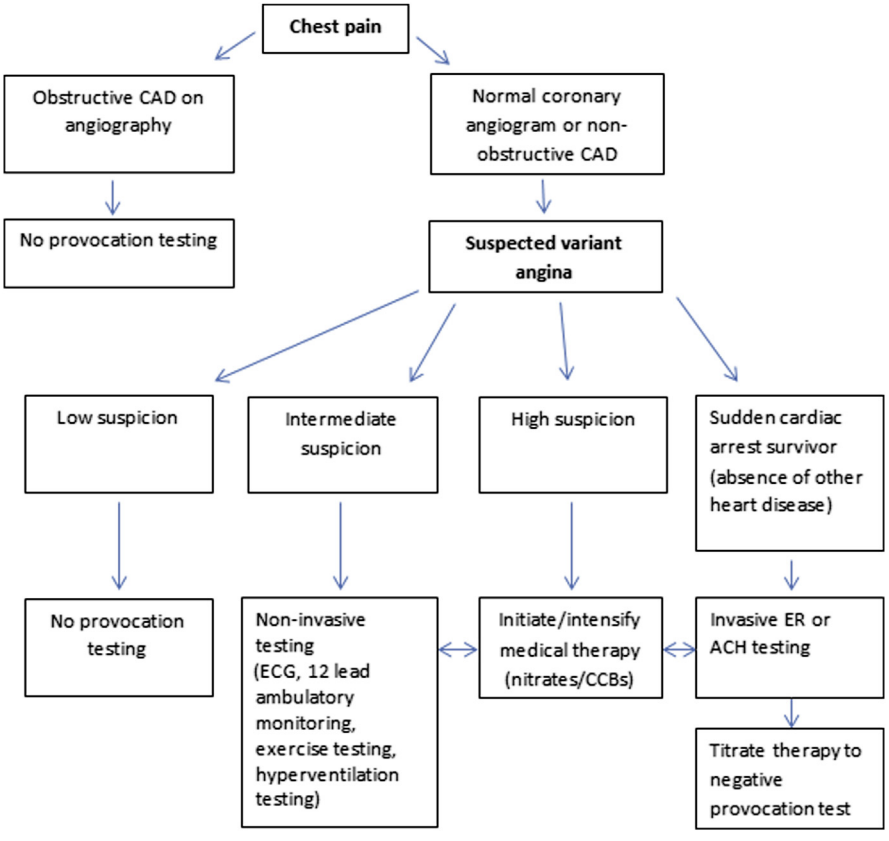

Figure 2 **Variant Angina Algorithm**

Suspicion is based on clinical factors: spontaneous episodes of angina occurring at rest and between night and early morning hours; marked diurnal variation in exercise tolerance (reduced during early morning hours); quick relief of angina with nitrates; suppression of attacks with calcium channel blockers (CCBs); smoking; and Asian descent. ACH = acetylcholine; CAD = coronary artery disease; ECG = electrocardiogram; ER = ergonovine.

patients with near-normal angiographic findings are described (20). The safety of bedside ER stress echocardiography is reported by Song et al. (19) in a retrospective analysis of 1,372 patients without significant myocardial ischemia (most evaluated by exercise stress testing). Overall, 31% of the patients had positive results, arrhythmia developed in 1.9%, and all episodes were transient and reversible. No mortality or MI was reported. Of the 16% of patients who also underwent invasive CS testing, the investigators reported agreement between tests in 93% of the patients, suggesting similar diagnostic accuracy. Specificity was 91% (19). The accuracy of bedside ER testing among patients without prior coronary angiography might be less diagnostic for spasm, due to provocation of occult obstructive coronary disease-related ischemia.

Safety and Practice Guidelines

Contemporary reports suggest that provocation testing is relatively safe (18); however, there are older reports of refractory spasm and recurrent spasm resulting in prolonged ischemia, MI, and death (52,53). A recent observational study evaluated 1,244 patients with vasospastic angina who underwent IC provocation tests (40% ER, 57% ACH, 2% ER+ACH, 1% other) (18). The overall incidence of arrhythmic complications was 6.8%, which is comparable to 7.0% during spontaneous angina events. They reported a 5.5% major adverse cardiovascular event rate during the 32-month follow-up period. After multivariable analysis, mixed (focal and diffuse) multivessel spasm predicted major adverse cardiovascular events (adjusted hazard ratio: 2.84; 95% confidence interval: 1.43 to 6.03, $p < 0.01$), but provocation-related arrhythmias—defined as ventricular tachycardia, ventricular fibrillation, and bradyarrhythmias—did not (18).

Prior American College of Cardiology/American Heart Association guidelines support limited use of provocative testing for spasm (54); however, current guidelines do not address this generally or specifically (e.g., invasive vs. noninvasive, ER vs. ACH, IC vs. IV administration) (56–58), whereas other international practice guidelines do (Table 2).

Conclusions

Provocative testing is effective for diagnosis of CS. Testing might be appropriate in properly-equipped facilities with experienced physicians for patients without obstructive coronary artery disease presenting with suspected variant angina, as outlined in our recommended algorithm (Figs. 1 and 2) (59). Both ACH and ER seem to have comparable diagnostic yield. With ER provocation testing, IC testing rather than IV is useful in identifying the culprit vasospastic vessel and allows for treatment of refractory spasm. There is a paucity of safety data on the use of bedside ER provocation testing with echocardiography monitoring. Larger, ethnically-diverse studies that include more women are needed to generate evidence-based guidelines with regard to the effectiveness and safety of ER and ACH provocation testing for the diagnosis of CS.

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Key Words: acetylcholine ■ coronary spasm ■ ergonovine ■ Prinzmetal's angina ■ provocation testing.