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Review

A Practical Approach to Invasive Testing in Ischemia With No Obstructive Coronary Arteries (INOCA)

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ABSTRACT

Up to 65% of women and approximately 30% of men have ischemia with no obstructive coronary artery disease (CAD; commonly known as INOCA) on invasive coronary angiography performed for stable angina. INOCA can be due to coronary microvascular dysfunction or coronary vasospasm. Despite the absence of obstructive CAD, those with INOCA have an increased risk of all-cause mortality and adverse outcomes, including recurrent angina and cardiovascular events. These patients often undergo repeat testing, including cardiac catheterization, resulting in lifetime healthcare costs that rival those for obstructive CAD. Patients with INOCA often remain undiagnosed and untreated. This review discusses the symptoms and prognosis of INOCA, offers a systematic approach to the diagnostic evaluation of these patients, and summarizes therapeutic management, including tailored therapy according to underlying pathophysiological mechanisms.

RÉSUMÉ

Jusqu'à 65 % des femmes et environ 30 % des hommes présentent une ischémie sans coronaropathie obstructive (INOCA [*ischemia with no obstructive coronary artery disease*]) révélée à la faveur d'une angiographie coronarienne invasive réalisée pour une angine stable. L'INOCA peut être attribuable à une dysfonction microvasculaire coronaire ou à un vasospasme coronaire. Malgré l'absence de coronaropathie obstructive, les patients atteints d'une INOCA présentent un risque accru de décès toutes causes confondues et d'événements indésirables, notamment l'angine récurrente et des événements cardiovasculaires. Ces patients sont souvent soumis à des examens répétés, dont le cathétérisme cardiaque, ce qui représente des dépenses de santé à vie qui rivalisent avec celles associées aux coronaropathies obstructives. Dans bien des cas, l'INOCA échappe au diagnostic et n'est pas traité. Dans le présent article de synthèse, nous nous penchons sur les symptômes et le pronostic de l'INOCA. Nous proposons une méthode systématique d'évaluation diagnostique de ces patients et résumons les modalités de sa prise en charge thérapeutique, notamment un traitement adapté aux mécanismes physiopathologiques sous-jacents.

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See page 715 for disclosure information.

Ischemic heart disease (IHD) is quite common, occurring in approximately 8%-9% of Canadian adults.[1] Over the past few decades, interest has been growing in patients with stable IHD and no obstructive coronary arteries, commonly known as ischemia with no obstructive coronary arteries (INOCA). The literature suggests that up to 65% of

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women and 32% of men undergoing invasive coronary angiography for stable angina have INOCA.[2,3]

Historically, the findings of no obstructive coronary arteries in the presence of symptoms and signs of ischemia was thought to be benign and was labelled as "cardiac syndrome X,"[4] but more recent studies have shown that the diagnosis of INOCA is associated with poor outcomes.[5] Myocardial ischemia can occur as a result of a number of conditions other than obstructive coronary artery disease (CAD), including myocardial bridging, metabolic abnormalities, systemic inflammation, and coagulation abnormalities.[6] INOCA can be due to coronary microvascular dysfunction (CMD) or epicardial vasospasm, which are important to distinguish from one another, given that the medical management for these conditions is different.[4,5]

Despite the absence of obstructive CAD, patients with signs and symptoms of ischemia have a higher risk of all-cause mortality.[7] The 10-year results in the **W**omen's **I**schemia **S**yndrome **E**valuation (WISE) study showed a 20% risk of all-cause mortality, and a 12% risk of cardiac mortality.[7] Furthermore, CMD predicts worse long-term outcomes, including the occurrence of death, myocardial infarction (MI), stroke, and heart failure.[8-10] In addition, INOCA patients have high rates of recurrent angina and repeat angiography, poor quality of life, and high cardiovascular and estimated lifetime costs that rival those for obstructive CAD.[11,12] Given the lack of guidelines for the diagnostic workup for INOCA, these patients often are not provided with any diagnosis after angiography reveals "normal" coronary arteries. As a result, patients with INOCA are often untreated, are repeatedly hospitalized, and undergo numerous unnecessary repeat procedures without any diagnosis or relief from their symptoms.[13-15]

Recent interest in developing new techniques and revising old testing protocols has expanded the available armamentarium of tests focusing on INOCA. The purpose of this review is to discuss what is known about INOCA and offer a systematic approach to the evaluation and management of patients with INOCA.

