# Invasive Evaluation for Coronary Vasospasm

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## Abstract

Vasospastic angina (VSA) occurs at rest and on exertion, with transient electrocardiographic ischemic changes. VSA presents with spontaneous coronary artery spasm (CAS); it has been associated with stable angina, acute coronary syndromes, and sudden cardiac death. CAS can be identified in normal arteries or non-obstructive coronary atherosclerosis, but is also prevalent in patients with coronary artery disease. The diagnosis is made with invasive coronary reactivity testing with provocation using acetylcholine (Ach). Epicardial spasms can be visualized through coronary angiography as a reversible epicardial vessel narrowing, while the diagnosis of microvascular spasm can be made when angina symptoms and ECG changes happen following intracoronary Ach without epicardial spasm. Identification of CAS allows for risk stratification and specific therapies targeting endothelial dysfunction and paradoxical vascular smooth muscle cell constriction. Therapies include calcium channel blockers as monotherapy or in a combination of a dihydropyridine and non-dihydropyridine. Short-acting nitrates offer acute symptomatic relief but long-acting nitrates should be used sparingly. This current update on invasive evaluation of VSA discusses unified Ach protocols.

## Keywords

Coronary vasospasm, coronary reactivity testing, acetylcholine, MI with non-obstructive coronary arteries, ischemia with non-obstructive coronary arteries

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Vasospastic angina (VSA) was first described by Prinzmetal et al., who said it was a variant of angina pectoris.[1] This variant angina occurs at rest and during exercise with classical angina and is accompanied with transient ECG changes resulting from partial to complete occlusion of the coronary arteries.

Patients with VSA present with spontaneous coronary artery spasm (CAS), which can manifest in multiple ways, ranging from stable angina, acute coronary syndromes, and sudden cardiac death.[2,3] CAS is heterogenous and can be found in patients with and without coronary atherosclerosis. This process can be visualized through invasive testing with coronary angiography, either spontaneously or after provocation; while focal or diffuse spasm in the epicardial arteries can be identified, it can also affect microcirculation.[4,5]

This review discusses the pathophysiology, clinical spectrum, and current updates on invasive evaluation of coronary vasospasm.

## Epidemiology

Given the dynamic nature of the disease, the exact prevalence of CAS is unknown. Prevalence depends on the population being studied, and is likely to be influenced by patient selection on the part of clinicians who actively investigate and treat VSA as a cause of chest pain in people without evidence of obstructive coronary artery disease (CAD).

Therefore, studies reporting the prevalence of CAS show a high variation. Ong et al. reported that nearly half of patients who underwent diagnostic angiography for assessment of stable angina demonstrated a normal or non-obstructive coronary angiogram.[6] Among the 124 patients who had angiographically normal or near normal coronary arteriography and underwent subsequent intracoronary (IC) acetylcholine (Ach) testing, 77 had provoked coronary spasms. Among the 77 patients with CAS, 35 (45%) of them demonstrated epicardial spasm with 42 (55%) showing microvascular spasm (MVS).

A multicenter study from Japan enrolled patients with suspected non-ST-elevation MI (NSTEMI) who underwent cardiac catheterization.[7] The Ach provocation test was performed in 221 patients with a coronary angiogram showing no CAD, and 175 (79.2%) of them had a positive study.

Montone et al. prospectively evaluated patients with a diagnosis of MI with non-obstructive coronary arteries (MINOCA).[8] All patients underwent coronary angiography with invasive provocative testing using Ach or ergonovine (ER). In 46.2% of patients, the test was positive. More recently,

a study with a larger population (n=317) with ischemia with non-obstructive coronary arteries (INOCA) or MINOCA investigated the prevalence of CAS and found 58.4% had a positive response to Ach test.[9]

Pirozzolo et al. reported in a study of patients with NSTEMI but without a culprit lesion that 58% had an abnormal Ach test, with 46% having epicardial spasm and 54% having MVS.[10]

In the CorMICA trial, 1,386 patients with stable angina who were referred for coronary angiography were screened for eligibility and 391 (28%) qualified for an invasive coronary angiography. In this cohort, 206 (53.7%) had obstructive CAD and 181 had non-obstructive or normal coronaries. Of the latter, 151 were enrolled in the study, where they were further evaluated with coronary reactivity testing. In this group, isolated CAS provoked by Ach was found in 17% of patients, while 21% were found to present with a combination of inducible vasospasm and coronary microvascular dysfunction (CMD). The predominant abnormality identified in this study was pure microvascular angina in 51% of patients (without spasm), highlighting the importance of vasospastic provocation as part of a comprehensive invasive ischemia assessment in patients with INOCA. Moreover, only 11.3% of the patients had no abnormalities provoked by either Ach or adenosine and were qualified as non-cardiac chest pain patients, which underlines the importance of identification of the proper type of INOCA rather than blindly empirically treating the global INOCA population in the same way.[11]

In current practice, in patients with normal or near normal coronary angiograms, provocative testing with Ach or ergot derivatives is infrequently performed. CAS therefore remains underdiagnosed and undertreated, as patients with chest pain syndromes are often not referred for further provocative testing to document VSA.

