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INOCA and microvascular angina in hypertensive women

INOCA y angina microvascular en la mujer hipertensa

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INTRODUCTION

Ischemic heart disease remains women's most common cardiovascular disease, accounting for one-third of all deaths. Myocardial ischemia can be caused by obstructive or non-obstructive atherosclerotic coronary disease, the latter known by its acronym INOCA (Ischemia with Non-Obstructive Coronary Artery disease), which includes non-significant epicardial coronary disease (< 50% stenosis), macro or microvascular coronary dysfunction (CMD), coronary artery spasm (CAS) and spontaneous coronary dissection.[1] Until now, it has been underdiagnosed due to the underutilization of functional studies evaluating microcirculatory or vasomotor disorders. It is estimated that 70% of patients with angina undergoing coronary angiography have INOCA. In the United States, they are around 3 to 4 million persons with this condition, and more than 60% correspond to women.[1,2] Women with INOCA are about four times more likely than men to have readmissions and cardiovascular mortality up to 32%.[3,4]

PATHOPHYSIOLOGY

The pathophysiology of INOCA is multifactorial, not yet fully clarified, and shares the same traditional risk factors associated with coronary atherosclerosis. Systemic arterial hypertension (SAH) is the most prevalent factor in 45 to 59% of cases.[4,5] The development of secondary left ventricular hypertrophy (LVH) is associated with symptomatic myocardial ischemia even without coronary lesions.[6] Bairey Merz et al[3] reported that SAH can also influence myocardial perfusion through vasomotor alterations, endothelial dysfunction (ED), atherosclerosis, and poor vascular autoregulation capacity due to remodeling or hardening of the coronary microvasculature, which together with the deregulation of the aortic-ventricular coupling and subendocardial hypoperfusion contribute to CMD.[6] Different studies have shown that ED includes attenuation of endothelium-dependent vasodilation due to reduced bioavailability of nitric oxide (NO) and increased vasoconstrictor response of endothelin-1 (ET-1), prostaglandin H2 and thromboxane A2, in porcine models.[7] Additionally, the increase in aortic stiffness is associated with an increase in systolic blood pressure (SBP) and a decrease in diastolic blood pressure (DBP), which leads to an increase in left ventricular afterload and oxygen demand, with subsequent derived ischemia of the reduction of the diastolic perfusion pressure of the myocardium.[8]

CLINICAL PICTURE

The most frequent symptom is angina, which unlike the typical presentation in obstructive coronary disease, in INOCA, is less intense and with different patterns and location variations. It is more frequently associated with dyspnea, nausea, weakness, fatigue, jaw pain, and intense tiredness, sometimes disabling. Angina can occur during stressful situations or at rest.

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The aggregation of several comorbidities is less frequent.[9] Uncontrolled BP accelerates structural and functional changes in blood vessels, which can potentially trigger myocardial ischemia events.

DIAGNOSIS

It is necessary to assess coronary vascular function to define pathophysiology with invasive or non-invasive diagnostic tests *(Table 1)*, according to the clinical context, risk factors, availability of resources, operator experience, and with the following criteria *(Figure 1)*:[1,10]

1. Clinical picture and objective evidence of ischemia.
2. Coronaries without significant obstructive lesions and fractional flow reserve (FFR) > 0.80.
3. Coronary flow changes: coronary flow reserve (CFR) < 2.0 in response to a vasodilator (adenosine), evidence of coronary spasm with acetylcholine (ACh) or

Table 1: Diagnostic methods in INOCA according to the pathophysiological mechanisms.