Coronary Microvascular Dysfunction

Microcirculation vessels contribute significantly to vascular resistance and the regulation of coronary blood flow (CBF). They are responsible for maintaining a coronary perfusion pressure above 40 mm Hg, which is considered the lower limit of pressure required to prevent myocardial ischemia.[16,17] Below this threshold, subendocardial vessels are fully dilated to compensate. Under normal circumstances, coronary flow can increase up to 4-5 times above resting values with vasodilatation. Factors increasing resting flow include heart rate, systolic blood pressure, and left ventricular contractility. The ability to maintain constant CBF is termed autoregulation, and the capacity to increase flow above resting values is referred to as coronary flow reserve (CFR).

The vascular endothelium is responsible for regulating vascular homeostasis. Vascular tone is modulated by metabolic substances that promote vasodilatation and allows adequate increase in flow. Acetylcholine (ACh) is an important factor in this vascular response,[18] causing arterial dilatation through receptors on endothelial cells. However, it will cause paradoxical vasoconstriction when the endothelium is dysfunctional.

Table 1. Clinical criteria for microvascular angina

1. Symptoms of myocardial ischemia
   a. Exertional and/or rest angina
   b. Angina equivalents (eg, shortness of breath)
2. Absence of obstructive coronary artery disease (< 50% diameter reduction or FFR > 0.80) by:
   a. Coronary computed tomographic angiography
   b. Invasive coronary angiography
3. Objective evidence of myocardial ischemia
   a. Ischemic ECG changes during an episode of chest pain
   b. Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4. Evidence of impaired coronary microvascular function
   a. Impaired coronary flow reserve (≤ 2.5)
   b. Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing.
   c. Abnormal coronary microvascular resistance indices (IMR > 25)
   d. Coronary slow flow phenomenon, defined as TIMI frame count > 25

ECG, electrocardiogram; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; TIMI, thrombolysis in myocardial infarction.

Nitric oxide (NO) is another important endothelium-derived substance involved in the regulation of vascular function. Patients with CMD have increased vascular tone, resulting in limited ability to dilate in response to stress.[19,20] Impaired vasodilatation also contributes to CMD, and it can be attributed to reduced production or action of mediators such as endothelium-derived prostaglandins.[21] This type of dysfunction is referred to as structural CMD. Increased endothelin activity may also contribute to microvascular endothelial dysfunction.[22] Other patients have functional CMD, characterized by increased CBF at rest, which is likely to be caused by an increased resting NO synthase, the enzyme responsible for catalyzing the production of NO.[20] On the other hand, some potential mechanisms for CMD may be sex-specific, thereby explaining the increased prevalence of CMD in women. The difference between sexes can be explained by the loss of estrogen protective effect after menopause.[23-26] Estrogen induces NO production via activation of NO synthase, but after menopause, the reduction in estrogen may result in reduced NO production and impaired coronary microvascular dilatation.[27] Estrogen also prevents collagen deposition in tissues. Therefore, after menopause, perivascular fibrosis can occur, possibly leading to microvascular stiffening, dysfunction, and in some cases, vessels rarefaction. The decreased NO availability also causes impaired coronary microvascular dilatation.[28]

Finally, high levels of high sensitivity C-reactive protein (hs-CRP), a marker of chronic inflammation, have been found to be associated with increased frequency of ischemic episodes in patients with INOCA.[29] Systemic inflammation has been demonstrated to correlate with microvascular abnormalities, the fact that women have more inflammatory biomarkers at baseline, including hs-CRP, is well established. Also, some evidence indicates that psychosocial stress may play a role in the pathophysiology of INOCA.[30]

Other phenomena have been identified also as possible mechanisms for CMD, including microvascular remodeling, smooth muscle dysfunction, extramural compression, reduced diastolic perfusion time, and vascular rarefaction.[31]

