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Myocardial ischemia: From disease to syndrome

Mario Marzilli [a,*], Filippo Crea [b], Doralisa Morrone [a], Robert O. Bonow [c], David L. Brown [d], Paolo G. Camici [e], William M. Chilian [f], Anthony DeMaria [g], Giacinta Guarini [a], Alda Huqi [a], C. Noel Bairey Merz [h], Carl Pepine [i], Maria Chiara Scali [a], William S. Weintraub [j], William E. Boden [k,*,1]

[a] Department of Surgery, Medical, Molecular and Critical Area Pathology, University of Pisa, Italy
[b] Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy
[c] Department of Medicine, Northwestern University, Chicago, IL, USA
[d] Cardiovascular Division, Washington University School of Medicine, St Louis, MO, USA
[e] Vita salute University and San Raffaele Hospital, Milan, Italy
[f] Department of Integrative Medical Sciences, Northeast Ohio Medical University, Rootstown, OH, United States of America
[g] Division of Cardiology, University of California, San Diego, San Diego, CA, USA
[h] Barbra Streisand Women's Heart Center, Cedars-Sinai Smidt Heart Institute, Los Angeles, CA, USA
[i] Division of Cardiology, Department of Medicine, University of Florida, Gainesville, USA
[j] Outcomes Research, MedStar Heart & Vascular Institute, MedStar Washington Hospital Center, USA
[k] VA New England Health Care System, Boston, MA, USA

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ABSTRACT

Although current guidelines on the management of stable coronary artery disease acknowledge that multiple mechanisms may precipitate myocardial ischemia, recommended diagnostic, prognostic and therapeutic algorithms are still focused on obstructive epicardial atherosclerotic lesions, and little progress has been made in identifying management strategies for non-atherosclerotic causes of myocardial ischemia. The purpose of this consensus paper is three-fold: 1) to marshal scientific evidence that obstructive atherosclerosis can co-exist with other mechanisms of ischemic heart disease (IHD); 2) to explore how the awareness of multiple precipitating mechanisms could impact on pre-test probability, provocative test results and treatment strategies; and 3) to stimulate a more comprehensive approach to chronic myocardial ischemic syndromes, consistent with the new understanding of this condition.

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1. Introduction

In recent years, conceptual models of ischemic heart disease (IHD) have continued to evolve. The hypothesis of obstructive atherosclerotic coronary artery disease (CAD) as the prevalent if not the only cause of myocardial ischemia is now being reconsidered, acknowledging that other mechanisms may precipitate myocardial ischemia, alone or in combination. This new understanding of myocardial ischemia as a multifactorial condition, is based on a large body of scientific evidence proving that obstructive coronary atherosclerosis is not consistently associated with myocardial ischemia and, conversely, that myocardial ischemia often occurs in the absence of obstructive atherosclerosis [1–6].

In addition to vascular mechanisms, non-vascular factors, including abnormalities in cardiac energy metabolism and changes in blood rheology secondary to platelet activation and/or inflammation will probably be considered in the near future among the mechanisms responsible for myocardial ischemic syndromes [7–9]. These concepts underscore the need for embracing a more inclusive understanding of myocardial ischemic syndromes than the traditional, "stenosis-centric" approach would allow.

This document will discuss the need and the implications of a paradigm shift in current clinical practice, consistent with the new understanding of the pathogenesis of myocardial ischemic syndromes.

2. The impact of multiple mechanisms of ischemia on diagnostic approaches

Current management is focused on the "epicardial coronary obstruction-first" approach, assuming that obstructive atherosclerosis

* Corresponding author at: Viale dei pini 293A, 56019 Vecchiano, Pisa, Italy.
E-mail address: mario.marzilli@med.unipi.it (M. Marzilli).
[1] Expert consensus from scientific meetings held in Pisa and Rome.

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remains the primary and proximate cause of myocardial ischemia, and that, in the presence of obstructive atherosclerosis, there is no need to search for other possible alternative or coexisting mechanisms of ischemia. Thus, despite guideline recommendations, contemporary practice remains largely centered on the management of obstructive epicardial CAD, with the therapeutic goal of removing flow-limiting coronary stenoses [10].

In the future, the identification of the precipitating mechanisms (s) of myocardial ischemia in the individual patient and the prevalence of non-obstructive mechanisms in patients with or without obstructive coronary atherosclerosis is expected to become a key step in the management of patients with chronic ischemic syndromes.

