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Is ischemia a disease or syndrome, the cause of angina, and now even a trial?

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Abstract: The clinical manifestations of myocardial ischemia are protean in nature and include a variable combination of typical or atypical angina symptoms, electrocardiographic changes, noninvasive findings of regional wall motion abnormalities, and reversible scintigraphic perfusion defects—the changes of which, importantly, may or may not be of epicardial coronary origin. Thus, mounting evidence indicates that the presence or absence of atherosclerotic coronary artery disease (CAD) should no longer be considered a surrogate marker for myocardial ischemia, as suggested by the high prevalence of minor or absent coronary obstruction among patients with proven myocardial ischemia. Whereas the management of CAD has been largely predicated on the plausible assumption that flow-limiting obstructions of the epicardial coronary arteries are the proximate cause of both angina and myocardial ischemia, there is scant evidence from many randomized trials and several meta-analyses that treating epicardial coronary obstructions in patients with stable CAD, particularly with percutaneous coronary intervention (PCI), reduces mortality and morbidity, as compared with optimal medical therapy (OMT). A crucial scientific question for which evidence has been lacking is whether more severe and extensive myocardial ischemia is the driver of adverse cardiovascular outcomes and whether an invasive strategy with myocardial revascularization would be superior to OMT alone in such patients. The results of the recent ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches), however, have failed to show—even in this higher-risk CAD subset—any incremental clinical benefit of revascularization as compared with OMT alone on cardiac event reduction. ■ *Heart Metab*. 2020;81:36-39

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It has been well-recognized for many decades that symptoms in patients with obstructive atherosclerotic coronary artery disease (CAD) are protean in nature and may vary widely across a spectrum that ranges from none (either with or without "silent myocardial ischemia"), to stable angina or anginal equivalent symptoms (eg, exertional dyspnea or decreased effort tolerance), to severe rest angina culminating in acute coronary syndromes (ACS) or myocardial infarction (MI) and, in some instances, sudden cardiac death. As cardiologists, we have dedicated ourselves to the scientific understanding of how best to diagnose and manage CAD and how we can best use the many tools within our diagnostic and therapeutic

armamentarium to improve both clinical outcomes and the symptomatic status of our patients. Since the advent of coronary angiography 60+ years ago, the diagnosis and treatment of CAD has been largely predicated on the plausible assumption that "significant" flow-limiting atherosclerotic obstructions of the epicardial coronary arteries are the proximate cause of both angina and myocardial ischemia. This intuitive belief, supported by both anatomical and physiological evidence that obstructive coronary stenoses result in regional ischemia and may, in the acute setting, presage acute MI, has profoundly influenced our approach to CAD management over decades, even in patients with chronic stable angina. This, in turn, has fostered a parallel belief that revascularization directed at surgically bypassing or percutaneously stenting obstructive coronary stenoses improves survival, reduces MI, decreases regional ischemia, and improves angina. Whereas this paradigm has been proven in patients with ST-segment elevation MI and in high-risk subsets of ACS patients, there is scant evidence from numerous randomized trials and several meta-analyses that treating epicardial coronary obstructions in patients with stable CAD, particularly with percutaneous coronary intervention (PCI), reduces mortality and morbidity, despite the continued evolutions in stent design and technology, as compared with optimal medical therapy (OMT), which includes intensive secondary prevention and lifestyle intervention.[1-5]

Nevertheless, PCI remains a widely used (and often preferred) treatment approach in clinical practice worldwide. The current and prevailing anatomically driven practice paradigm has not been challenged, despite the existence of compelling evidence that the majority of angina patients (both men and women) do not have significant flow-limiting coronary obstructions, and most patients with significant obstructions may never experience angina.[6] Thus, there is a need to uncouple the pathophysiological link and widely-held belief that "significant" epicardial coronary obstructions are the singular cause of both angina and ischemia. Yet, both clinical event trials of PCI vs OMT and the ORBITA trial (Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina)[7] raise concerns about whether all angina is due to epicardial CAD, or whether other pathophysiological processes may be at play, such as microvascular dysfunction, impaired coronary flow reserve, coronary vasospasm, superimposed inflammation, and perturbations in myocardial energy or myocyte metabolism. For these reasons, a plausible counterhypothesis (or alternative paradigm) is that microvascular angina/ischemia may coexist with epicardial CAD in the same patient, which could explain why 30% to 40% of patients who undergo PCI for stable CAD develop recurrent angina within weeks/months of initially successful PCI.[8,9]