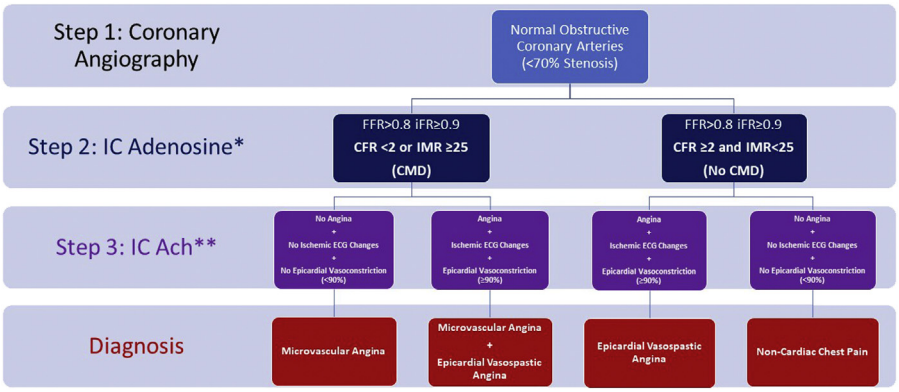

Figure 1. Invasive evaluation of ischemia with no obstructive coronary artery disease (INOCA). Ach, acetylcholine; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; ECG, electrocardiogram; FFR, fractional flow reserve; IC, intracoronary; iFR, instant flow reserve (also known as instantaneous wave-free ratio); IMR, index of microcirculatory resistance. *Intravenous infusion of adenosine (140 μg/kg per minute). **Incremental concentrations of ACh (10^{-6}, 10^{-5}, 10^{-4} mol/L) sequentially infused over 2 minutes, followed by vasospasm provocation testing (ACh bolus, 100 μg for left coronary artery or 50 μg right coronary artery). Adapted from: Kunadian et al.[34] with permission from Europa Group.

Clinical presentation

The classic symptoms of CMD include angina, exertional dyspnea, and possible heart failure.[26,32] Many patients with CMD have a normal physical exam, unless they are in heart failure. Although a positive stress test is one of the criteria for the diagnosis of CMD, conventional stress testing, with or without imaging, is not sensitive or specific for CMD, and it is no longer necessary to establish a diagnosis of CMD (Table 1).[32-34] CMD is most frequently diagnosed in women, usually at midlife. Traditional cardiovascular risk factors, such as smoking, diabetes, hypertension, dyslipidemia, and older age, are associated with CMD.[3,32,35,36] Also inflammatory diseases are associated with CMD.[37]

Documentation of myocardial ischemia

Noninvasive stress testing is often the initial step in assessment of chest pain. Using either noninvasive functional imaging of ischemia or anatomic imaging using coronary computed tomography angiography (CCTA) is currently recommended for establishing a diagnosis of IHD in patients with symptoms suggestive of angina.[38]

Excluding significant CAD

To make a diagnosis of CMD, ruling out obstructive CAD is necessary. Lesions causing < 50% of diameter reduction with conventional angiography are usually considered nonsignificant and are less likely to cause myocardial ischemia and symptoms. Arterial narrowing in the range of 50%-70% may benefit from coronary artery pressure flow measurements to assess the physiologic impact of the lesions. Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are the 2 recommended techniques (Fig. 1).[39,40] Both modalities determine the hemodynamic impact of a lesion by measuring pressure differences across the coronary artery stenosis, from which a ratio of pressures is derived. FFR measurement is performed at maximal hyperemia following adenosine injection. A value of < 0.80 is considered significant and suggests a high likelihood that the lesion will cause ischemia.[39,41-43] iFR, however, is obtained in a non-hyperemic setting, with significant values being < 0.90 (Fig. 1).

Assessment of the microvasculature

Given poor anatomic visualization of the microcirculation, functional assessment is critical. Such assessment is considered a class IIa (level B) recommendation in patients with symptoms of angina and no evidence of significant obstructive CAD.[34,38] The **Cor**onary **Mic**rovascular **A**ngina (CorMicA) study demonstrated that patients benefit when CMD is accurately diagnosed and properly treated.[44] Many noninvasive modalities allow for the assessment of CFR. For instance, transthoracic Doppler echocardiography of the left anterior descending coronary artery has been documented to assist in the diagnosis of CMD.[45-48] Unfortunately, this technique requires extensive training to use and can be very difficult to perform on the other coronary arteries. Positron emission tomography (PET) scanning is another technique that is well validated, accurate, and reproducible.[49,50] Cardiac magnetic resonance imaging has greater availability than PET scanning.[34] These modalities allow the assessment of non-endothelial dysfunction, and both PET and cardiac magnetic resonance imaging have been recommended by the 2021 American Heart Association/American College of Cardiology Guidelines for Evaluation and Diagnosis of Chest Pain, for the diagnosis of CMD in patients with INOCA.[51] However, only invasive coronary angiography allows for direct assessment of the coronary microvasculature pathophysiology, as described in the following section.

