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INOCA and MINOCA: are they invisible to the eyes?

INOCA y MINOCA: ¿son invisibles a los ojos?

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ABSTRACT

Coronary ischemic phenomena without obstructive arteries (INOCA-MINOCA) remain enigmatic clinical entities characterized by evidence of myocardial injury without obstructive coronary atherothrombotic etiology. Although it is attributed to multiple possible mechanisms, in recent years, significant advances in the underlying pathophysiological understanding have made it possible to get a better guide for treatment. Although it is more benign than infarcts with obstructive arteries, its prognosis is not very predictable and is being evaluated by ongoing studies. This article presents an updated view of these pathologies.

INTRODUCTION

Angiographically, one in four coronary angiographies (CCG) performed for myocardial ischemia present epicardial coronary atheromatous disease (EAD) with occlusion < 50%. This paper summarizes a current approach for a diagnostic algorithm and treatment of patients admitted with angina with or without high-sensitivity troponin T increase (TrIUS).[1]

These conditions have recently become relevant due to the diagnostic and therapeutic challenge, impact on quality of life, and not insignificant mortality.

According to their clinical presentation, clinical syndromes characterized by angina with coronary arteries without significant angiographic lesions encompass ischemic pathologies known by their acronyms INOCA and MINOCA.[1]

Operational definitions

INOCA (ischemia and non-obstructive coronary artery disease) relates to heterogeneous disorders characterized by signs and symptoms of chronic myocardial ischemia in the absence of EAD > 50% in CAG.

MINOCA (myocardial infarction with non-obstructed coronary arteries) is the set of diseases associated with myocardial damage meeting the criteria of the 4th Universal Definition of Acute Myocardial Infarction (MI): MI type 1 or 2 with elevated TrIUS > 99th percentile, in the absence of angiographic EAD > 50%, and the subtypes: normal, mild (< 30%) and moderate (> 30% < 50%), with or without electrocardiogram (ECG) abnormalities. The exclusion criterion of any other manifest cause for acute presentation than MI is added to the definition.[2,3]

INOCA

Up to 70% of patients undergoing CAG for angina do not have obstructive (> 50%) EAD but have demonstrable ischemia, which is more commonly seen in women.[4] These patients present a broad clinical spectrum, often misdiagnosed as non-cardiac, leading

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to inappropriate diagnosis, evaluation, and treatment.[1]

Heterogeneous pathophysiological mechanisms of coronary microvascular dysfunction (CMD) and epicardial vascular dysfunction are responsible for the angina. CMD and vasospastic angina (VSA) isolated or combined with EAD should be evaluated and confirmed with CAG imaging studies, coronary CT angiography, PetScan, and pharmacological tests (acetylcholine-adenosine) to assess vascular reactivation / coronary flow reserve (FFR)/CMR during CAG, necessary to elucidate INOCA endotypes for therapeutic purposes.[1,2,4]

Microvascular angina (MVA): clinical manifestation of myocardial ischemia caused by CMD due to structural microvasculature remodeling or vasomotor disorders that affect the coronary arterioles. Both mechanisms of vascular dysfunction can coexist and contribute to MVA.

Vasospastic angina (VSA): clinical manifestation of myocardial ischemia caused by dynamic epicardial coronary artery disease associated with a spastic vasomotor disorder characterized in invasive tests with >90% luminal reduction of the associated vessel with ST electrical changes.

The coexistence of these phenomena is associated with a worse prognosis. Age, diabetes, arterial hypertension (HBP), and dyslipidemia are associated with altered CMD. However, the link between traditional cardiovascular risk factors (TCVRF) and INOCA is not well established, except for smoking, which strongly correlates with DMC altered.[4] A very outstanding aspect is the presence of proinflammatory markers in women with INOCA. Contemporary studies evaluate the potential role of inflammation in the modulation of the coronary microvascular response.[4]

MINOCA

Diagnostic criteria have recently been outlined to define MINOCA to exclude non-ischemic causes of myocardial injury (Takotsubo, myocarditis, heart failure (HF), pulmonary thromboembolism, cerebrovascular events (stroke), renal failure, etc.) due to overlapping of the different spectra of myocardial injury in the real world.[5]

Diagnostic algorithm

A miscellany of etiologies underlies the etiopathogenesis of MINOCA: atheromatous coronary causes (rupture, plaque erosion), non-atheromatous (coronary spasm (CAS), spontaneous coronary artery dissection (SCAD), thromboembolism), CMD, oxygen supply/demand mismatch. It is therapeutically relevant to follow a specific diagnostic/etiological protocol with complementary studies to the CAG as a) invasive coronary imaging: intravascular ultrasound (IVUS), optical coherence tomography (OCT), b) functional: provocation test (VEC, FFR, and measurement of microvascular resistance dysfunction), and c) Non-invasive: ECG, transesophageal/transthoracic echocardiography, Holter ECG and Cardiac MRI to confirm the diagnosis of true MINOCA and rule out other causes of myocardial injury.[5]

Etiologies and prevalence

It represents 4-10% of myocardial infarctions, is more frequent in women (> 50%) with less TCVRF, but is commonly associated with hypertension, dyslipidemia, and smocking, in a younger population than patients with obstructive thrombotic EAD.