Clearly, the clinical manifestations of myocardial ischemia are multifaceted and include a variable combination of typical or atypical angina, electrocardiographic changes, noninvasive findings of regional wall motion abnormalities, and reversible myocardial perfusion defects using perfusion imaging—the changes of which, importantly, may or may not be of epicardial coronary origin. Thus, the presence or absence of coronary atherosclerotic obstructions should no longer be considered a surrogate marker for myocardial ischemia, as suggested by the high prevalence of minor or absent coronary obstruction among patients with proven myocardial ischemia.[10]

In partial acknowledgment of this multifactorial origin of angina and ischemia,[6] the European Society of Cardiology recently promulgated new guidelines that replaced the earlier stable CAD terminology[11] with the more encompassing nomenclature "chronic coronary syndromes" (CCS).[12] On first appearance, the migration in terminology from "stable coronary artery disease (SCAD)" to "CCS" imparts descriptive symmetry with ACS, yet the tenacious retention of the term "coronary" continues to propagate an overly simplistic and unidimensional concept that epicardial obstruction/stenosis is the principal cause of angina and ischemia and, hence, the dominant focus of both diagnosis and treatment. Whereas the term "syndrome" connotes a broader disorder that potentially embraces many pathogenetic causes of angina and ischemia, the new guidelines continue to rely heavily on both the noninvasive and angiographic assessment of obstructive epicardial CAD as the principal driver of decision-making and management, and which is also heavily influenced by stenosis removal—either percutaneously or surgically. Accordingly, a more accurate and inclusive binary classification that centers on both the acute and chronic manifestations of *myocardial ischemia* (including nonepicardial causes) would seem preferable to the traditional "coronary-centric" taxonomy of ACS and CCS.

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It thus seems logical that a more physiologically sound classification would be to consider myocardial ischemia as the "center of the diagnostic and therapeutic universe," as Marzilli and coworkers have proposed previously,[6] thus permitting the introduction of a more physiologically correct nomenclature centered on *acute and chronic (or nonacute) myocardial ischemic* syndromes that are inclusive of both coronary and noncoronary pathogenetic mechanisms, including asymptomatic (or silent) ischemia.

However, despite previous neutral/negative strategy trials of PCI vs OMT in stable CAD patients,[1-5] a critical scientific question for which evidence has been lacking to date is whether more severe and extensive myocardial ischemia is the driver of adverse cardiovascular outcomes and, as a corollary, whether an invasive strategy with myocardial revascularization would be superior to OMT alone in this presumably higher-risk stable CAD cohort.[13] In fact, it has been argued that if PCI does not improve death/MI and may not promote durable angina relief in CAD patients, as the ORBITA trial findings indicate, the entire "ischemia-revascularization hypothesis" may likewise be called seriously into question.[14] The recently published results from the ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches)[15] tested this important hypothesis in 5179 patients with moderate to severe inducible myocardial ischemia at baseline who were randomized to an invasive strategy of revascularization with PCI or coronary bypass surgery plus OMT versus a conservative strategy of OMT alone during a median 3.2-year follow-up, where the trial primary end point was a composite of cardiovascular death, MI, hospitalization for ACS or heart failure, or sudden cardiac death. The secondary end point was a composite of cardiovascular death or MI. For both the primary and secondary end points, there was no significant incremental benefit of the invasive strategy with revascularization on top of OMT alone. Notably, there was a 1.9% absolute early hazard associated with the invasive strategy for both the primary and secondary end points at 6 months, whereas there was a 2.2% absolute late benefit with the invasive strategy that appeared to be driven by a reduction in spontaneous MI.[14] Whereas the reduction in the secondary end point of angina and improvement in quality of life, as expected, was improved by the invasive strategy, there were no differences in the end points of all-cause mortality or net clinical benefit, which included the five-component primary end point plus stroke.

In summary, myocardial ischemia is a very important manifestation of angina pectoris and is a common clinical disorder that afflicts millions of patients worldwide. There needs to be a greater appreciation for the many causes of myocardial ischemia beyond obstructive epicardial CAD and a renewed recognition that, to date, we now have abundant data derived from multiple, contemporary randomized trials with robust clinical outcomes that have failed to demonstrate incremental event rate reduction with an invasive strategy of revascularization as compared with OMT alone in nonacute myocardial ischemic syndromes. Clearly, angina and ischemia have many causes, and both evaluation and treatment need to be tailored to the individual patient, but an important guiding principle is that our therapeutic decision-making should be informed by the compelling scientific evidence derived from previous trials[1-4] as well as ISCHEMIA.[15] ■

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