Periprocedural medication management. Prior to microvascular testing, all beta-blockers, alpha-blockers, calcium-channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists (ARAs), and diuretics should be held for at least 48 hours.[3,52,53] Nitrates should also be held, except for sublingual spray that can be used up to 4 hours before the procedure. Caffeinated products should be avoided for 24 hours before the procedure.[3,53] Nicotine should be avoided for at least 4 hours prior.[53]

CFR. As a surrogate of myocardial blood supply, CFR accounts for both epicardial and microvascular capacity, and it is obtained by the ratio between maximal and resting CBF.

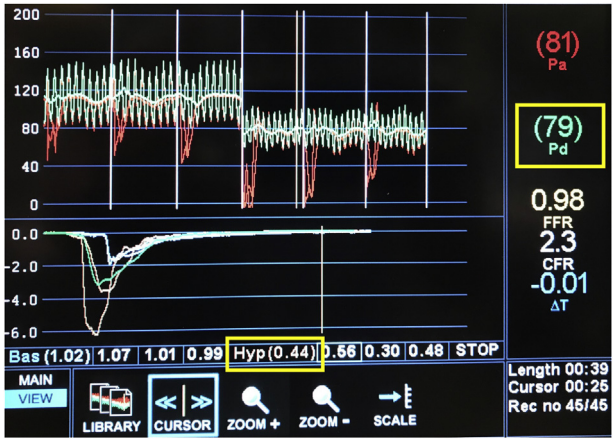

Figure 2. Practical measurements of index of microcirculatory resistance (IMR), where IMR = Pd × Hyp T_{mn}; IMR = 79 × 0.44; IMR = 35. Bas, baseline; CFR, coronary flow reserve; FFR, fractional flow reserve; Hyp, hyperemic; Pa, aortic pressure; Pd, distal pressure; T_{mn}, mean transit time.

Two invasive methods are presently available to measure CFR. The first technique involves a guidewire tipped with a piezoelectric ultrasound transducer. This Doppler guidewire, which is also equipped with a pressure sensor, allows phasic CBF velocity measurements. The second technique requires a pressure/temperature sensor-tipped guidewire that produces a thermodilution curve. CFR can then be derived from the numbers obtained.

Studies have shown good correlation between the 2 approaches, with some evidence suggesting that CFR obtained with thermodilution tends to be higher than when measured by Doppler.[54,55] Unfortunately, obtaining high-quality signals using the Doppler guidewire method of measuring flow velocity can be challenging, with the quality of CFR Doppler tracing being insufficient in approximately 8%-15% of patients.[54,56]

Index of microcirculatory resistance. The index of microcirculatory resistance (IMR) assesses the microcirculation without being affected by hemodynamics in the epicardial vessels.[57] The inverse of the mean transit time (T_{mn}) is strongly correlated with the absolute flow.[56,58] With the thermodilution method, using the same pressure/temperature guidewire used for CFR, IMR is derived by dividing the distal coronary pressure (Pd) by the inverse of the T_{mn}, a surrogate for coronary flow (Fig. 2). In theory, this index is independent of epicardial anatomy, since both distal pressure and flow tend to drop in the presence of significant epicardial coronary lesions. The T_{mn} must be obtained in a state of maximal hyperemia, during which minimal microvascular resistance is achieved. The equation for the calculation of IMR is derived from the relation between resistance (R), pressure gradient (ΔP), and flow (Q; Table 2). IMR has better reproducibility than CFR, as it is not significantly altered by hemodynamic fluctuations in heart rate, blood pressure, and contractility.[59,60]