Among atherosclerotic causes, plaque rupture accounts for 60-70% of type 1 and 2 MI, common in MINOCA (13-40%) with or without visible thrombus on OCT. IVUS better identifies plaque erosion but is less frequent.[5,6]

Among non-atherosclerotic causes, CD (epicardial luminal obstruction > 90%) is more common in young subjects (5-15%) and is associated with the use of illicit drugs (e.g., cocaine) and drugs (pseudoephedrine, anti-migraine). CMD documented by positive functional tests related to vasospasm explains up to 30% of MINOCA and 3% isolated. Endocardial defect (ECD) is a common cause between 40 and 62 years of age; commonly in women with fibrodysplasia disease or those related to collagen, autoimmune, pregnancy and puerperium diseases, CAG is usually

sufficient for diagnosis in these cases. Embolic etiologies (intracardiac thrombi, paradoxical embolisms, tumors) and thrombotic etiologies associated with thrombophilia represent 1-4% of MINOCA causes and are difficult to diagnose in practice.[5-7]

Use of cardiac magnetic resonance in MINOCA

This non-invasive diagnostic method is highly relevant to confirm the diagnosis of MINOCA; an early evaluation is recommended, in a period of 7 to 14 days after the onset of symptoms, being helpful to exclude non-ischemic myocardial injury conditions such as Takotsubo and myocarditis. The cardiac magnetic resonance (CMR) imaging protocols allow the evaluation of anatomy and function, the detection of myocardial edema, acute cell membrane damage, and chronic myocardial fibrosis with patterns that will enable differentiation between MI and myocarditis.[5]

However, in some patients with MINOCA criteria, it will not be possible to demonstrate the area of infarction by this technique.

Prognosis

The mortality of MINOCA ranges between 2-4%, being lower than that of infarcts with atherothrombotic EAD (6.7%), but with increased costs due to morbidity associated with new events that increase hospitalizations, HF, stroke, and deterioration of quality of life.[6,7]

Therapeutic approach

Current treatment guidelines for both entities recommend general measures such as changes in lifestyle and control of TCVRF.

INOCA treatment is a challenge, depending on endotypes for appropriate treatment. VSA and MVA benefit from both treatments with calcium antagonists (CA) and beta-blockers such as carvedilol or nebivolol, associated with inhibitors of the renin-angiotensin-aldosterone system due to their beneficial effect by improving coronary reserve flow (CRF) and decreasing periarteriolar fibrosis, reducing symptoms and cardiovascular events.[1,2,8]

Drugs such as trimetazidine (myocardial metabolism modifier) and nicorandil (coronary microvasculature vasodilator) could help improve symptoms in patients with INOCA.[1]

Sublingual nitrates remain a therapeutic option for acute episodes of VSA, being ineffective in prolonged use.[2] The first pharmacological line in these patients is non-dihydropyridines CAs such as diltiazem. The association with amlodipine (CA dihydropyridines) could synergize to reduce symptoms in refractory cases.

Ranolazine can be used in MVA to improve the altered CRF, increasing the myocardial perfusion index.

Statins are indicated in INOCA and MINOCA with proven atherosclerotic etiology due to the regression and stabilization of plaques responsible for the pathology, improving endothelial dysfunction, and directly impacting the reduction of morbidity and mortality.[1] It is considered that there is a class effect, so that no one can be recommended.

A systematic review has shown the benefit of cardiovascular rehabilitation in these patients: improvement in symptoms, documented ischemia, with improvement in functional capacity and quality of life.[4,5]

Antiplatelet therapy (single or dual) does not differ from the initial MI recommendations. However, there is no evidence of benefit from its prolonged use.

In patients with SCAD, low-dose aspirin is recommended for long-term use for secondary prevention. Neither endovascular treatment (coronary angioplasty) nor myocardial revascularization (bypass) is a therapeutic option. These are reserved for hemodynamic instability due to plaque rupture with thrombi or severe TIMI flow impairment due to anatomical location and extension of compromised myocardial mass.

CONCLUSION

INOCA and MINOCA are associated with a higher incidence of cardiovascular events, repeat hospital admissions, unnecessary CCGs, impaired quality of life, adverse short-term and long-term cardiovascular outcomes, and increased healthcare costs.

The available evidence on the treatment of INOCA and MINOCA is still limited, with most recommendations based on expert opinion.

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