## Presentation of Coronary Artery Spasm

Patients with CAS may present with angina at rest or on exertion, and chest pain can be accompanied by diaphoresis, nausea, vomiting, and syncope.[12] Compared to classical angina, VSA occurs more frequently in the evening or early morning and at rest; it may be precipitated by hyperventilation, and may have a more rapid response to sublingual nitroglycerin (NTG). CAS can also be associated with tachyarrhythmia, bradyarrhythmia, and ventricular arrhythmia, leading to ICD implantation in some patients.[13]

CAS can present in different ways, depending of whether it is due to epicardial spasm or MVS. Although classically understood to present with ST-segment elevation, CAS due to either epicardial spasm or MVS may present with other ischemic changes on an ECG, such as ST-segment depression and prominent U waves. Differentiation between the etiologies of epicardial spasm and MVS requires invasive testing.[12]

Montone et al. used invasive provocative testing to differentiate between epicardial spasm and MVS.[14] Patients with confirmed epicardial spasm were often men, smokers, presented with MINOCA, and had an increased burden of coronary atherosclerosis. Patients with MVS had a higher prevalence of diastolic dysfunction.

Early studies suggested that patients presenting with complete and focal transient occlusion of a coronary artery after CAS provocation were found to have a non-significant plaque prior to the spasm at the occlusion level.[15] It was suggested that tolerance to spasm may be reduced in the presence of a plaque, as only a minor reduction in the radius will result in a major reduction of the lumen area. Therefore, only mild spasm can result in total occlusion of the coronary in patients with mild plaques already slightly reducing the lumen diameter or radius.

Notably, CAS is only one of many causes of MINOCA, and patients with MINOCA due to CAS are often initially misdiagnosed with MI resulting from coronary artery disease (MI-CAD) because of the presence of elevated troponins and symptoms consistent with cardiac ischemia. After improvement with NTG and nitroprusside, focal spasm is often found to be the cause of their angina.

Despite mechanistic differences between MINOCA and MI-CAD, studies have shown they have similar clinical outcomes regarding mortality and hospital readmission.[16] However, the most recent meta-analysis showed a lower 12-month all-cause mortality in patients with MINOCA (3.3% compared to 5.6% with MI-CAD; OR 0.60 (95% CI [0.52–0.70]); p<0.001).[17] Still, such a mortality rate is higher than expected for a population of the same age.

## Risk Factors for Coronary Spasm

CAS is more prevalent in women than in men, and women are more likely to have MVS than epicardial spasm.[13,18] Coronary spasm is more likely to occur before and during menstruation when estradiol levels are low.[19] Low estrogen has been shown to dysregulate nitric oxide (NO) production, a vasodilatory compound that is reduced in CAS.[19] Hormonal supplementation may be beneficial in these patients.

Smoking, a cause of low-grade inflammation, and elevated high-sensitivity C-reactive protein from any cause are recognized risk factors for CAS.[20] Similarly, environmental exposure to air pollution has also been associated with MINOCA and positive provocative testing.[21] Varying levels of particulate matter in the environment may also differentially predispose individuals to epicardial or MVS.

Acute inflammatory states and stressors can also precipitate vasospasm, including physical or emotional stress, alcohol use, cocaine abuse, and magnesium deficiency.[22] Cocaine-induced spasm may be orchestrated through increased release of vasoactive mediators, such as histamine from mast cells, although the exact mechanism is unknown. Various drugs can also induce CAS, including psychostimulants, vasoconstricting agents, and immunosuppressive medications, such as calcineurin inhibitors and fluorouracil.[13,23]

Myocardial bridging is an anatomical variant in which the epicardial coronary arteries pass through cardiac muscle layers and become compressed during systole. Montone et al. found that patients with this condition are more likely to have a positive acetylcholine test and it may be a predictor of MINOCA.[24]

CAS can be a component of a more systemic syndrome in some patients. Patients with CAS may present with concomitant vasospastic disorders such as Raynaud's phenomenon and migraines. Several case reports have described Kounis syndrome, an acute coronary syndrome that includes VSA, which is triggered by an allergic reaction and involves mast cell activation.[25] Elevated mast cells and eosinophils may predispose patients to vasospasm due to infiltration of these cells into the coronary artery adventitia.[26,27]

The Japanese Coronary Spasm Association (JCSA) developed the JCSA prognostic risk score for patients with VSA based on data from 1,429 patients, including longitudinal follow-up.[28] This risk score is composed of

seven predictors of major adverse cardiac events (MACE): smoking; angina at rest alone; organic coronary stenosis; multivessel spasm; ST-segment elevation during angina; β-blocker use; and history of out-of-hospital cardiac arrest. MACE in this study was a composite of cardiac death, non-fatal MI, unstable angina, heart failure, and appropriate ICD shock at a median 32 months. Patients were stratified into one of three prognostic groups: low (score 0–2); intermediate (score 3–5); and high (score 6). Each increment in risk stratum was associated with a two- to three-fold relative risk increase for MACE.[28]

## Pathophysiology of Coronary Spasm and Agents Used for Diagnosis

Coronary arteries control the blood supply to the cardiac tissues by balancing vasoconstriction and vasodilation. Multiple mechanisms that contribute to the pathogenesis of CAS have been proposed. Local or diffuse coronary artery hyper-reactivity and inappropriate vasoconstrictive events play a role in CAS.

Vasoconstrictor stimuli can induce spasm in coronary segments or, sometimes, more diffusely along the artery and in multiple arteries in patients with VSA.[29]

Vascular smooth muscle cell (VSMC) hypercontractility causes direct vasoconstriction at the site of CAS where endothelium function could be preserved.[30] The endothelium plays an important role in the regulation of coronary vascular tone; one of the components of the endothelium-derived relaxing factor (EDRF) is the NO released by the endothelial cells, which promotes vasodilation.