Measurement technique. The thermodilution-based system allows the measurement of both CFR and IMR. Currently, the most-used system is the RadiAnalyzer console (Abbott Vascular, Santa Clara, CA). A therapeutic dose of intravenous (IV) heparin should be administered to achieve an activating clotting time of at least 250 seconds.[34] Following diagnostic angiography, the pressure/temperature sensor guidewire (PressureWire X Guidewire, Abbott Vascular) is flushed with normal saline (NS). The wire should then be connected to the transducer, and the whole system, including the aortic pressure transducer, should be set to zero. Following the aortic pressure and wire calibration, the wire should be inserted in the guide catheter and positioned at the tip of the catheter. After proceeding to equalization, the wire should be advanced into the distal two-thirds of the chosen vessel (> 6 cm).[61] The left anterior descending coronary artery is usually the target vessel.[34,36] The right coronary artery (RCA) or a dominant left circumflex may also be interrogated. Before starting the measurements, the operator should flush the guide catheter with room temperature NS for at least 30 seconds to clear contrast and air bubbles.[55] The guide catheter should be well engaged in the coronary ostium. Once the coronary flow is back to baseline, the operator will rapidly inject 3 mL of room-temperature saline a total of 3 times. Ideally, a 3-mL syringe and a 3-way valve stopcock should be used for injections. After the injections, the console will determine the resting mean T_{mn}. The operator will assess the recorded values and examine the T_{mn} curves. The temperature should decline by at least 2 °C. The difference between the 3 numbers should not be > 30%. Variations may happen due to instability of guide catheter engagement in the coronary ostium, coupled with a fast and strong NS injection. If variability is significant or if all 3 T_{mn} are > 0.25, measures should be repeated. The value found to be the outermost from the mean T_{mn} should be excluded and replaced with a new measurement. These are the baseline values.

Table 2. Derivation of index of microcirculatory resistance (IMR)

Absolute coronary flow ≈ $1/T_{mn}$
$R = \Delta P / Q$
$\Delta P = Pd - Pv$ and $Q \approx 1 / T_{mn}$
IMR = Pd − Pv / ($1 / T_{mn}$), where Pv is neglectable and can therefore be removed from the formula
When simplified, becomes: IMR = Pd × T_{mn}

R = IMR.

Δ P, pressure gradient; Pd, distal pressure; Pv, venous pressure; Q, flow; T_{mn}, mean transit time.

Once baseline values have been properly documented, hyperemia is then induced with IV adenosine. Adenosine allows the evaluation of non-endothelial-dependent microvascular reactivity. The target infusion rate is 140 mcg/kg per minute. Although the IV method is regarded as the gold standard, intracoronary (IC) adenosine also can be used to achieve hyperemia.[53,62,63] Side effects are more prevalent with IV infusion of adenosine.[64-66] However, because of a short-acting duration (~20 seconds), IC administration of adenosine is not the route of choice when a steady-state hyperemia is required.[67,68]

The clinician should wait 2 minutes to ensure a proper physiological response to the drug has occurred. Before proceeding to the measurements, the guide catheter should be flushed once again to clear any saline that may have warmed in the catheter. Three new thermodilution curves will then be obtained.

Once 3 values of T_{mn} are obtained in a state of hyperemia, the CFR can be calculated by dividing the resting T_{mn} by the

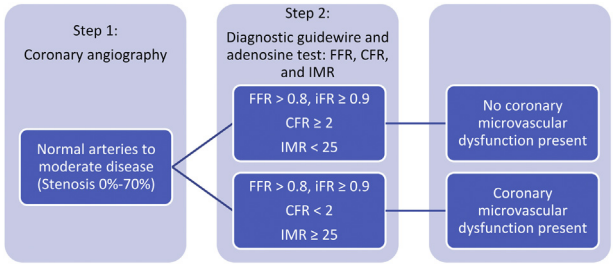

Figure 3. Invasive evaluation of ischemia with no obstructive coronary artery disease (INOCA I). CFR, coronary flow reserve; FFR, fractional flow reserve; iFR, instant flow reserve; IMR, index of microcirculatory resistance.

one obtained in hyperemia. IMR can be calculated as well, by multiplying the mean Pd (measured simultaneously during hyperemia with the same wire) by the T_{mn} obtained with hyperemia (Fig. 3).

