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EDITORIAL COMMENT

Unrevealing what is beyond our glance

Desvendando o que está para além do nosso olhar

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Symptoms or signs of ischemia with no epicardial coronary artery disease (ANOCA/INOCA) is highly prevalent in patients referred for assessment of coronary artery disease (CAD). It represents a superfamily of subgroups (endotypes) with specific pathophysiologic mechanisms, comprising a highly heterogeneous population. There are substantial variations in key domains, such as, etiology/pathophysiology, patient demographic characteristics, comorbidities, clinical manifestation, and presence of concomitant obstructive CAD. INOCA is associated with high morbidity, with increased risk of cardiovascular events, impaired quality of life, and substantial economic burden. Notwithstanding this important group of patients is frequently overlooked, and often remain undiagnosed, with consequential impact on their quality of life and on the health care system. The working diagnosis of INOCA include examination of clinical context, ischemia detection and documentation of non-obstructive CAD. Currently available non-invasive imaging is unable to fully characterize INOCA endotypes, the direct invasive assessment of both epicardial and microcirculatory responses to vasodilatory or vasoconstrictive stimuli represent unique advantages of interventional diagnostic procedures. Despite the current focus on INOCA by the scientific community and clinical practice guidelines, awareness of this condition is still sub-optimal in our daily practice, with many patients ending up without a diagnosis or a tailored treatment.

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In this issue of the Portuguese Journal of Cardiology, Ferreira et al. report the analysis of their initial experience with a standardized protocol for invasive assessment of ischemia with no obstructive coronary disease.[1] It is an elegant small sample size (20 patients) analysis of a single center experience, using a standardized published protocol recommended in clinical practice guidelines,[2] with short term clinical reassessment. The results were overall in line with previous published series regarding: prevalence of INOCA and its main endotypes, feasibility and safety of the procedure, therapeutic stratification and symptomatic improvement. In addition to the analytical results, one of the most important virtues of this report is the influence that it may have on local practice by raising physicians awareness of INOCA and reassurance of the feasibility and safety of this interventional diagnostic procedure.

Having a universal definition and a comprehensive diagnostic approach are of paramount importance to standardize clinical practice and research, contributing to: (1) increased awareness; (2) facilitated communication between physicians and between physicians and patients; (3) increase in diagnosis, leading to a better understanding of the problem; (4) further characterization of INOCA endotypes and identification of possible therapeutic targets; (5) identification of gaps in knowledge, directing future research; and ultimately (6) improve quality of life, decrease morbidity and relief the health care system.

Despite the growing interest and evidence on the subject, and the attempt to standardize definitions and practice in

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guidelines, there are still many unsolved questions in almost all domains that define this condition.

Regarding clinical manifestation, symptoms do not discriminate between epicardial obstructive disease, epicardial spasm or microvascular dysfunction (MVD). The presentation encompasses a wide range of symptoms, including classic anginal chest pain, as well as other angina-equivalent symptoms (dyspnea, fatigue, weakness, back pain, dyspepsia, nausea, vomiting or even sleep disturbances). Importantly, clinical presentation exhibits sex variation and symptom burden may vary over time.[3] For these reasons, these patients are often misdiagnosed as of non-cardiac origin, leading to under-investigation and under-treatment, with consequent patient dismay and depression.[4] Indeed, clinical presentation, demographic characteristics and comorbidities are key determinants of CAD pretest probability, guiding subsequent assessment, with bias for selection of the patients with highest probability of having obstructive CAD. This actually influences the actual makeup of the INOCA population, limiting our ability to fully characterize this heterogeneous condition, including its true prevalence, demographic characteristics, endotype distribution and prognosis in the general population.

Most of the estimates of prevalence come from catheterization laboratory registries, and more recently from CT registries, in unselected populations referred for assessment of obstructive CAD. The vast majority of these patients (>90%) do not have obstructive CAD, with up to 70% having INOCA.[2] Among those patients without obstructive CAD with angina and or ischemia on non-invasive testing, undergoing invasive coronary functional testing (CFT) the prevalence of MVD lies between 30 and 54% including both endothelial dependent and independent MVD.[2] Epicardial vasospasm prevalence has high variability among different populations, testing protocols and spasm definition; it has probably been underestimated in European populations by undertesting. The prevalence of both microvascular and epicardial spasm in more recent series goes up to 60%, with microvascular spasm being slightly more frequent.[2,5] Furthermore some patients with obstructive CAD, may also suffer from MVD, something that may explain the persistence of symptoms in about one quarter of the patients one year after revascularization.[6]

While most of the evidence suggests that women are more affected (50–70%), some datasets show equal gender distribution.[7] The fact that men usually undergo ischemic assessment more often than women, and that there is a variable prevalence of different endotypes among the studied populations with MVD being more common in women and epicardial spasm in men,[2] may account for this discordance.