In conditions of endothelial dysfunction (ED) and atherosclerosis, insufficient secretion of EDRF causes inappropriate vasoconstriction. Several triggers, such as stress, ER, or Ach, can provoke this process.[31]

Rho-kinase (ROCK) is an enzyme that plays a pivotal role in the organization of the actin cytoskeleton of human cells. Increased ROCK activity may cause ED and increased VSMC contractility as well as activate inflammation and vascular remodeling. ROCK plays a role in the pathogenesis of coronary vasospasm, which makes it an appropriate target in patients with VSA.[32] ROCK reduces myosin phosphatase activity by phosphorylating the myosin-binding subunit of the enzyme and thus augments VSMC contraction at a given calcium concentration; this is known as calcium sensitization, and is believed to explain the mechanism of vasospasm in the coronary arteries.[33]

Other studies have proposed that ROCK can reduce the bioavailability of NO in humans with atherosclerosis.[34] Low-grade inflammation has also been found to be correlated to CAS, with inflammation biomarkers (C-reactive protein, monocyte chemoattractant protein-1, and interleukin-6) found to be elevated in patients with VSA.[35]

Autonomic nervous system perturbation may also lead to coronary vasospasm induced by catecholamines, or by other stimuli such as exercise, or a cold pressor test that increases sympathetic tone.[36,37] Magnesium deficiency, oxidative stress, and genetic predisposition have also been found to contribute to coronary spasm.[38,39]

Ach and ER are the two agents used to test the endothelium-dependent mechanisms of epicardial vasomotor disorders. Those vasodilatory agents act paradoxically by causing vasoconstriction in the presence of a dysfunctional endothelium. While the exact mechanisms of ED remain unclear, it is likely to be multifactorial, involving abnormally increased levels of vasoconstrictor agents such as endothelin-1 in atherosclerotic tissues and impaired availability of vasodilatory substances such as NO and EDRF.[40–43] Additionally, abnormal signal transduction involving G-protein and other metabolites from the endothelium to the underlying VSMCs may contribute to the abnormal hyperactivity.[44,45]

ER is an ergot alkaloid with serotoninergic agonism inducing hypersensitivity of the 1D serotonin receptor subtype in vascular smooth muscle cells. This agent was one of the first drugs used to study VSA.[44] Originally, ER was injected intravenously and later IC, and ischemia was assessed through electrocardiographic changes, echocardiographic wall motion abnormalities, or angiography. However, the occurrence of complications, such as ventricular arrhythmias, acute MI, hypotension, and death, led to non-invasive administration of any provocation drug no longer being carried out. Moreover, ER is no longer available in the US and in most regions of the world.

Ach is a neurohormonal parasympathetic mediator of coronary vascular tone. In normal physiologic healthy endothelium, Ach binds to muscarinic receptors (M3 receptors), causing calcium-dependent vasodilation through endothelial NO production, microvascular smooth muscle dilation, and a subsequent increase in coronary blood flow (CBF).

Ach also binds to M3 receptors directly on VSMCs, again in a calcium-dependent physiology, causing paradoxical direct vasoconstriction of arterioles and epicardial vessels when it is given in higher doses. Ach can also unmask impaired vasorelaxation ability of epicardial vessels.[46–49]

There are several variations in provocation testing, which are outlined below.

## Diagnosis

### Diagnostic Criteria

When VSA is suspected, diagnostic work-up should be pursued. VSA diagnosis has three components: clinical manifestations of VSA; documentation of myocardial ischemia during spontaneous episodes; and demonstration of CAS.

The most commonly used diagnostic criteria were proposed by the Coronary Vasomotion Disorders International Study Group (COVADIS) and have three elements: nitrate-responsive angina during spontaneous episode; transient ischemic ECG changes during spontaneous episode; and CAS, defined as transient total or subtotal coronary artery occlusion (>90% constriction) with angina and ischemic ECG changes either spontaneously or in response to a provocative stimulus.[50]

Vasospasm can involve both epicardial and microvascular compartments of the coronary circulation. When CAS follows IC Ach with usual symptoms of angina and ischemic ECG changes, it is considered an epicardial spasm. When angina symptoms and ECG changes happen following IC Ach without a change in epicardial diameter, a diagnosis of MVS or endothelial-dependent CMD will be made.[18,51,52]

The diagnosis of microvascular angina proposed by COVADIS requires: the presence of symptoms suggestive of myocardial ischemia; objective documentation of myocardial ischemia; absence of obstructive CAD <50% coronary diameter reduction and/or fractional flow reserve (FFR) >0.80); and confirmation of a reduced coronary blood flow reserve and/or inducible MVS.[53]

In patients who undergo testing with Ach with a coronary Doppler wire, the diagnosis of epicardial ED can be made using infusion of low endothelial doses of Ach with simultaneous measurements of hyperemic CBF and coronary flow reserve (CFR-ACH).

