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How was myocardial ischemia promoted from disease to syndrome?

Mario Marzilli, MD, PhD

Professor of Cardiovascular Medicine, University of Pisa

Correspondence: Prof Mario Marzilli, Viale dei pini 293°, 56019 Vecchiano (PI), Italy
E-mail: mario.marzilli@med.unipi.it

Abstract: The understanding of myocardial ischemia has dramatically changed in recent years. From a concept entirely focused on coronary atherosclerotic obstructions, we are moving to a complex, dynamic, multifactorial model. The clinical translation of this new model necessitates major changes in diagnostic and therapeutic strategies in order to identify the responsible mechanisms and to tailor therapy. ■ *Heart Metab*. 2020;81:3-6

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A glimpse into the past

Diagnostic and therapeutic approaches to myocardial ischemia have been traditionally based on the assumption that this condition is caused by the progressive growth of atherosclerotic plaques within the walls of epicardial coronary arteries. This process reduces the lumen, therefore preventing an adequate increase of blood flow when cardiac work increases and causing myocardial ischemia.[1] This pathogenic model has been found to be very attractive by cardiologists and widely accepted. The clinical implications of this concept are that the presence of a "significant" stenosis reliably predicts myocardial ischemia, that its absence challenges the diagnosis of ischemia, and that its removal is an effective treatment for myocardial ischemia.

The 2006 ESC Guidelines on the management of stable angina pectoris (*European Heart Journal,* doi:10.1093/eurheartj/ehl002), fully supported this model, stating 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] This model was recently re-proposed.[3]

However, in 2013, the "ESC guidelines on the management of stable coronary artery disease" enlarged the list of the mechanisms that can precipitate myocardial ischemia, and included functional mechanisms. In *Table 3* of the document, "Main features of stable coronary artery disease," these Guidelines proposed five mechanisms for ischemia: fixed stenosis, dynamic stenosis, focal vasospasm, diffuse vasospasm, and microvascular dysfunction, with only one, fixed stenosis, being directly related to coronary atherosclerotic obstructions.[4]

Where are we now?

The 2019 ESC Guidelines abandoned the wording "stable angina," maintained the term "coronary," and substituted the word disease with syndrome.[5] So, the latest version of the Guidelines was renamed as "Guidelines for the diagnosis and management of chronic coronary syndromes."

It is of interest to quickly review the evidence that has driven this major shift in our understanding of myocardial ischemia.

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In a large USA database, collecting almost 400 hundred thousand coronary angiograms, the prevalence of a stenosis of ≥50% was around 50% both in patients with, and without, ischemia documented on noninvasive testing.[6]

In the CONFIRM Registry, a stenosis of ≥50% was found only in 50% of male patients with typical angina, over 70 years old and in less than 30% of female patients over 70 years old.[7] The prevalence of "significant" stenosis was even lower in younger patients with typical angina, with no significant difference between patients with typical angina and asymptomatic patients.

In a larger voluntary registry-based report of 375 886 patients with stable angina pectoris, 51% of women and 33% of men had no significant coronary artery stenosis (defined as >70% stenosis).[8] Thus, there is only a vague relationship between a traditional flow-limiting stenosis in an epicardial coronary artery and symptoms of angina.

One of the studies that have contributed to unveiling the limited role of coronary stenosis in chronic ischemic syndromes has been, paradoxically, the FAME 2 trial.[9] This trial was designed to assess the additive benefit of fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) on top of medical therapy in patients with typical angina and/or documented myocardial ischemia. The study enrolled a total of 1220 patients. After invasive coronary angiography, 332 patients (27%), were not randomized to medical therapy alone or medical therapy plus PCI because they had no stenosis with a FFR <0.80.[10] Interestingly enough, the three groups of patients (no stenosis, stenosis removed, stenosis not removed) had similar rates of death, myocardial infarct (MI), and post-PCI angina. So, the FAME 2 trial clearly demonstrated that chronic myocardial ischemia can be diagnosed in patients with and without a significant stenosis and that removal or "conservative" management of the stenosis does not impact on outcomes.

In the more recent CORMICA Trial, including 391 patients with angina symptoms and/or documented myocardial ischemia, the prevalence of nonobstructive myocardial ischemia was even greater.[11]

Based on available evidence, the relationship of myocardial ischemic syndromes to coronary atherosclerotic obstructions can be summarized as follows:

1. The majority of patients with typical symptoms and/or signs of ischemia do not have atherosclerotic obstructions in the coronary vessels
2. The vast majority of patients found to have coronary atherosclerotic obstructions do not have symptoms or signs of myocardial ischemia
3. In patients with both ischemia and atherosclerotic obstructions, the percutaneous removal of these obstructions does not impact on clinical outcomes.

