OPINION ARTICLE

Is the Anatomy the New Paradigm in the Chronic Coronary Syndromes?

¿Es la anatomía el nuevo paradigma en síndromes coronarios crónicos?

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The condition widely known as chronic stable angina used to be considered as uncomplicated and generally easy to solve by percutaneous revascularization. However, this is no longer the case. Understanding of its true significance has evolved towards characterizing different pathophysiological forms currently and widely known as chronic coronary syndromes (CCS). This paper intends to briefly describe the most relevant data from the latest evidence and to reflect on the meaning of myocardial ischemia when making clinical decisions about revascularization in the year 2023.

We need to distinguish at least 4 subtypes of CCS: severe left main coronary artery (LMCA) lesion/severe proximal multivessel lesions; severe diffuse multivessel disease; severe focal lesion; and non-severe diffuse disease/without angiographically significant lesions, with microcirculation involvement. These are all synonyms of atherosclerosis and vascular dysfunction with considerable overlapping. The role of clinical cardiology is to be able to include the patient in the right part of the spectrum in order to maximize the treatment benefits. This analysis will not include microvascular disease with no significant epicardial lesions, as it demands a different approach. Concisely, evaluation ideally involves invasive tests of coronary physiology, including an acetylcholine test to rule out epicardial (and microcirculation) vasospasm, as well as the calculation of the coronary flow reserve and the microcirculatory resistance index. Furthermore, if a non-invasive evaluation is chosen, quantification of the absolute flow via a cardiac positron emission tomography (PET) is the most informative test. (1,2) Another possibility is the semiquantitative evaluation provided by the stress ECG through the anterior descending artery flow reserve. Please note that an abnormal flow reserve cannot be ruled out by absence of myocardial ischemia on a "conventional" single photon emission computed tomography (SPECT) or a stress echo. (3)

Further understanding of ischemic heart disease has increased, and the paradigm is changing again. From the anatomy to the ischemia, a little more than two decades have passed, ¿and now from the ischemia to the anatomy again? As reflected by the guidelines from nearly all scientific associations, a short time ago, (4,5) the presence of myocardial ischemia ≥10% was considered as high-risk for events and was an unquestioned cut-off point when deciding on an invasive revascularization strategy for chronic coronary disease. Ischemia was the focus of every decision. This outdated concept has been updated by the extensive observational study performed by Dr. Rory Hachamovitch et al. from Cedars-Sinai Medical Center and published in Circulation in 2003, which included more than 10 300 patients. (6) With all the evidence and data from the ISCHEMIA study, one question shocked the clinical scenario three years ago: has significant ischemia ceased to be a *sine qua non* sign of revascularization, even with symptoms present? The answer was yes. Why? Essentially because we have observed that "sustained long-term intensive" drug therapy has shown clinical efficacy and safety to the detriment of an invasive approach. Why? There is no simple answer to this question, but we could easily mention the following: stabilized (or even reduced) plaque with the resulting clinical and imaging slowdown in disease progression, myocardial protection, vascular function improvement, and symptom control. A healthy lifestyle (7) (exercise, a Mediterranean diet, avoidance of smoking, and stress control), a goal-directed therapy [angiotensin converting enzyme inhibitors/angiotensin receptor blockers, (7) β-blockers, (8) statins, (9) ezetimibe, (10) and PCSK9 inhibitors], and an eventually improved antithrombotic management, apart from aspirin in high-risk patients [P2Y12 receptor blockers (11) and antiXa-rivaroxaban (12,13)], have shown the strengths of selecting a conservative therapy. In addition, a deeper understanding of coronary circulation pathophysiology has introduced new concepts in clinical cardiology, such as coronary flow reserve (CFR), which has become a major prognostic

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marker providing additional information with no direct correlation both with the extent of coronary disease and the myocardial ischemia.

The ISCHEMIA study (2020) (14) and its long-term follow-up interim analysis with a mean of 5.7 years, and known as ISCHEMIA-EXTEND, (15) being recently published (November 2022), continue to follow the path first led by the revolutionary COURAGE study (2007), (16) and later by BARI 2D (2009) (17) and FAME-2 (2012), (18) among others: in patients with good ventricular function, myocardial ischemia *does not appear to be* a relevant prognostic marker, and revascularization regarding this has no significant impact on the disease course under the best available drug therapy (BADT). These studies were designed to compare a conservative drug strategy against revascularization in a scientific period when coronary angioplasty was essentially seen as the solution for stable angina. Many lessons have been learnt since then.