In patients with a normal endothelial function, Ach results in a >20% increase in coronary diameter from baseline and in an increase in CBF by >50%. Diagnosis of ED or endothelial dependent CMD is made on the basis of a lack of increase of CBF>50% and a CFR-ACH of ≤1.5, and a lack of dilation or visible but not severe spasm seen on angiogram or assessed by quantitative coronary angiography.[54]

The use of the thermodilution wire in the assessment of ED has not been widely adopted and has not been validated to measure CBF or CFR-ACH with Ach. Therefore, thermodilution wire techniques are used only to assess endothelial-independent CMD with adenosine-induced hyperemia. The vessel diameter change during hyperemia under Ach are normally assessed with quantitative coronary angiography.

## Invasive Testing Indications

Chest pain is the most common symptom of ischemic heart disease. Up to 70% of patients who experience angina symptoms or have clinically suspected MI and undergo coronary angiography have a normal or near normal angiogram.[55] These patients are now suspected to be presenting with INOCA in the setting of stable angina or with MINOCA in the setting of acute MI.

Historically, these patients would not have been evaluated for potential alternative causes of cardiac chest pain, and were commonly classified as having non-cardiac or atypical chest pain, even when the symptoms were suggestive of a cardiac source (retrosternal squeezing sensation with radiation to arms, nausea, and diaphoresis, for example). Alternative causes of MI, such as embolization or spontaneous coronary artery dissection, would also be primarily investigated.

Making a clear diagnosis is of paramount importance, and includes identifying MI mimickers, such as myopericarditis, takotsubo cardiomyopathy or pulmonary emboli. CAS is implicated in 46% of patients with MINOCA and, in this population, provocative testing has been shown to be safe and can be used to identify spasm as a primary cause of MI.[8] INOCA is associated with a lower quality of life and a higher incidence of adverse events, such as increased mortality, morbidity, and rehospitalization rates, hence the importance of identifying patients with CAS or mixed VSA and CMD.[56,57]

Patients with typical chest pain, signs of ischemia, or MI with unobstructed coronaries warrant further evaluation with testing to identify the underlying etiology. While non-invasive stress studies can sometimes identify ischemia in patients with spasm, the resting nature of the condition makes it often difficult to identify this way. Moreover, pharmacological administration of IV vasodilators, such as dipyridamole or adenosine, will mitigate spasms and often lead to negative imaging studies.

As such, invasive provocative testing remains the gold standard, as part of the work-up for INOCA diagnosis. Procedures should be performed in centers that have the equipment, drugs, and expertise to assess CMD and spasm. The indications for provocative spasm testing have been defined by the COVADIS group.[58]

The decision on who should undergo invasive provocation of spasm should be individualized, after the potential benefits of making the appropriate diagnosis and guiding patient therapy and procedural risks have been weighed up. This is discussed below.

As most patients will have already undergone a coronary angiography showing non-obstructive coronaries, insurance providers can sometimes deny pre-authorization for an additional angiography, and further explanation from the clinical provider with expertise in the field is often required to justify the procedure.

In addition to making a proper diagnosis and reassuring patients without clear evidence of spasm, avoiding empirical medication trials will avoid drug side-effects.

## Procedure Description

## Pharmacological Provoking Agents in Invasive Spasm Testing

Invasive pharmacological assessment of VSA is performed in the cardiac catheterization laboratory with functional coronary angiogram and coronary reactivity testing. It is performed with IC injection of Ach, which is the most commonly used vasospastic agent and accepted widely for the definitive diagnosis of CAS in patients with INOCA.[46,59]

While most operators will deliver the drug from the tip of a guide catheter with a non-selective bolus delivery in the left main, others will prefer the use of an end-hole or dual-lumen microcatheter advanced selectively into the left anterior descending (LAD) or left circumflex (LCx).

All medications, food and substances with vasoactive properties need to be discontinued at least 48 hours before testing to allow for washout of these agents, as a residual effect would counteract provocation testing and consequently decrease study sensitivity.[60–62]