In addition, the high recurrence rates of symptoms and signs of ischemia after stenosis removal indirectly support the concept that the presence of a stenosis in patients with chronic ischemic syndromes does not imply "per se" a causative role.

A few years ago, we happened to review most of the evidence, and the conclusion was that the link between obstructive coronary atherosclerosis and ischemic heart disease is much more elusive than commonly thought and that obstructive atherosclerosis is just one element in a complex multifactorial process that includes inflammation, microvascular dysfunction, endothelial dysfunction, vasospasm, platelet and coagulation disorders, and critical coronary stenosis.[12] And this list was by no means intended to be a complete one.

The recently published 2019 ESC Guidelines have officially acknowledged the multifactorial nature of myocardial ischemia, calling it a syndrome. However, the clinical implications of this new concept have not been fully explored and the relative role of the proposed mechanisms has not been discussed.

However, the Guidelines included a table *(Table 5)* entitled "Pre-test probabilities of obstructive coronary artery disease in 15 815 symptomatic patients according to age, sex, and the nature of symptoms in a pooled analysis of contemporary data" which confirms that only a minority of patients with typical angina has obstructive coronary atherosclerotic disease. For instance, in the age range 50 to 59, only 32% of males and 13 % of females have obstructive coronary artery disease. The obvious implication is that in 68% of male angina patients and 87% of female patients aged 50 to 59, angina is not associated with obstructive coronary artery disease.

So, in less than 12 years, coronary atherosclerotic obstructions, from being considered the most common cause of angina, if not the only one, have been downgraded to playing a secondary role, especially in females. Females, according to recent epidemiological data, present with ischemic syndromes more often than men and in many settings suffer a worse prognosis, yet they do have a much lower coronary atherosclerotic burden.

The "promotion" of myocardial ischemia from disease to syndrome is indeed a Copernican revolution, positioning myocardial ischemia at the center of attention instead of the atherosclerotic plaque; but much needs to be done to translate this new concept to consistent diagnostic and therapeutic protocols.

Cardiologists are familiar with the management of syndromes like hypertension and heart failure. However, when it comes to myocardial ischemia, we are very reluctant to abandon the old "stenotocentric" model in favor of the new multifactorial model. Despite many reviews and position statements from both the American Heart Association and the European Society of Cardiology, many clinicians still suppose that the absence of obstructive CAD excludes the possibility of an acute MI.[10] And, in daily practice, most cardiologists feel uneasy when asked to manage ischemic patients without knowing the coronary anatomy. Similarly, despite so many randomized controlled trials and metanalyses showing the lack of additive benefit of PCI on medical therapy, interventions are still perceived by many doctors and patients alike as a "superior" therapy.

Several factors have contributed to the diffusion of these misconceptions, including biased data reporting, overestimation of PCI benefits, marked underestimation of adverse effects of PCI, industry pressure, intra-lab competition, operator's personal satisfaction, self-referral, lack of clinical follow-up, and opinion leaders' imitation.

Scientific institutions should feel the compelling responsibility to promote evidence-based medicine and to limit the use of expensive and risky procedures of unproven value. The alternative is that what will not be done by academic institutions based on scientific evidence will be imposed by financial institutions based on cost:benefit ratio.

Where do we go from here?

Cardiology will have to face hard challenges in the near future:

1. Identifying all the mechanisms that may precipitate myocardial ischemia, acting alone or in combination. In addition to atherosclerotic obstructions, microvascular dysfunction and vasospasm are already widely accepted. In 2012, we proposed six possible mechanisms.[12] In the Editorial associated with our paper, Pepine and Douglas proposed a much longer list, including vascular and nonvascular mechanisms,[13] and the 2013 ESC Guidelines listed five[4]
2. Abandoning the current practice of assessing the sensitivity and specificity of a provocative tests using the presence and absence of atherosclerotic obstructions as the gold standard. Instead, we need more relevent diagnostic protocols to identify which of the many proposed mechanisms are responsible for ischemia in the individual patient
3. Identifying appropriate triggers to perform provocative tests, starting from a rational use of those already available: exercise, dypiridamole, dobutamine, acetylcholine, ergonovine, etc
4. Testing the efficacy of antianginal agents, matching their mechanism of action with the mechanism of ischemia. ■

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