Artículo de Opinión

Coronary atherosclerosis and myocardial ischemia

Aterosclerosis coronaria e isquemia miocárdica

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INTRODUCTION

Coronary atherosclerotic obstructions have been proposed as the consistent cause of myocardial ischemia[1]. According to this model, the presence of a "significant" coronary obstruction is expected to be always associated with a reduced coronary blood flow reserve that in turn causes myocardial ischemia.

The 2006 ESC Guidelines, reflecting this conception, stated that "the most common cause of myocardial ischemia is atherosclerotic Coronary Artery Disease, rare cardiac conditions in the absence of obstructive atheromatous coronary disease, are not considered in this document"[2].

Today, coronary atherosclerotic obstructions can be easily diagnosed with invasive and not invasive methods and can be easily removed by surgical or percutaneous procedures.

So, the hypothesis of a close link between coronary atherosclerosis and myocardial ischemia offers an easy and straightforward approach to management of ischemic patients and still constitutes the background of recommended diagnostic and therapeutic protocols[3].

However, a large body of evidence strongly challenge this conception and suggest a more complex and dynamic nature of myocardial ischemic syndromes[4].

The purpose of this article is to challenge this simplistic understanding of myocardial ischemia and to present evidence supporting a multifactorial and dynamic nature of myocardial ischemic syndromes.

STENOSIS SEVERITY AND MYOCARDIAL PERFUSION

In a study quantifying the effects of coronary atherosclerotic obstructions on myocardial flow reserve (MFR), it was observed a wide scatter in values of MFR measured by PET when plotted versus diameter stenosis measured by CTA. Surprisingly enough, normal values of MFR were also found downstream a severe stenosis or even in area perfused by totally occluded vessel. Conversely, abnormally low values of MFR were measured in areas perfused by normal vessels. When MFR was plotted versus percentage of diameter stenosis categories, a large overlap was observed from fully patent vessels to severely (>70%) obstructed vessels[5].

Authors concluded that the association between stenosis severity and flow was modest, preventing the estimate of the impact of the atherosclerotic obstructions on myocardial perfusion in the individual patient.

Similarly, the relationship between anatomic severity of a stenosis and its impact on coronary hemodynamic is much less predictable than commonly thought.

In a study comparing Fractional Flow Reserve (FFR) and Intravascular Ultrasound (IVUS), it was observed that no patients had a reduced FFR if the minimal cross-sectional area of the vessel was >2.4 square mm and, even more surprisingly, that a normal FFR could be measured even in vessels with a cross sectional area as low as 1 square mm[6]. These data contradict the popular assumption that FFR reliably evaluates stenosis "significance" and that a vessel cross sectional area below 4 square mm is consistently associated with myocardial ischemia.

Moreover, in one of the validation studies intended to prove the usefulness of FFR for risk stratification in patients with intermediate stenosis, adverse events were reported at follow-up in patients with both abnormal and normal FFR values, challenging the predictive value of FFR for severe adverse events[7].

MYOCARDIAL ISCHEMIA AND CORONARY ATHEROSCLEROTIC OBSTRUCTIONS.

Several clinical studies have strongly challenged the idea that myocardial ischemia is consistently associated with coronary atherosclerotic obstructions.

In one of the largest studies ever conducted, patterns of non invasive testing and the diagnostic yield of catheterization were determined among almost four hundred thousands patients without known coronary artery disease that had been included in the **CathPCI** registry of the National Cardiovascular Data Registry of the American College of Cardiology. Only one third of patients referred for elective cardiac catheterization

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was found to have obstructive coronary artery disease, and no significant difference was found in the prevalence of ≥50% stenosis between patients with a positive noninvasive test and patients with a negative noninvasive test[8].

Similar conclusions were reached by the **CONFIRM** Registry that tested the guideline probabilities in patients referred to noninvasive testing for coronary artery disease. Among fourteen thousand consecutive patients undergoing coronary computed tomographic angiography, the prevalence of ≥50% stenosis was similar in patients with typical angina and in asymptomatic patients. Less than 50% of male patients with typical angina and less than 30% of female patients with typical angina had a ≥50% stenosis[9]. Interestingly enough, women, that are known to have much less coronary atherosclerotic obstructions than men in any age range, suffer of chronic myocardial ischemia as frequently as men if not more[10].