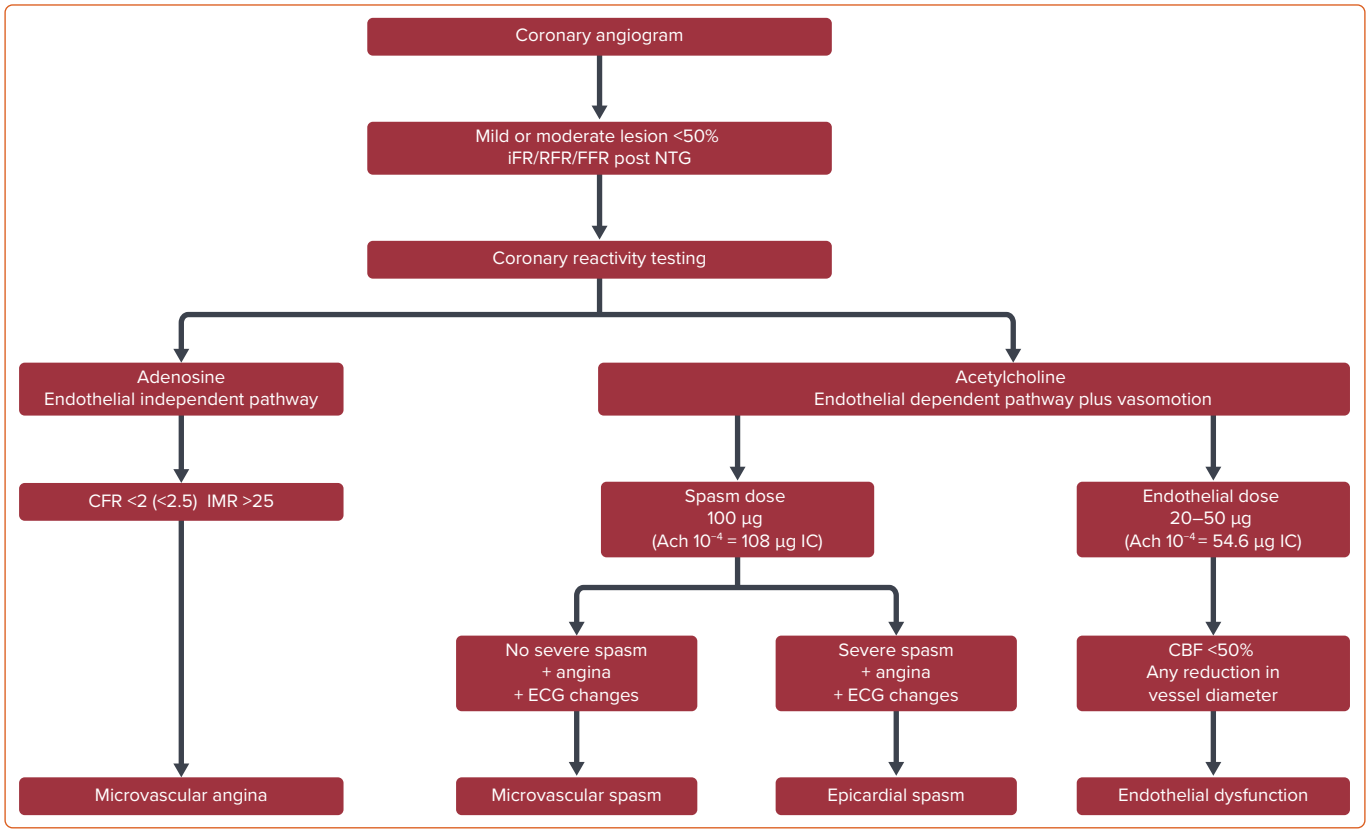
Safety parameters and the dose administered will vary, depending on the side of the coronary tree being tested. For the right coronary artery (RCA), insertion of a temporary pacemaker may be considered because of the potential for severe bradycardia or heart block.

Ach testing entails injecting two or three incremental doses of Ach to observe the presence or absence of spasm response. Currently, multiple protocols for Ach exist, which suggest various dosages, dilutions, infusion times, target vessels, and angiographic thresholds for positive test differences.[63,64] A consensus has not been reached over the various protocols, which contributes to the variation reported previously and warrants a deeper understanding of CAS.

Methods of administration are described in the procedural steps below.

*Figure 1* illustrates the procedural steps for provocative vasospasm. Access for the procedure was traditionally femoral to avoid use of calcium channel blockers (CCB) or nitrates, which can blunt the coronary response to Ach. However, the radial artery can safely be used and the vasoactive radial cocktail can vary depending on local practices (i.e. none, CCB, and/or nitrates), and it should be kept in mind that this may blunt the reaction to Ach. In some protocols, NTG is used with the initial diagnostic angiogram and before measurement of iFR/RFR; this may precede Ach infusion and, again, blunt the response. In some protocols, the sequence of administering Ach precedes adenosine and NTG to avoid any possible effect on the vessels' reactivity to Ach. The use of a smaller, thin-wall 6 Fr sheath and guide catheter is better to reduce

## Figure 1: Procedural Steps for Coronary Function Testing




*Ach = acetylcholine; CBF = coronary blood flow; CFR = coronary flow reserve; FFR = fractional flow reserve; IC = intracoronary; iFR = instantaneous wave-free ratio; IMR = index of microvascular resistance ; LCx = left circumflex; LM = left main; NTG = nitroglycerin; RFR = resting full-cycle ratio.*

potential spasm; 6 Fr catheters are required for thermodilution methods if also performed.

The procedure begins with a baseline diagnostic angiogram of the left coronary artery (LCA) and the RCA, which, in some protocols, is done before any medication administration and in others after NTG; this serves as a reference vessel diameter in a relaxed state.[60] A Doppler or thermodilution coronary guidewire is inserted into the coronary artery (which will be used to assess CBF and pressures) and an angiogram is performed to rule out any guidewire-induced or spontaneous vasospasm.

For any moderate to severe epicardial stenoses resting indices, instantaneous wave-free ratio (iFR) and resting full-cycle ratio (RFR) can be performed after NTG without adenosine to rule out hemodynamically significant epicardial disease, which excludes further testing for variant angina.

The measurement of fractional flow reserve (FFR) under IV adenosine is optional, depending on the epicardial stenosis status. In normal coronaries, these measurements are not mandatory. Single-vessel selective injection of the vasoactive provoking agent Ach is performed. The vessel of choice is usually the LAD, which perfuses the biggest portion of the myocardial mass and the corresponding microcirculatory bed. However, the LCx and the RCA can also be used. Single-vessel LAD assessment and analysis leads to a quicker procedure, limits the likelihood of bradycardia that can occur in dominant LCx or RCA systems, and can prevent rare global coronary vasospasms, which in turn can lead to ventricular arrhythmias as a complication. Multivessel analysis may be needed if the initial coronary tests are negative and clinical suspicion remains high.

