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OPINION ARTICLE

A Breakthrough in the Pathogenesis of Ischemic Heart Disease: the MINOCA and INOCA Challenge

Avances en la patogénesis de la enfermedad isquémica coronaria: el desafío que representan los MINOCAS e INOCAS

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Classical coronary syndromes as angina pectoris, ischemia and myocardial infarction, which were described many years ago, are generally attributed to the presence of different degrees of coronary artery obstruction caused by atherosclerotic plaques.

Atherosclerosis is a chronic inflammatory disease affecting both sexes that starts in childhood, and even in intrauterine life, (1) and progresses throughout the years, especially in subjects with cardiovascular risk factors. In this inflammatory process, and in the presence of a specific or inadequate metabolic environments, such as diabetes mellitus or those resulting from traditional risk factors, β-lipoproteins and glycated proteins oxidize becoming antigenic and causing endothelial dysfunction. This favors the penetration of these molecules into vascular subendothelial layers where they generate an immunogenic reaction, activating monocytes that are transformed into macrophages, which, together with other cells involved in this process, create a lipid inflammatory core. Vascular smooth muscle cells, recruited by inflammation, change from a contractile phenotype to a secretory phenotype and generate collagen, which surrounds the lipid inflammatory core and promotes calcium deposition, completing the formation of the atheromatous plaque. (2) This complex process (briefly described here) involves a multitude of molecules that are produced as a result of oxidation, inflammation, apoptosis, angiogenesis, degradation of the fibrous cap, influx of red cells, tissue factor expression and other components that determine the progression of the atherosclerotic plaque over time. (3)

THE CORONARY VASCULAR ACCIDENT. A BRIEF HISTORY

A coronary vascular accident (CVA) is classically considered the result of atherosclerotic plaque ulceration or rupture with thrombus formation during the repair process, which blocks or occludes the artery with the resulting consequences. If the obstruction is not severe and of limited duration and endothelial function is preserved, the thrombus is rapidly fibrinolysed, the condition may progress asymptomatically, with no symptoms for the patient, and is not detected by diagnostic tests. On the other hand, when the size of the thrombus is significant and the obstruction persists, the endothelium cannot respond and ischemia develops, leading to necrosis and even multiorgan failure that compromises the patient's life.

Until the mid-20th century, "coronary artery disease" was confirmed by the electrocardiogram; "myocardial infarction" by abnormal Q waves, "ischemia" by variations of T waves and "injury" by modifications of the ST segment. (4) Thereafter, coronary angiography allowed to correlate the anatomic findings with their clinical manifestations, giving rise to a myriad of unsuspected possibilities, including CVA without detectable arterial disease, myocardial ischemia and injury ending in infarction or regressing, even with disappearance of the electrocardiographic signs, although many patients developed heart failure or other clinical conditions.

At the same time, several biomarkers began to be evaluated. Some of them were unspecific, as erythrocyte sedimentation rate and neutrophils in acute coronary syndromes, until the development of new biomarkers as high-sensitive cardiac troponins and their kinetic changes.

Progressively, new methods increased diagnostic specificity. Intravascular ultrasound, optical coherence tomography, tests with vasoactive drugs, echocardiography, computed tomography angiography, helical computed tomography, magnetic resonance imaging, calcium scores and other techniques allowed detecting not only CVA without significant obstructive coronary artery disease but also to estimate myocardial damage, contractility and ventricular function.

These new diagnostic tools made it possible to document what was previously assumed. Invasive and non-invasive imaging studies have helped determine the importance of microvascular dysfunction and its

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role in coronary syndromes occurring in subjects with or without coronary artery obstructions. The possibility of detecting changes in the vasodilator capacity of the epicardial coronary arteries and microcirculation has opened an important diagnostic pathway. Microvascular angina (MVA), also known as cardiac syndrome X, was defined as angina pectoris with no evidence of coronary artery obstruction, The concept of MVA, however, may extend further to include patients with different degrees of obstruction. Moreover, recent data indicate that microvascular dysfunction is responsible, to a great extent, for angina after a percutaneous coronary intervention, coronary revascularization or heart transplantation. Microvascular angina has also been observed in subjects with hypertrophic and dilated cardiomyopathies, takotsubo or takotsubo-like syndromes and myocardial infarction. But almost all cases of CVA with apparently normal or structurally diseased coronary arteries are accompanied by vasoconstriction of the systemic circulation. (5, 6)