ACh evokes an endothelial-dependent vascular response. It acts on epicardial vessels as well as on the microvasculature, allowing assessment of microvascular spasm, defined as the presence of chest pain and ischemic electrocardiogram (ECG) changes without evidence of coronary spasm during angiogram.[34] Change in CBF should be measured after ACh infusion to assess microvascular vasospasm (class IIb).[69] A normal response is defined as coronary artery dilatation of $>$ 5%, which suggests normal endothelial-dependent microvascular function.[53] An increase in CBF of $>$ 50% at the highest dose of ACh also suggests a normal endothelial-dependent microvascular function.[53]

Different protocols of ACh administration have been described.[6] The first method uses sequential infusion of incremental IV ACh at concentrations of 0.182, 1.82, and 18.2 mcg/mL at 1 mL/min for 2-minute periods using a mechanical infusion pump.[6,53,70] Measures of CFR and IMR are recorded with each dose. An alternative, more straightforward approach is manual intracoronary (IC) injection of Ach, starting with a test dose of 20 mcg followed by incremental doses of 20, 50, and 100 mcg injected at 5-minute intervals, over 20 seconds, into the left coronary artery (LCA).[71] Each dose should be diluted in NS to achieve a total volume of 5 mL.[71,72] Some centers inject this dosage over a 3-minute period.[6,73] The last and highest dose in either protocol is the dose used to assess for the presence of epicardial coronary vasospasm, in patients with suspected vasospastic angina (see below). A diagnostic angiogram is performed 1 minute after the start of each injection, as well as if angina symptoms or ECG changes occur. If the LCA shows no abnormal result, the same procedure can be repeated in the RCA with an incremental dose of 20-50 mcg. The maximal dose in the RCA is 80 mcg, and in the LCA, 200 mcg.[34,74] The final step is to repeat the angiography of the tested arteries after administration of IC nitroglycerin.

If the Doppler technique is chosen, the operator will be working with the ComboWire XT or the FloWire Doppler guide wire, both from Philips Healthcare. Only the ComboWire XT allows for measurement of pressure and flow velocity (FFR or iFR) without need of exchanging the guidewire. Once the wire is positioned into the artery, the console records a Doppler-derived blood flow velocity, and automatically derives the average peak average. Then, the CBF can be estimated with the following formula:

$$CBF = 0.5 \times APV \times (D^2 \pi) / 4,$$

where APV is the average peak average, and D represents the vessel diameter usually measured by quantitative coronary arteriography or IC imaging 5 mm distal to the Doppler wire. The CFR can be calculated by dividing the CBF during hyperemia by the value at rest.[53,75] This technology does not allow for measurement of IMR.

Reference values of CFR and IMR. According to most studies, a CFR value $\geq$ 2.0 is considered normal (Fig. 1).[76-82] In the WISE study, a threshold of 2.5 was chosen, which was also the lower limit of normal in studies with PET and other ischemia-identifying modalities.[76,83,84] The cutoff for normal IMR is $<$ 25, a value derived from the 3 main studies that reported IMR in healthy subjects (Fig. 1).[85-87]

Vasospastic Angina

Dysfunction involving the epicardial arteries usually presents as vasospastic angina (VSA), also known as Prinzmetal angina or variant angina, in which clinical manifestations are caused by reversible vasoconstriction of one or multiple epicardial segments of a coronary artery. Vascular smooth muscle hyperreactivity seems to be the driving mechanism. Endothelial dysfunction also contributes to the occurrence of this disorder. A contemporary study suggests that approximately 30% of patients with nonobstructive CAD undergoing coronary functional testing have both epicardial coronary spasm and increased microvascular resistance.[26] The coexistence of these 2 conditions also was associated with a worse prognosis.[88]

Clinical presentation

Episodes of VSA occur more often when patients are at rest, especially between midnight and early morning, and they can be precipitated by hyperventilation and by certain drugs, such as ephedrine-based products, cocaine, sumatriptan, and amphetamines.[89-91] These angina episodes will be associated with ischemic changes on ECG.[92]

The prevalence of VSA remains unknown, but it appears to be more frequent in Japanese populations, compared with White persons.[93] Smoking appears to be a risk factor for VSA, whereas diabetes, hypertension, and dyslipidemia are not associated with VSA.[94,95] The majority of VSA patients have a normal stress test, but in 10%-30% of cases, patients have exercise-induced spasm.[96-98] The Japanese Circulation Society (JCS) guidelines suggest a 24-48-hour Holter monitor recording to observe for ischemic ECG changes associated with chest pain episodes, particularly overnight episodes.[52]

Indications for coronary vasospasm testing

Provocative testing is indicated in patients suspected to suffer from VSA based on symptoms (class I indication).[92] Table 3 shows the diagnostic criteria for VSA. Testing is a class II indication for symptomatic patients who have been diagnosed with coronary spasm by noninvasive evaluation.[92]