Injection of provocative agents at different concentrations from low to spasm dose will then follow. An initial test dose of 20 µg of Ach through either a slow injection bolus over 20–60 seconds or via infusion of 0.182 µg/ml at 1 ml/min over 3 minutes for a total of 0.546 µg is given to confirm no severe adverse reaction to Ach. Incremental doses with 3–5 minutes washout periods will follow (*Figure 2*).[11,65,66]

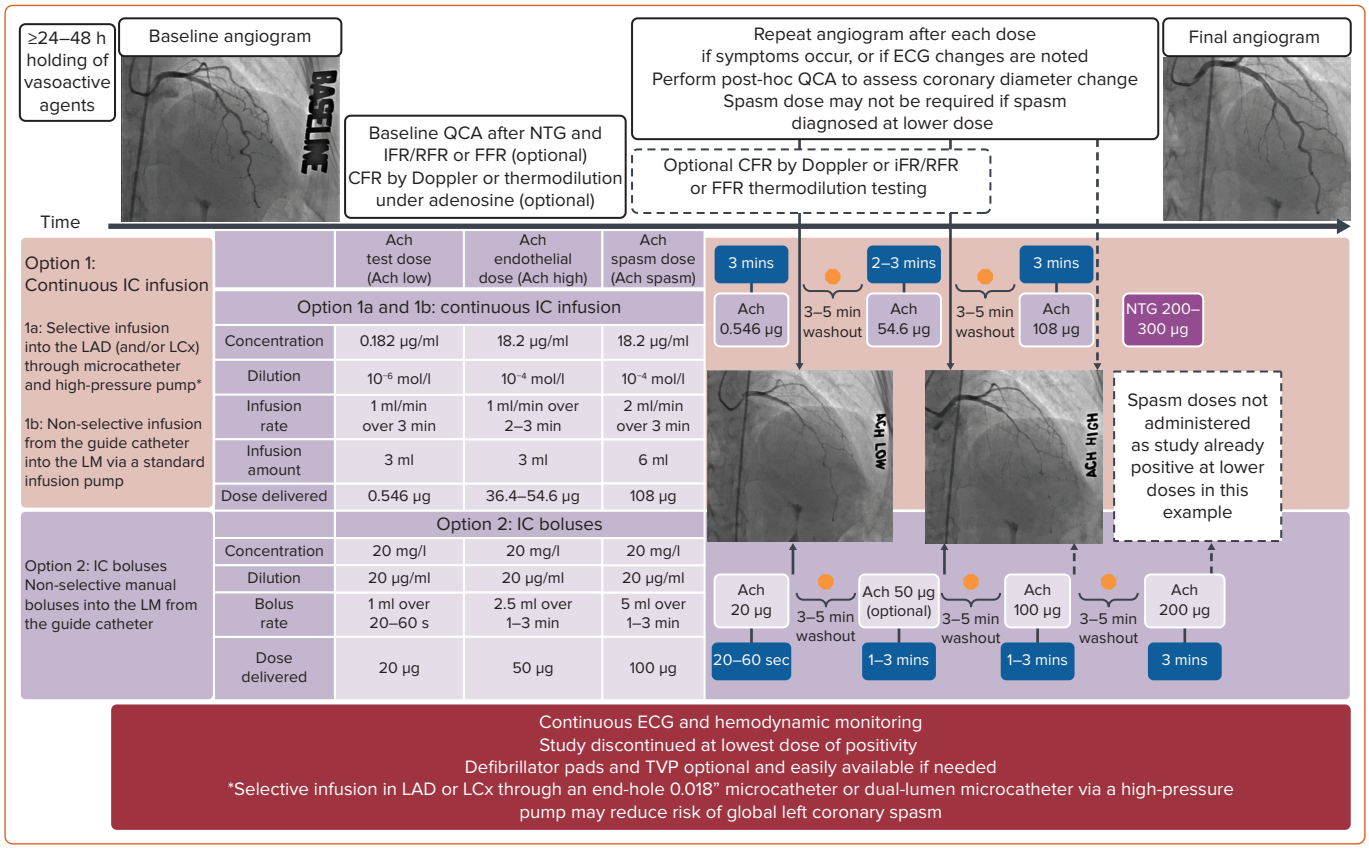
A maximum dose of 200 µg through slow bolus can safely be administered without affecting the specificity; however, this higher dose is predominantly used in men when the suspicion of CAS is high and spasm is not provoked by the traditional spasm dose of 100–108 µg, and no greater than 80 µg should be administered in the RCA. However, a recent meta-analysis did not show any major difference in safety or positivity rate from maximum doses of Ach of 100 µg versus 200 µg.[67]

*Figure 2* also displays commonly used protocols with different Ach doses, administered either through a microcatheter directly into the coronary or via boluses from the guide catheter.

A study will be considered positive if a transient, total, or sub-total occlusion of a coronary artery with signs/symptoms of myocardial ischemia (anginal pain and ischemic ST changes) is provoked or is spontaneously observed without any provocation.[62,68] When it occurs at any given dosage, a diagnosis of spastic angina can be made and no further escalation of the dose is required.