MINOCA AND INOCA

The acronyms MINOCA, for "Myocardial Infarction with Non-obstructed Coronary Arteries" and INOCA, "Ischemia and Non-obstructive Coronary Arteries" have recently emerged, indicating that significant coronary obstruction is not necessary for a CVA to occur. (6) New denominations are always surprising and generate enthusiasm, even though they had been reported more than 80 years ago with other names. (7) Since these conditions are common in young and female patients, they were considered to be low risk and with a more favorable outcome; (8) however, this concept has proved to be erroneous.

Approximately 10% of the patients with myocardial infarction present MINOCA, ranging between 1% and 14% according to different series. (7) MINOCA is more common in women < 55 years, it is not always associated with cardiovascular risk factors and may course with small or no electrocardiographic changes. The clinical presentations of MINOCA are quite heterogeneous and include MVA, takotsubo syndrome, pulmonary embolism, myocarditis, cardiomyopathies and other conditions with elevated cardiac troponins or creatine kinase. Vascular obstructions are absent or non-significant, but notably patients with MINOCA or INOCA have similar morbidity and mortality and survival as those with classic myocardial infarction or obstructive coronary artery disease. (8)

CORONARY ARTERY OBSTRUCTION

According to autopsy studies, plaque rupture or erosion is the cause of myocardial infarction in 65%-75% of the cases, followed by superficial erosion of the endothelium, while intimal dissections or microaneurysms are less common causes. (11) The majority of atheromatous plaques grow towards the arterial wall before encroaching upon the lumen of the artery when they are large enough to produce obstruction. (12)

Falk et al. reported that 68% of infarctions were caused by lesions <50% and 18% by lesions <70%. Only14% were caused by lesions >70%. (13) As a result, it seems that obstruction is an important but not determining factor in the production of a CVA.

Using intravascular ultrasound, Riufol et al. found plaque erosion and rupture on the culprit lesion, but 79% of the cases presented other plaque erosions in the same artery and in 12.5% of the cases plaque erosion was found in other coronary arteries. Thus, it was hypothesized that other conditions, besides plaque rupture or erosion, were necessary for a CVA to occur. (14)

Khot et al. reported that 19.4% of the patients with myocardial infarction did not present traditional risk factors, and 49% had only one. (15) Thus, other factors besides plaque rupture and luminal obstruction are needed for a CVA.

The inflammation generated by the atheromatous plaque does not disappear with the CVA but persists according to the patient's risk, and is magnified with a new inflammation generated for the repair of the vascular lesion. (17) In addition, balloon angioplasty, stent implant and myocardial revascularization surgery constitute insults to the endothelium causing inflammatory reactions. Thus, the magnitude and persistence of the new inflammatory reactions are harmful factors that can exacerbate the problem. Kalkman et al. demonstrated that patients with CVA undergoing percutaneous coronary interventions and stents had greater incidence of new CVA and greater morbidity and mortality than patients with medical treatment with similar myocardial damage and ejection fraction. These new factors led to differentiate type IV myocardial infarction in the new classification of myocardial infarction. (18-20)

In 1929, Edgar Allen developed a simple technique to detect vascular obstructions in patients with thromboangiitis obliterans. He simply made a simultaneous compression of the radial and ulnar arteries to induce pallor of the hand and fingers and then released the compression, calculating the time of return to normal color. In this way, he gave rise to the concept of arterial vasoconstriction or spasm. (21) Some decades ago, this technique was improved using vascular ultrasound to measure endothelial-dependent vasodilation. In addition, most CVA, as takotsubo syndrome or vasospastic angina are associated to emotional factors in predisposed subjects. (22)

CONCLUSIONS

The diagnostic and therapeutic contribution of recognizing the cases of MINOCA and INOCA is relevant. It also entails greater responsibility for clinical and interventional cardiologists who are more likely to indicate invasive tests and revascularization procedures in many cases in which the presence of coronary artery lesions is only an innocent witness rather than

the culprit of the coronary syndrome. INOCA and MINOCA in the clinical setting represent a breakthrough in the knowledge of the pathophysiology of coronary syndromes.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material).

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