PREVALENCE OF CORONARY ATHEROSCLEROTIC OBSTRUCTIONS IN ANGINA PATIENTS

Recent clinical studies offer additional evidence that the link between atherosclerotic obstructions and myocardial ischemia is much more elusive than commonly thought.

In a study on ambulatory patients with stable angina pectoris, the prevalence of obstructive coronary artery disease at coronary angiography was as low as 16,5%[11].

In the patients included in the **FAME 2** trial because they presented with typical angina and /or documented myocardial ischemia, 27% had no significant stenosis at invasive assessment[12]. In the **CORMICA** trial, that applied similar inclusion criteria, the prevalence of non-obstructive disease was 39%[13].

The prevalence of non-obstructive coronary disease is even higher in studies where both patients with typical and atypical angina have been considered[14].

The 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes offer an update on the pretest probabilities of obstructive coronary artery disease in symptomatic patients, including patients with typical angina, atypical angina, non-anginal chest pain and dyspnea *(Knuuti J, et al. Eur Heart J 2020).*

In patients with typical angina, age 50-59, the probability of an obstructive coronary artery disease is 32% if male, and 13% if female. And these figures are even lower in all the other groups of patients included in the analysis. So, the message is that the vast majority of patients with typical angina do not have an atherosclerotic obstruction. This is a major shift from the previous guidelines and suggests that non-obstructive mechanisms play a prominent role in precipitating myocardial ischemia, and can no longer be considered a "rare condition" *(Fox K, et al. Eur Heart J 2006).*

IMPACT OF OBSTRUCTION REMOVAL ON PROGNOSIS AND QUALITY OF LIFE OF ANGINA PATIENTS.

Since the introduction of percutaneous revascularizations procedures, several randomized clinical trials (RCT) have compared medical therapy with angioplasty and stenting, the most recent one being the hotly-debated and not -yet- published **ISCHEMIA** trial. From what is known, the primary finding of the Ischemia trial was a null result. In patients with moderate-to-severe ischemia on stress testing, an initial invasive approach of management with cardiac catheterization and revascularization showed no reduction in major adverse cardiovascular events when compared with a conservative approach of optimal medical therapy. This conclusion is consistent with most previous RCT and meta-analysis and is expected to slowly change clinical practice over time[15].

EXPECTED CHANGES IN CLINICAL PRACTICE

Many cardiologists and patients alike, still perceive the invasive approach as a superior therapy as compared to the conservative approach, despite the clear recommendation of Guidelines from both sides of the Atlantic to consider revascularization in patients with symptoms despite optimal medical therapy and despite the growing concern about the long lasting adverse effects of PCI[16].

With the growing awareness of the absence of atherosclerotic obstructions in the majority of patients presenting with typical angina pectoris, the role of revascularization as the optimal treatment will be inevitably downgraded and the identification of the mechanism or the mechanisms responsible for the ischemic syndrome will become a major diagnostic challenge. In the past, too often patients have been dismissed and the diagnosis of angina denied despite the typicality of symptoms and/or the presence of documented myocardial ischemia because of the absence of a coronary stenosis. In the future, this behavior will become less and less acceptable.

Invasive and noninvasive diagnostic tools are currently available for angina from microvascular dysfunction and for angina from vasospasm. These investigations are expected to become progressively more accessible and popular in the future. However, the list of mechanisms that may be responsible of myocardial ischemia is far from being complete and for many of the proposed mechanisms there is no specific diagnostic tool *(Marzilli M, et al. J Am Coll Cardiol 2012).*

A similar development can be expected for pharmacologic treatments. Current guidelines consider different scenarios but their recommendations do not focus on the precipitating mechanism in the individual patient *(Knuuti J, et al. Eur Heart J 2020).* A therapeutic strategy tailored to the specific need and mechanism in each patient promise to be more effective and better tolerated than current approach[17].

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