3. The prevalence of non-obstructive mechanisms in angina patients

Several studies have reported an inconsistent association of atherosclerotic obstructions with typical angina and/or documented myocardial ischemia (Table 1). In a study of 163 angina patients, only 24% presented with obstructive CAD [11]. Of note, 15 of the 39 patients with flow-limiting lesions presented with "normal" stress test, confirming the elusive link between obstructive lesions and inducible myocardial ischemia. In the FAME 2 trial, that included 1220 patients, 332 subjects (27%) with angina and/or documented ischemia had a fractional flow reserve [FFR] > 0.80 [12]. In the CORMICA Trial, obstructive epicardial disease was present in 210 subjects of 391 (53.7%) [13].

In the American College of Cardiology National Cardiovascular Data Registry, only half the patients with a positive test had a stenosis >50% at angiography [5]. Similarly, in the CONFIRM Registry, the prevalence of stenoses >50% was 50% in male patients, and 30% in female patients, with lower figures in younger subjects [6]. In a large registry of 375,886 patients with stable angina pectoris, 51% of women and 33% of men had no hemodynamically significant coronary stenosis [14].

According to the 2019 ESC Guidelines on Chronic Coronary Syndromes, the pre-test probability of obstructive coronary artery disease is 32% in male patients with typical angina, age 50–59, and 13% in female patients with typical angina, age 50–59 [10].

Based on these data we can conclude that obstructive atherosclerotic lesions, far from being consistently associated with myocardial ischemia, are actually absent *in more than half of patients* presenting with typical angina and/or myocardial ischemia. In addition, the persistence of angina in 20–40% of patients, after "successful" revascularization, suggests that other mechanisms may contribute to precipitation of myocardial ischemia even in patients with obstructive atherosclerosis [15].

4. Sensitivity and specificity of provocative tests

The lack of a consistent association between coronary stenosis and ischemic syndromes, imposes to reconsider current criteria for the assessment of sensitivity and specificity of diagnostic tests. Traditionally assessment of sensitivity/specificity was based on presence or absence of a significant stenosis rather than on presence or absence of myocardial ischemia. The possibility that myocardial ischemia could be absent in patients with a "significant" stenosis or conversely that ischemia can be present in the absence of a coronary stenosis, was not considered.

Thus, a negative stress test in the presence of a stenosis is still diagnosed as a "false negative" and, a positive test in a patient without a significant stenosis is diagnosed as a "false positive". This construct appears overly simplistic and no longer tenable. Positivity or negativity of a provocative test should be assessed only on the presence or absence of symptoms and signs of myocardial ischemia, being aware that triggering ischemia will strictly depend from the correspondence of the selected stressor (exercise, dobutamine, dypiridamole, adenosine, acetylcholine, etc.) with the mechanism responsible of ischemia. Until this approach will be more widely adopted, the risk for patients is that myocardial ischemia can be overlooked because of the absence of a stenoses or potentially over-diagnosed because of the presence of a coronary stenosis. In the first case, the patient will be denied appropriate treatment, in the second case, he might receive inappropriate procedures. The main limitation of this approach is that we lack reliable triggers for many of the mechanisms that can induce myocardial ischemia. Exercise and dobutamine are useful tools to unravel a flow limiting stenosis, dypiridamole and adenosine can identify an impaired microvascular dilating capability, acetylcholine and ergonovine can trigger a vasospasm, but we have no tool to asses reliably coronary inflammation, primary metabolic derangements, etc.

The complex and dynamic nature of myocardial ischemia needs to be further underscored. Pathophysiologic mechanisms interact through intricate feedback pathways and probably in a patient-specific manner. For instance, microvascular dysfunction and inflammation may interact in some, but not all patients. Similarly, the effect of endothelial dysfunction on the coronary microcirculation is likely to be complex and variable according to sex, while coronary spasm is likely to be modulated by endothelial function, inflammation and components of the cytoskeleton [16,17].

In an "ischemia-centered" diagnostic strategy, the reproduction of typical symptoms and/or transient diagnostic ECG changes, and/or regional wall dysfunction and/or perfusion abnormalities should be accepted as evidence of myocardial ischemia, irrespective of coronary anatomy and even if the precipitating mechanism is not clearly identified. In addition, the diagnosis of myocardial ischemia should not be denied because of "negative" tests prior to consider whether the appropriate ischemic stressor has been administered.

