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EDITORIAL COMMENT

Ischemia with non-obstructive coronary disease as detected by myocardial scintigraphy: A benign or malignant prognosis?

Isquémia com doença coronária não obstrutiva avaliada por cintigrafia miocárdica: um prognóstico benigno ou maligno?

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Angina pectoris, the most common symptom of ischemic heart disease, affects approximately 112 million people worldwide.[1] However, a large proportion, up to 70%, of patients with angina and evidence of ischemia undergoing coronary angiography have no obstructive coronary disease, defined as the presence of >50% coronary stenosis.[2] As shown in large studies involving patients with both angina and/or ischemia and absence of obstructive coronary disease, women are particularly affected, with a frequency of about 50–70% versus 30–50% in men.[3,4]

These findings define the condition of ischemia with nonobstructive coronary arteries (INOCA), which encompasses two main endotypes, coronary microvascular dysfunction (CMD) and epicardial coronary vasospasm.[2,5,6] CMD is characterized clinically by angina and ischemia, which is typically caused by effort and reproduced by stress tests, although atypical presentation may occur. Myocardial ischemia may result from structural changes of the microvasculature with reduced conductance, or from vasomotor disorders affecting the coronary arterioles, causing dynamic arteriolar obstruction.[6] Vasospastic angina, typically unrelated to exercise unless on top of obstructive coronary disease, causes ischemia by dynamic epicardial coronary artery spasm. Other causes such as myocardial bridging, diagnosed by coronary angiography and/or cardiac computed tomography, may lead to effort angina.

INOCA is not a benign condition, since it has been found to be associated with an increased long-term risk of adverse clinical events including myocardial infarction, recurrent ischemia, heart failure, hospitalizations and cardiac death, as well as lower quality of life with recurrent angina and lower functional capacity.[4,7] An annual major adverse cardiovascular event (MACE) rate of 2.5% is seen in women with CMD.[6] Of note, CMD is a strong determinant of prognosis even in patients with coronary stenosis of intermediate severity.

A significant proportion of patients with INOCA present to the catheterization laboratory and their results are often considered as false positives for ischemia, leading in them receiving inappropriate reassurance. Current knowledge on CMD and/or vasospastic angina as potential causes for INOCA, particularly in patients with exertional chest pain,

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indicates a need for additional assessment in these patients, using coronary vasoreactivity testing after coronary angiography. Accurate identification of the mechanism underlying INOCA has a profound impact on its management, and a thorough diagnostic assessment should be performed on which to base selection of the best strategy. However, these tests are rarely performed since they are time-consuming and costly, their use is not widely standardized, and they often require specific scheduling for invasive or non-invasive assessment.

For a diagnosis of CMD, invasive determination of coronary flow reserve and the microvascular resistance index is the reference method, but positron emission tomography, cardiovascular magnetic resonance imaging and stress Doppler echocardiography may provide accurate data for establishing the diagnosis.[1]

However, there is currently a gap in knowledge concerning the prevalence of INOCA mechanisms in this population, since the accuracy of non-invasive techniques, the methods most widely available for assessment, and the best cut-offs for detecting CMD and coronary vasospasm are not well established.

In the study by Lampas et al. published in this issue of the *Journal*,[8] the authors retrospectively reviewed the five-year prognosis of a cohort of 285 patients who underwent a single-photon emission tomography (SPECT) study due to angina symptoms and fulfilled two criteria: a positive myocardial SPECT scan for reversible ischemia and absence of significant coronary lesions on coronary angiography. They found 1.7% mortality from non-cardiac causes but no cardiac mortality at follow-up, concluding that INOCA as detected by SPECT is associated with an excellent prognosis. However, significant morbidity was also found, particularly a 10.9% rate of hospitalizations for cardiac causes, including arrhythmias, acute coronary syndromes and coronary interventions. Additionally, another 10.9% of the patients developed heart failure, albeit presenting with New York Heart Association functional class $\leq$2.

The study is retrospective and includes a relatively small population, which limits conclusions. Moreover, since no coronary reactivity tests were conducted, besides the few cases with myocardial bridging, the underlying mechanisms are unknown, preventing assessment of their association with outcomes. Also, the impact of other potential prognostic factors such as clinical features, type of angiographic lesions or extent of ischemia were not taken into account and could act as underlying confounders.

On a positive note, patients with left bundle branch block were excluded from the population, ensuring a more homogeneous cohort and preventing this condition from affecting the accuracy of SPECT for diagnosing ischemia.

The authors of the present study put forward an optimistic viewpoint regarding late outcomes of INOCA patients as identified by SPECT and coronary angiography. However, this view could be challenged. Despite the absence of cardiac mortality, the 21.8% MACE rate represented an important cause of morbidity and concern, suggesting the need for systematic surveillance of INOCA patients and further investigation of the underlying mechanisms.

There are few studies addressing the prognostic significance of INOCA as assessed by myocardial perfusion scintigraphy. A recent study by Liu et al.[9] assessed prognosis at 15$\pm$20 months of 232 INOCA patients with abnormal myocardial perfusion imaging by a D-SPECT camera using detectors made from cadmium zinc telluride (CZT) and found a prevalence of 21.1% of MACE, including angina, heart failure and stroke. Another recent study[10] analyzed the long-term outcomes of patients with INOCA diagnosed by CZT-SPECT, coronary angiography and the microvascular resistance index, and found a 30.5% rate of MACE for INOCA (40% for patients with CMD) at 35-month follow-up. These findings are in line with the present study.

SPECT is a widely used technique for ischemia detection and its role in detecting INOCA should not be undervalued, but assessment by other means is necessary. Of note, myocardial perfusion scintigraphy methods are evolving, and state-of-the-art techniques should be applied to ensure the greatest accuracy. At the same time, findings based on SPECT should not be extended to other imaging modalities for ischemia testing, since technical methodologies and their diagnostic accuracies are not directly interchangeable.

Future prospective studies with larger populations than those available in published series, especially by SPECT but also using other modalities, should address the outcomes of INOCA patients, assessing multiple variables, including the pattern of coronary artery disease, the location and degree of ischemia and, importantly, the type of underlying mechanism as determined by appropriate coronary vasoreactivity testing. Identifying predictors of outcomes in INOCA patients is crucial for proper management.

Conflicts of interest

The author has no conflicts of interest to declare.

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