Lastly, regardless of the provocation medication administered, NTG is injected afterwards and repeat angiography is performed to confirm reversal of the spasm and coronary reactivity to NTG.[62]

## Figure 2: Spasm Provocation Testing with Incremental Doses of Acetylcholine




*Ach = acetylcholine; CFR = coronary flow reserve; FFR = fractional flow reserve; IC = intracoronary; iFR = instantaneous wave-free ratio; LAD = left anterior descending; LCx = left circumflex; LM = left main; NTG = nitroglycerin; RFR = resting full-cycle ratio; TVP = transvenous cardiac pacing; QCA = quantitative coronary angiography.*

Throughout the study, the patient is monitored for angina symptoms and with continuous 12-lead ECG and hemodynamics.

Repeat angiography will be performed in the same projection as the baseline, without catheter or side branch overlap. When vasospasm occurs, pictures are obtained at any dosage of Ach. With spasm, the vessel narrowing can be focal and localized in the main artery or in a branch of a large coronary artery, or be more diffuse from the proximal to the distal segment. *Figure 3* demonstrates an example of diffuse LAD vasospasm.

## Safety and Adverse Events

Despite a class 2a recommendation from the most recent American Heart Association/American College of Cardiology 2021 chest pain guidelines in patients suspected of INOCA, routine adoption of provocation testing has been limited, possibly due to safety concerns on top of limited availability.[69]

Additionally, IC Ach (the only provoking agent available in the US) remains off label due to the absence of safety studies, which adds to providers' apprehension. Ach used in the US is derived from intraocular agents diluted for IC use.

In the current era of selective coronary testing, several studies have reported low event rates, with the most recent meta-analysis from Takahashi et al. confirming a 0% mortality rate with 0.5% of patients presenting major complications, mostly reversible ventricular arrhythmias. The most common side-effects included hypotension, bradycardia, and transient paroxysmal AF, all of which collectively occurred <0.5% of the time and were mainly reversible. Events were more common with RCA compared with LCA testing, supporting current practice to focus on the LCA or selectively the LAD for testing.[67,70,71]

## Sex Differences in Testing

Though the prevalence of CAS has been shown to be greater in women than men, a small retrospective study of Japanese patients by Sueda et al. demonstrated that male patients had significantly higher positive testing rates with Ach compared with ER (80.6% versus 60.6%).[72] In the same study, more striking findings were noted in women, with a greater Ach sensitivity over ER (96.7% versus 32.8%). Overall, Ach-provoked spasms occurred more frequently both in men and women and this is therefore believed to be a superior testing method.

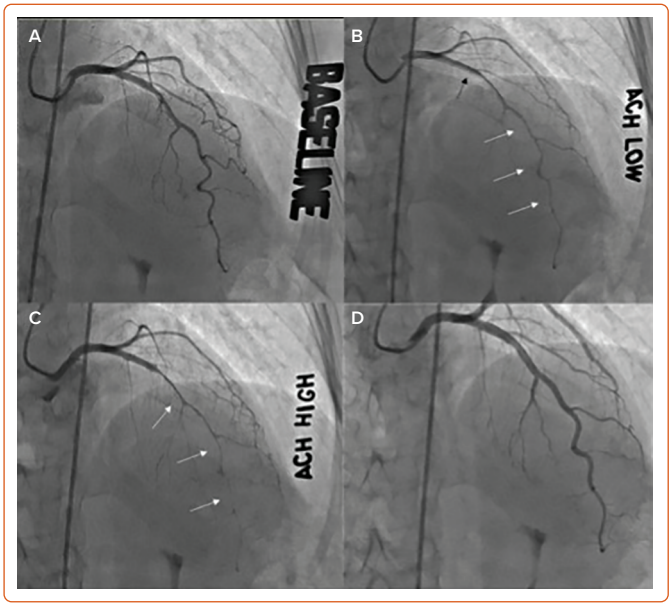
Other studies have shown that women may be more sensitive at lower doses of Ach compared to men.[73,74] Additionally, diffuse coronary spasms seem to be more prevalent over focal vasospasms in women with Ach provocation. This is notable because diffuse spasms have been shown to portend a better prognosis over focal ones.[75]

Lastly, sex differences in coronary function testing regarding epicardial spasms versus MVS have been noted, with one study showing men have more epicardial spasms than MVS compared to women.[76]

## Test Limitations

Patients can have catheter-induced spasms, which can be often observed in RCA proximal segments. Catheter-induced vasospasm usually resolves by catheter removal and NTG injection. This should be carefully assessed by the operator, as false-negative results have been observed and reported in the past.[77] One explanation for some false negatives is that the

### Figure 3: Case Example of Induced Coronary Spasm with Acetylcholine




*A: Baseline angiography. B: Microcatheter with Doppler guidewire in place in the LAD (black arrow); low-dose Ach selective infusion through the microcatheter with high pressure pump inducing moderate to severe spasm (white arrow). C: High-dose Ach confirming definitive coronary spasm, with >90% mid and distal LAD stenosis. D: Complete reversal of stenoses with IC nitroglycerin. Ach = acetylcholine; IC = intracoronary; LAD = left anterior descending.*

provocation test was performed when the disease activity of the coronary vessels was reduced because of the fluctuating nature of CAS.

Kashima et al. reported that false negative provocation tests were more often observed in patients on CCB at the time of and prior to the provocation test.[78] This underlines the importance of withholding medication with vasoactive properties for at least 48 hours before the spasm provocation study.[60,61]

If radial spasm occurs, administering a dose of 100 µg NTG and waiting for 15–30 minutes before starting the provocation procedure may be acceptable. Furthermore, using an Ach dose of 200 µg if spasm is not seen with the 100 µg dose, especially in patients for whom a high suspicion of CAS remains after the 100 µg dose, is advocated.[67]

## Impact of Positive Test on Management and Prognosis

A positive diagnosis carries a prognostic value of future increased cardiovascular events.[9] Several treatment strategies have been evaluated, some of which can help mitigate these negative outcomes.