A list of mechanisms proposed as causes of myocardial ischemia is presented in Fig. 1, in an arbitrary order from left to right, including those perceived as definite (microvascular dysfunction, spasm, stenosis), probable (endothelial dysfunction, platelet dysfunction, microembolization), possible (oxygen transport, energy substrates, mitochondrial dysfunction, aberrant origin). It is assumed that these mechanisms may precipitate angina and/or ischemia in isolated fashion or in combination.

At the current state of knowledge, we have limited capacity of identifying the causing or prevailing mechanism in the individual patient. Common hints include the presence of symptoms and/or signs of ischemia at rest in patients with vasospastic angina and the lack of clinical benefit from PCI in patients with microvascular dysfunction. However, this is in clear contrast with the variety of mechanisms listed above. Until further evidence becomes available, the best way of understanding the underlying mechanism in patients suffering chronic ischemic syndromes appears intersection of information from a carefully taken medical history and the results of more than one provocative testing when feasible. When sufficient data will be available, the construction of algorithms that will predict the underlying mechanism in advance can be aspired.

5. Risk assessment in chronic coronary syndromes

Prognosis of patients with myocardial ischemic syndromes is commonly considered to be dictated by severity and extension of coronary

Table 1
Prevalence of stenosis in recent angina studies.

	Total number of Pts	Pts with significant stenosis	Pts without a significant stenosis
RCT			
FAME 2 [12]	1220	888	332 (27%)
PROMISE [28]	4996	549	4447 (90%)
SCOT-HEART [29]	1778	452	1326 (75%)
ORBITA [30]	200	143	57 (29%)
CORMICA [13]	391	206	151 (39%)
Registries			
Lin F [11]	163	40	123 (76%)
Patel MR [5]	398.978	149,739	249.239 (62%)

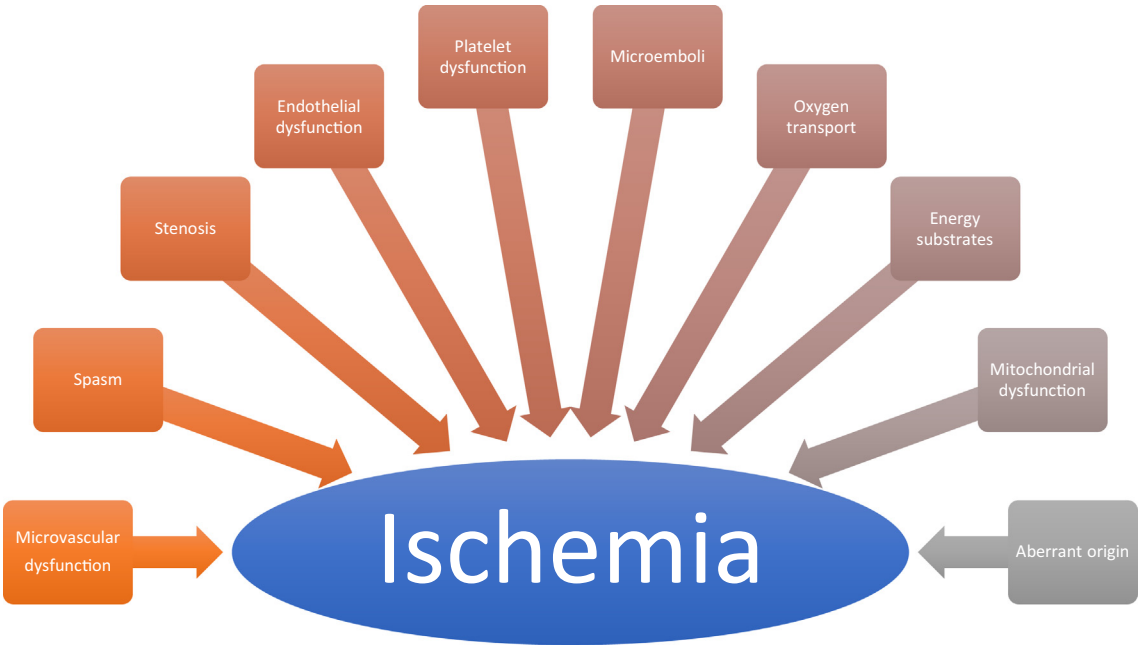

Fig. 1. Mechanisms of myocardial ischemia 1.

atherosclerosis. Recent reports challenge this assumption [18,19]. In the Danish registry on Ischemic Heart Disease, patients with angina and normal coronary arteries had an 85% increased risk of major adverse cardiovascular events (MACE) (cardiovascular mortality, hospitalization for MI, heart failure, or stroke) and a 52% increased risk of all-cause mortality, with no difference between men and women, compared to the control population. Interestingly enough, in this Registry, patients with stable angina frequently had non-obstructive CAD: 65% of women and 32% of men, with an increasing trend over time.