Pathophysiological mechanism	Diagnostic method
Atherosclerotic lesions and their characteristics • Plaque erosion (acute thrombosis in the presence of an intact fibrous cap) • Plaque ulceration (atherosclerotic plaque ulceration with superimposed thrombus) • TIMI frame count	AngioCT, OCT, IVUS
Coronary microvascular dysfunction • FFR > 0.8 • CFR < 2.0 • IMR ≥ 25	Functional tests with adenosine: FFR, CFR, IMR, angiography + diagnostic guide, PET, AngioTC, RMC in stress TTE dipyridamole stress Doppler
Epicardial coronary spasm • Luminal diameter reduction ≥ 90% • Angina • ECG changes suggestive of ischemia	Coronary angiography, ACh test, resolution with IC-NTG
Coronary embolism/thrombosis • Presentation as ACS • Filling defects with partial or total occlusion of the vessel lumen • Floating filling defect in the lumen with the passage of contrast medium on both sides of the defect	Coronary angiography, IVUS, OCT, search for hypercoagulable states, Holter (AF)
Spontaneous coronary dissection • Presentation as ACS or shock, in a young woman • Multiple radiolucent lumens and extraluminal contrast staining • Obstruction of the coronary artery by IMH • Intima disruption	Coronary angiography, OCT, IVUS
Contribution/demand mismatch • Angina or equivalent • ECG changes suggestive of ischemia • Evaluation of the mass index (LVH)	Identifying triggering factors: stress, pregnancy, anemia, thyrotoxicosis, inflammatory or connective tissue diseases, and others TTE and stress test

Data can be found in the diagnostic methods according to each pathophysiological mechanism.
OCT = optical coherence tomography. IVUS = intravascular ultrasound. AngioCT = coronary angiotomography. PET = positron emission tomography. ACh = acetylcholine. IC-NTG = intracoronary nitroglycerin. FFR = fractional flow reserve. CFR = coronary flow reserve. IMR = index of microcirculatory resistance. TTE = transthoracic echocardiogram. ECG = electrocardiogram. IMH = intramural hematoma. ACS = acute coronary syndrome. AF = atrial fibrillation. LVH = left ventricular hypertrophy.