In addition, the heterogeneous nature of INOCA, including a variety of endotypes with different pathophysiological mechanisms further contributes to the aforementioned uncertainties. The current European Association of Percutaneous Cardiovascular Interventions' consensus document[2] defines three main endotypes according to the results of CFT, including acetylcholine provocation. These endotypes are: (1) epicardial vasospastic angina; (2) microvascular angina, 2.1 endothelium independent and 2.2 endothelium dependent; and (3) both microvascular and epicardial vasospastic angina (since there is a considerably overlap between these entities). This document also recommends a stratified therapy according to the endotype. Despite the value of this attempt to standardize definitions in order to guide the therapeutic approach, this classification does not clearly reflect all the pathophysiological mechanisms underlying ischemia/symptoms. There are two major vasomotor abnormalities that can be identified by current functional tests: (1) abnormal vasodilation of the microcirculation and (2) abnormal vasoconstriction of the microcirculation or the epicardial vessel. Four main endotypes can therefore be defined based on the underlying mechanism reflected by results of CFT. Abnormal vasodilation comprises: (1) structural MVD with a CFR <2.5 and an IMR >25 reflecting increased resistance of the microcirculation due to intimal thickening±capillary rarefaction, (2) functional MVD with a CFR <2.5 and an IMR <25, resulting from low vascular tone with increased flow at baseline and a dumped vasodilatory response to adenosine, in relation with inducible nitric oxide synthase (iNOS) hyperactivity and/or increased cellular oxygen consumption (MVO2).[8] Abnormal vasoconstriction comprises: (3) microvascular spasm reflecting endothelial dependent MVD, manifested by clinical and EKG signs of ischemia without epicardial spasm in response to acetylcholine, and (4) epicardial coronary vasospasm that combines clinical and electrocardiogram signs of ischemia with a >90% focal or diffuse spasm of the epicardial vessel in response to acetylcholine. A mixed result of CFT, indicating an overlap of mechanisms, may define a 5th endotype. Even after CFT, approximately half of the patients without obstructive CAD may remain without diagnosis, and the prevalence of myocardial bridging (MB) in this population is higher (58% vs. 30%) than in the general population.[9] Even if it is long believed that MB was inconsequential, it may be the cause of angina in these patients. It has been shown that the dynamic systolic compression may extend to early diastole resulting in delayed relaxation of the vessel and adenosine induced significant diastolic gradients (diastolic FFR) in segments with MB.[9] MB may, therefore, be a sixth endotype, introducing further complexity to the INOCA classification.

In opposition to the previous belief that this condition was benign, INOCA is associated with up to four- and five-times' increased mortality and adverse cardiac events, respectively.[10] Major adverse cardiovascular events do not appear to vary by gender,[2] however some comorbidities such as chronic kidney disease, diabetes, obesity, hypertension and previous history of obstructive CAD have been identified as predictors of prognosis.[11]

Different endotypes may carry different prognosis, as shown by Lee et al., patients with a high IMR and a low CRF have worst prognosis than patients with a low CRF and normal IMR.[12] Additional research is needed to understand the impact of patient demographics and INOCA endotypes on prognosis.

The management of INOCA represents a major unmet need due to the lack of large-scale randomized studies with a homogeneous patient group, thus making it difficult to generate evidence-based recommendations. The CorMicA randomized controlled trial of stratified medicine according to INOCA endotype, reported improvements in anginal symptoms and QOL, but did not assess adverse cardiac events.[13] Two outcome trials are currently underway: the Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD

(WARRIOR); and the International Coronary Microvascular Angina Trial (iCorMicA) of stratified medicine in angina.

Future perspectives

Regarding diagnosis, the emerging angiographic and CT derived automated flow analysis technology may simplify the assessment of microvascular function, without the need for wires or adenosine. From the therapeutic perspective, the Reducer device has shown a mechanistic effect in anecdotal cases reports and symptomatic benefit in small series and is currently being studied in sham-controlled trials in INOCA populations.

Conclusion

These areas of uncertainty should guide our interest and research to improve the management of this highly prevalent and frequently overlooked entity with profound impact on the individual's health and on society. Reports that raise awareness among clinicians providing tools to counteract therapeutic nihilism are extremely important at this stage of knowledge. Currently the approach should be multidisciplinary, patient-centered and based on different lines of intervention addressing quality of life and prognosis.

Conflicts of interest

The authors have no conflicts of interest to declare.

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