Lifestyle changes and avoidance of precipitating agents are of utmost importance, as many patients are unable to tolerate medical therapy because of side-effects. Therefore, smoking cessation and avoidance of drugs that potentiate coronary vasoconstriction, such as cocaine and sympathomimetic agents, are especially important in patients with VSA.[79,80]

Furthermore, exercise and a healthy lifestyle will assure overall cardiovascular health. Statins and angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers have been recommended in most patients with ED if they can tolerate them, such as those with hypertension. Ishii et al. studied the effects of statin therapy on patients with VSA and found it was correlated with a lower rate of cardiovascular events in VSA without significant coronary atherosclerotic stenosis.[81]

More specific antianginal therapies such as CCB and nitrates remain the mainstays of therapy for VSA.[82] CCBs dilate VSMCs and have negative inotropic and chronotropic effects.[83] Most recently, they were studied in the EDIT-CMD trial, which showed no improvement in CFR but a reduction in CAS in patients with VSA who were on diltiazem 360 mg versus those on placebo.[84] A greater proportion of patients on diltiazem progressed from having epicardial spasm to MVS or no spasms at all compared to those on placebo (47% versus 6%; p=0.006). This study once again demonstrated that CCBs can alleviate epicardial spasm, without apparent effects on microvascular non-endothelium-specific CMD.

In practice, CCBs can be used in combination with one dihydropyridine agent (such as amlodipine or nifedipine) being used in addition to a non-dihydropyridine (verapamil or diltiazem) to potentiate each other's effect on VSMC relaxation while avoiding bradycardia. High doses of each agent will often be required to stabilize the disease.

CCBs have also shown to be beneficial when used in combination with a statin.[85] Yasue et al. randomized 64 patients with coronary spasm induced by intracoronary Ach into fluvastatin plus CCB versus CCB alone groups and found that adding fluvastatin reduced Ach-induced coronary spasm at 6-month follow-up.[86] CCBs are therefore the first-line therapy for INOCA attributed to coronary spasm, with improved prognosis, angina relief, and quality of life, and decreased severity of epicardial narrowing in response to provocation testing.

Nitrates help to reduce symptoms, dilate the coronary vasculature and reduce ventricular filling pressures.[87] Short-acting nitrates play an important role in the treatment of acute VSA episodes as much as for any acute angina episode for any patient with CAD, and sometimes in the chronic prevention of VSA in combination with CCB.[55,65]

Although nitrates remain widely used in patients with VSA, long-term use of long-acting nitrates may result in further ED, mediated by oxygen free radicals.[88] Long-term use of nitrates is also associated with tolerance and rebound vasoconstriction after drug discontinuation, which may be mediated by desensitization of soluble guanylyl cyclase, increased autocrine levels of endothelin, and vascular superoxide production, all of which increase vasoconstrictor sensitivity.[89]

As such, in several retrospective, observational cohorts, long-term use of nitrates in patients with vasospastic angina has been associated with higher risks of adverse cardiovascular events.[90,91] While nitrate use may simply be a marker of more severe underlying disease, long-acting nitrates should be reserved whenever possible as adjunct therapy in patients with VSA refractory to CCB.

β-blockers should be avoided in clear vasospastic syndromes, as alternative treatments with better evidence exist.[92] However, in patients with mixed VSA and CMD, most studies support the use of nebivolol for its vasodilatory effect, which may improve parameters of microvascular function without causing vasospasm. Further studies on nebivolol in VSA are needed.

## Conclusion

Coronary vasospasm is an important cause of INOCA and MINOCA. Diagnosis relies mainly on invasive cardiac catheterization with spasm provocation and reactivity testing.

There are multiple protocols for spasm provocation, with IC Ach being the most commonly used agent because of its availability, good safety profile, and ease of use. However, consensus on techniques and dosages for Ach administration are lacking, resulting in significant variability in methods and sometimes approaches to diagnosis.

There is a consensus, however, that treatment should be tailored according to the type of INOCA identified, and should therefore be based on the results of a provocation study that tests both endothelial pathway function with Ach and endothelial-independent function with adenosine to identify CMD.

Treatment of isolated VSA may differ from that for VSA in the setting of concomitant CMD or CAD. Confirming or excluding the diagnosis in this patient population will reassure the patient with non-cardiac chest pain, will give a clear diagnosis to a worried patient who had often been told "nothing was wrong in your heart," and prevent the blind empirical use of antianginals with side-effects such as hypotension or bradycardia.

In summary, invasive testing for coronary vasospasm is part of a comprehensive assessment of INOCA and MINOCA, with the aims of achieving symptom relief and improving the quality of life and prognosis in these patients. ❑

## Clinical Perspective

- Coronary vasospasm can be evaluated only through invasive studies with reliable accuracy.
- The most commonly used provocation agent in the invasive coronary artery spasm assessment is acetylcholine.
- Multiple protocols for acetylcholine use are available; practical and commonly used protocols are discussed in this paper.
- Unified protocols and results interpretation are paramount to accurate diagnosis and a standardized approach to treatment in vasospastic angina.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