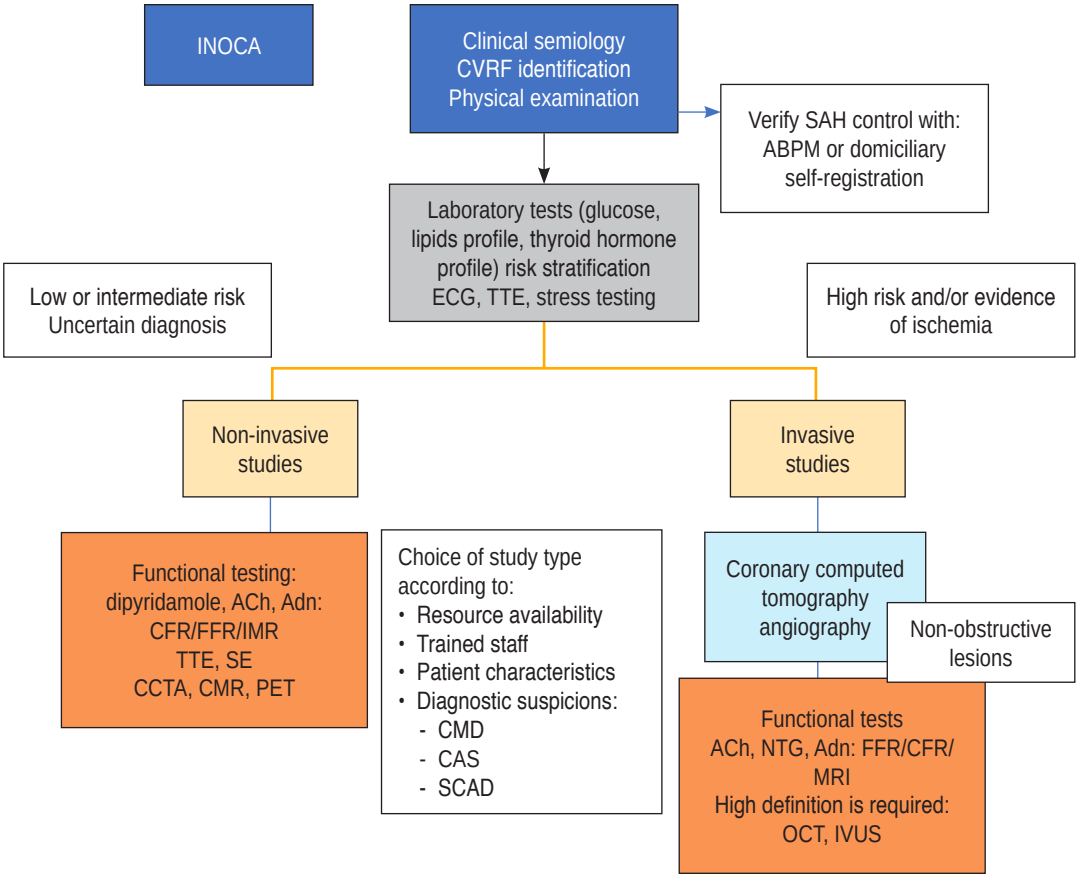

Figure 1: Flowchart for the evaluation of hypertensive patients with INOCA. Diagnostic evaluation of patients with a suspected diagnosis of INOCA.

CVRF = cardiovascular risk factors. SAH = systemic arterial hypertension. ABPM = ambulatory blood pressure monitoring. ECG = electrocardiogram. TTE = transthoracic echocardiogram. CMR = cardiac magnetic resonance. PET = positron emission tomography. CTA = coronary angiotomography. ACh = acetylcholine. Adn = adenosine. NTG = nitroglycerin. FFR = fractional flow reserve. CFR = coronary flow reserve. MRI = microcirculatory resistance index. OCT = optical coherence tomography. IVUS = intravascular ultrasound. CMD = coronary microvascular dysfunction. CAS = coronary artery spasm. SCAD = spontaneous coronary artery dissection. SE = stress echocardiography.

TIMI (thrombolysis in myocardial infarction) flow change frame count (> 3 beats for vessel filling at rest).

NON-INVASIVE METHODS

The transthoracic echocardiogram (TTE) evaluates the degree of LVH. The velocity of the coronary flow can also be measured through pulsed wave Doppler in the coronary artery at rest and after the administration of dipyridamole. Using this method, the iPOWER study demonstrated that 26% of women with INOCA had changes in FRC velocity < 2.0.[11] Functional studies with coronary tomography angiography (CT angiography) and cardiac magnetic resonance imaging (CMR) of stress with dobutamine or adenosine allow detection of alterations in subendocardial perfusion in patients with INOCA, calculating the myocardial perfusion reserve index and the index of microcirculatory resistance (IRM) (≥ 25 U is indicative of CMD).[1,10] Positron emission tomography (PET) helps evaluate CFR, calculating the ratio of coronary myocardial flow during adenosine induction of maximal hyperemia and at rest.

INVASIVE METHODS

Angiography is the gold standard. If significant coronary lesions are not observed, it is indicated to assess coronary flow and the arteries' diameter with endothelium-dependent tests such as acetylcholine (Ach) and with endothelium-independent tests such as adenosine and nitroglycerin, the CFR, the IMR, and the FFR.

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) allow the evaluation of vascular remodeling and morphology with functional studies. OCT has been shown to have prognostic value when linked to the assessment of adventitial vasa vasorum and intraplaque neo-vessels to indices of microvascular spasm, epicardial spasm, and IMR in patients with INOCA.[12]

TREATMENT

Maintaining strict BP control, secondary prevention with lifestyle modifications, cardiac rehabilitation, and drug treatment is essential. However, most of the pharmacological recommendations are based on observational studies with inconsistent results, and to date, the underuse of drugs in adherence to the guidelines has been observed. Pauly et al. reported that administering quinapril compared with a placebo for 16 weeks improved CFR and symptoms.[13] In another study in patients with SAH, administration of perindopril for one year produced regression of periarteriolar fibrosis and increased CFR.[14] In patients with abnormal vasodilator reserve or CD, calcium antagonists improve exercise tolerance and symptoms. An observational analysis showed that statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and beta-blockers significantly reduced major cardiovascular events and heart failure.[15] Dual antiplatelet therapy without thrombi, coronary embolism, and ulcerated or eroded plaques is controversial and has not shown risk reduction.[10]

CONCLUSIONS

SAH is a highly prevalent CVRF in patients with INOCA and contributes to CMD, so its control is essential to reduce ischemia events. Diagnosis should include vascular function tests, and specific treatment should be established based on the phenotyping of the patient with INOCA.

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