Some of the milestones worth considering are:

- The COURAGE and ISCHEMIA/ ISCHEMIA-EXTEND studies showed that revascularization fails to change prognosis in patients with obstructive epicardial disease and significant ischemia under the BADT.
- The FAME-2 study showed that revascularization guided by fractional flow reserve (FFR) reduced urgent revascularization and *marginally* reduced spontaneous infarction after 5 years.
- The ISCHEMIA study also showed that revascularization of a severe isolated proximal lesion of the descending anterior artery (≥ 50%) failed to reduce events, as typically thought in the past.
- The COURAGE and ISCHEMIA studies showed that angina is relieved by revascularization, although during the follow-up the differences with respect to the BADT are reduced or disappear.
- According to the ORBITA study, (19) angioplasty did not improve times of exercise or the frequency of precordial pain in patients with anatomical and functionally significant stenosis. This clever trial cleared up doubts about the potential "anti-angina placebo effect" of the percutaneous intervention itself when using a sham procedure as control.
- APPEAR (20) and CLARIFY (21) were large observational studies proving that most patients with chronic coronary artery disease had mild symptoms or remained asymptomatic.

It seems clear that patients with CCS and good ventricular function do not benefit from a systematic revascularization strategy as compared to the BADT in the case of focal anatomical lesions leading to ischemia. However, it is also evident that the multivessel anatomical and diffuse disease with a high atherosclerotic burden, as in patients with diabetes, is clearly favored by revascularization: this is confirmed by the BARI 2D, FREEDOM study, (22) the ISCHEMIA substudy, (23) COURAGE 10-year follow-up, (24) and the FAME 3 trial. (25) Support is also provided by another major and inescapable pathophysiological concept: thrombotic or plaque events are caused by various mechanisms in vulnerable lesions that, in many cases, are not anatomically obstructive. (26) In this subtype of patients, revascularization by coronary artery bypass grafting should protect the distal myocardium passing over a number of vulnerable (and non-vulnerable) lesions, in contrast to the angioplasty which revascularizes in a focal manner.

These ideas have resulted in a new model to assess the heart vasculature, together with the advances in multislice computed tomography (MSCT), which is currently available, and, in my opinion, this will be a game changer for CCS management. MSCT provides a precise non-invasive evaluation of obstruction sites, grades, and scope (particularly, in the main and proximal vessels), as well as plaque features (vulnerability). Something even more disruptive is the recent application of new softwares to estimate the coronary fractional flow reserve (FFR-CT) during the same study and with high precision. FFR derived from the MSCT or FFR-CT, when applying computational fluid dynamics, estimates FFR values in all epicardial coronary arteries with no need for any additional drugs, images, or protocol changes.

Two randomized studies of more than 14 000 patients [PROMISE (27) and SCOT-HEART (28)] and the DANISH registry, (29) with 86 700 patients, showed superiority in terms of CCS management using MSCT versus ischemia-evocative tests for death and myocardial infarction. Early and precise anatomical knowledge can be used to quickly dismiss high-risk patients (proximal multivessel or left main coronary artery), achieve better stratification, and work on treatment optimization/enhancement.

In addition, in 2021 Reynolds et al. published an important ISCHEMIA substudy in Circulation, (30) which showed that the severity of ischemia was not associated with death or infarction after 4 years, and that the scope of anatomical disease was independently associated with non-fatal infarction (HR 3.78, 95% CI 1.63–8.78) and all-cause death (HR 2.72, 95% CI 1.06–6.98) after 4 years. These data have been confirmed for the group of patients with severe proximal lesions in two or more vessels, including proximal left anterior descending artery.

Therefore, the paradigm is shifting towards assessment of new anatomical and functional aspects in CCS, which leads us to reinterpret a condition with a complex course, and evidence that avoids the dogmatic clinical routine of suspecting ischemia. In this setting, a MSCT is recommended by many authors as the main and initial element in the study/decision algorithm. "Systematic management" guided by a finding of ischemia through myocardial perfusion (SPECT) or stress echo is now left behind. Anatomy would serve to rule out proximal multivessel and LMCA prognostic disease, and eventually ischemia assessment studies would be used to readjust treatment in case of

symptoms, or their persistence, with a relative impact on intervention indication. Ischemia seems to be a complementary and substitute feature for the burden of atherosclerotic coronary disease, ¿except if higher than 15%? This question and new prognostic value emerges from an extensive retrospective analysis of more than 43 000 patients under cardiac rest-stress SPECT from 1998 to 2017 with a median follow-up of 11.4 years, recently published by Rozanski et al. (31) This needs to be confirmed by prospective studies.

The future goes beyond anatomy in this new CCS era: the characteristics and scope of atherosclerotic disease across the entire coronary tree and flow reserve in every artery, plus novel myocardial perfusion techniques within the same procedure. Impressively, all these elements will continue to evolve permanently towards a more precise diagnosis and clinical interpretation. (32,33)

To conclude, ischemia has been moved (though not removed) from central decision-making, and MSCT-aided anatomy has now become the most relevant prognostic marker in this respect. For practical reasons, the present revascularization indication should be guided by *symptoms incompatible with quality of life under the best available drug therapy, high-risk anatomy, and/or acute coronary syndrome.*

"There is no sin in finding out there is evidence that contradicts what we believe. The only sin is not using that evidence as objectively as possible to refine that belief going forward." @AnnieDuke.

Conflicts of interest

None declared.
(See authors' conflict of interests forms on the web/Additional material.)

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