Table 3. Diagnostic criteria for vasospastic angina

Nitrate-responsive angina, with at least one of the following:
Rest angina, especially between night and early morning
Marked diurnal variation in exercise tolerance, with worst capacity in the morning
Symptoms possibly precipitated by hyperventilation
Symptoms suppressed by calcium-channel blockers
Transient ischemic ECG changes during episodes, with 2 of the following in at least 2 contiguous leads:
ST segment elevation $\geq$ 0.1 mV
ST segment depression $\geq$ 0.1 mV
New negative U waves
Coronary artery spasm, defined as transient coronary narrowing of > 90% associated with ischemic ECG changes and anginal pain, either spontaneously or in response to a provocative stimulus (acetylcholine, ergonovine or hyperventilation)

ECG, electrocardiogram.

Episodes of VSA can be associated with transient ischemic ECG changes, which can be observed on a Holter or other monitor. Unfortunately, documentation of VSA on an ECG remains infrequent. The 2 main agents used for provocative testing for coronary reactivity and spasm are ACh and ergonovine (ER). A positive reaction is defined as a transient coronary narrowing of $\geq$ 90% associated with ischemic ECG changes and anginal pain.[92] Catheter-induced spasm, which tends to happen in the proximal RCA, should not be considered a positive response.

Procedure

All anti-anginal medications should be stopped 24-48 hours prior to testing, which should be performed in the morning if possible.[74] The standard method for provocation with ACh requires the insertion of a temporary pacing electrode in the right ventricle, with backup pacing at 40-50 beats per minute, as testing the RCA can result in refractory bradycardia.[52] Before provocation, an angiogram should be performed. The same views will be repeated after administration of the provocation drug. To document ischemic changes, a standard 12-lead ECG should be recorded either continuously or every 30 seconds.

Injection of Ach. The doses are similar to what is used for microvascular spasm testing: incremental doses of 20, 50, and 100 mcg, up to 200 mcg. If the LCA provocation does not evoke ischemia, the same procedure can be repeated in the RCA with an incremental dose of 20-50 mcg, up to 80 mcg (Table 4).

Injection of ER. Both IV and IC administration of ER have been described,[99] but IC injection is preferred, to avoid the risk of diffuse or multivessel spasm and possible hemodynamic instability that occurs with IV administration.[100] In the largest cohort of patients undergoing provocation testing with IV administration of ER, the risk of major adverse reaction, including MI and ventricular tachycardia, was 0.03%.[101] An additional advantage of IC injection is the possibility of individual evaluation of each coronary artery, for which numerous protocols have been previously described (Table 4).

The dose of ER is 20-60 mcg into the LCA. Testing in the RCA should be performed only if provocation fails in the LCA. ER should be injected over a period of 3-5 minutes, and angiography should be performed 1-2 minutes after injection, or with the development of chest pain and ECG changes.[52] A final angiography test post-IC injection of nitroglycerin should always be performed.

ACh vs ER. No significant difference in spasm provocation was shown when ACh and ER were administered in the same patients to check their response.[102,103] Different findings were observed in a retrospective analysis, in which the frequency of provoked spasm with ACh was significantly higher than that with ER tests.[104] ACh tends to cause a more diffuse spasm, compared to a more focal pattern with ER.[104] Testing with ACh followed by ER testing is safe. ACh should be tested before ER, given its shorter effect duration. A period of 10 minutes between the 2 is sufficient and safe.[74] Adding ACh to ER provoked spasm in 92% of the subjects who did not react to either ACh or ER alone.[105]

Hyperventilation. The hyperventilation test is a class II recommendation for patients suspected of having VSA.[52] A resting ECG should be obtained. Patients are then instructed to breathe rapidly (rate > 30 respirations per minute) for 5 minutes.[106,107] An arterial pH > 7.65 confirms effective hyperventilation.[108-110] At the onset of chest pain, hyperventilation should be stopped, and an ECG should be performed to document ischemic changes.