6. From a hierarchical to a tailored approach in drug therapy

The new understanding of myocardial ischemia, call for a re-evaluation of current management protocols. The identification of the mechanism(s) that induce ischemia in each patient appears of paramount importance for a tailored therapeutic approach. However, 2019 ESC Guidelines still propose a stepwise approach, identifying first line, second line, third line, and even fourth line antianginal agents [10]. To further complicate medical decisions, guidelines acknowledge that there are circumstances where the second line agents can become first line [10].

This hierarchical or stepped-care approach has been recently challenged, based on a number of considerations [20,21]:

- Absence of any effort to match the antianginal agent with the precipitating mechanism of myocardial ischemia.
- Limited if any consideration for comorbidities that can interfere or contraindicate some antianginal agents: hypertension, diabetes, peripheral vascular disease, depression, etc.
- Lack of evidence to support recommendations. In a recent analysis of trials published over the last 50 years, no superiority emerged for any of the agents listed as fist line versus those listed as second line [21]

Beta-blockers and ivabradine are useful in the presence of flow-limiting obstructions, but they are ineffective when ischemia is caused by epicardial or microvascular spasm. Organic nitrates, acting as an exogenous substrate for nitric oxide (NO), are probably useful when endothelial dysfunction disrupts the endothelial L-arginine/NO pathway, resulting in decreased availability of bioactive NO with reduced endothelium-dependent relaxation, but induce tolerance with loss of efficacy [22]. When epicardial coronary or microvascular spasm is documented, calcium channel blockers should be the first choice [23]. A metabolic approach with trimetazidine or ranolazine could be the best option, in most patients, including those in whom the mechanism responsible for angina and ischemia is not clearly identified [24].

7. Indications for myocardial revascularization

Numerous trials and several metanalyses, have failed to prove a prognostic benefit of PCI on top of medical therapy. These conclusions have been confirmed by the recently published ISCHEMIA trial [25]. Among patients with stable coronary artery disease and moderate to severe ischemia, an initial invasive strategy did not reduce the risk of ischemic cardiovascular events or death over a median of 3.2 years, as compared to an initial conservative strategy. Similar results have been reported in a companion study including patients at higher risk of severe adverse events associated with advanced kidney disease [26].The ISCHEMIA Trial did not include patients with left main disease, therefore the results do not apply to this high risk subgroup [26].

A better understanding of the mechanisms precipitating angina and ischemia in each patient has the potential to limit the number of unnecessary procedures, and, consequently, to improve the global cost-benefit ratio of PCI. The persistence of angina and/or ischemia after PCI is commonly attributed to technical factors such as incomplete revascularization and/or in-stent restenosis [27]. However, a recent prospective study, in which care was taken to exclude confounding factors, confirmed that "successful" uncomplicated PCI leaves 30% of patients with symptoms and signs of myocardial ischemia [15]. Unnecessary procedures could be avoided if alternative mechanisms were investigated prior to PCI, not only in patients without significant stenosis at angiography [13], but also in patients with a significant stenosis.

8. Conclusions

The purpose of this document is to stimulate changes in cardiology practice consistent with the multifactorial nature of myocardial ischemic syndromes.

Available evidence strongly encourage to migrate away from the monolithic chronic coronary "disease" to the broader and more

inclusive construct of "myocardial ischemic syndromes" that recognizes the importance of many underlying causes. This new perception of myocardial ischemia as a multifactorial condition is expected to downgrade the role of coronary stenosis, and in greater attention to alternative mechanisms of ischemia, including epicardial spasm, coronary microvascular dysfunction, and alterations in cardiac energy metabolism. Thus, we need to re-orient our thinking away from a model of epicardial flow-limiting coronary obstructions as the sine qua non of angina and ischemia and embrace a more comprehensive paradigm, incorporating other ischemia-causing mechanisms.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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