Complications

Serious cardiac complications, including sustained MI, ventricular arrhythmias, cardiogenic shock, and cardiac arrest, occur rarely with the administration of these vasoactive agents.[111] In a large cohort, the occurrence of serious cardiac complications on the day of the provocation test was studied. The rate of complications remained low, at < 1% in the group overall, with the risk being significantly higher with ACh use compared to ER use (0.4% vs 0.9%, $P < 0.001$).[112] A large cohort study (n = 21,512) assessed the occurrence of serious cardiac complications on the day of the provocation test. The rate remained low, at < 1% in the group overall, with the risk being significantly higher with ACh use compared to ER use (0.4% vs 0.9%, $P < 0.001$).[112] Defibrillation occurred in 0.6% of cases, with 1 periprocedural death. Previous smaller studies have reported a rate of cardiovascular death ranging from 0% to 3.2%[73,94,101,111,113,114]

Prognosis and Treatment

CMD is known to predict increased risk for major adverse cardiac events (MACE), including cardiovascular death,

Table 4. Provocation testing intracoronary (IC) dosing protocols

Acetylcholine	20−100 (LCA); 20−50 (RCA)[71,114,141,142]
	20−100 (LCA); 20−80 (RCA)[102-105,143]
	10−100 μg for suspected vessel; for contralateral vessel: 20−100 μg if LCA, 20−50 μg if RCA[144,145]
Ergonovine	20−60 (LCA); 20−60 (RCA)[114,141]
	1−30 (Reference[144])
	6−50 (Reference[100])
	64 (LCA); 40 (RCA)[102,104,105,143]

Values are μg IC, unless otherwise indicated.
LCA, left coronary artery; RCA, right coronary artery.

nonfatal MI, nonfatal stroke, and hospitalization for congestive heart failure.[36,115,116] CMD also is associated with progression to unstable angina.[117] This entity is a potential precursor of atherosclerosis and an independent predictor of cardiac mortality.[116,118,119] An abnormal IMR value also has been found to be associated with a poor prognosis.[60] Abnormal CBF response to ACh ialso is associated with an 8%-12% increase in the hazard of MACE over a median of 9.7 years.[8]

INOCA occurs more frequently in women. Additionally, women with INOCA appear to have worse outcomes, compared with those of men. A large Canadian study of 13,695 patients demonstrated that women with INOCA had an almost 3-fold higher risk of MACE (adjusted hazard ratio = 2.43, 95% confidence interval 1.08-5.49) within the first year of cardiac catheterization, compared with that for men.[120]

The optinal management of patients with INOCA remains unclear. Strict control of cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and smoking, is essential.[34] Patients with CMD and microvascular angina likely will benefit from treatment with a beta-blocker, to which a CCB may be added if needed. Treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker should be considered in all patients with coronary dysfunction, as these agents improve CFR and small-vessel remodeling,[121] and they also may contribute to symptom reduction.[122,123] Patients with low CFR may also benefit from ranolazine, although the evidence to date is conflicting, in terms of symptom benefit,[124,125] and it has no known prognostic benefit.[126] Short-acting nitrates may be used, but long-acting nitrates are usually not effective and/or are not well tolerated, and they may in fact worsen symptoms in this population, owing to a steal effect.[34,127] Statins also should be considered for their anti-inflammatory properties and their beneficial effect on coronary endothelial dysfunction.[128-131]

Vasospastic angina is often underdiagnosed, but it has important clinical consequences, including ischemia, acute coronary syndrome, arrhythmia, and sudden cardiac arrest.[132-134] A small study showed that positive spasm testing (n = 174 of 240) after injection of ACh was associated with death, recurrent acute coronary syndrome, and revascularisation.[135] However, another study (n = 437) found no such association.[136] The importance of identifying vasospasm resides in the benefit of tailored therapy, which has been shown to reduce angina and improve quality of life.[44] These patients should be started on a CCB as a first-line therapy, as this is an independent predictor of MI-free survival in patients with VSA.[137] Long-acting nitrates also can be used as adjuvant anti-anginal therapy.[34,138] With its coronary microvascular dilatory effect, nicorandil may be added to the therapy, but patients often report significant side effects.[139] Patients with VSA should receive lipid-lowering therapy if they meet the criteria based on current guidelines.[140]

Conclusion

Among patients, those with ischemic symptoms and no significant CAD are an important group. Standard evaluation with a uniform approach is needed. Evaluating patients for microvascular dysfunction and coronary vasospasm is safe. Identifying the underlying etiology for symptoms has prognostic value and allows initiation of appropriate therapy to improve quality of life. Additional studies are required to evaluate the effect of tailored therapy for microvascular disease or coronary vasospasm on other cardiovascular outcomes, including mortality.

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