From disease to syndrome: how did we get there

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Doralisa Morrone

THE CLINICAL CASE

"A 53-year-old woman with no risk factors was admitted to the hospital because of worsening angina and positive exercise stress test [...]. A few hours after admission, she had a recurrence of pain with ST elevation on the inferior electrocardiogram (ECG) leads that responded to intravenous nitrates, followed by an increase of markers of myocardial necrosis with no coronary stenosis at the coronary angiography [...]. The discharge diagnosis was inferior ST-elevation myocardial infarction with normal coronary arteries. She remained symptom free for about a month. Then, during a very stressful period of her life, she began to present with anginal pain during effort, sometimes on emotion [...]. The pain did not subside promptly with the termination of exercise but lasted 5 to 15 minutes, with a poor response to nitroglycerine. The ECG stress test was positive, with 2-mm ST-segment depression in leads V2 through V6, and a repeated angiography showed normal coronary arteries. Despite an increased dosage of beta-blockers, the symptoms did not improve. During hospital admission the ECG showed small Q waves in leads II, III, and aVF. An echocardiography dipyridamole test caused the same type of chest pain that had brought her to the hospital and showed it to be associated with diagnostic ST-segment depression in leads V2 through V5 without changes in regional wall motion. Methylergometrine maleate testing caused akinesia of the mid-cavity inferior and inferoseptal walls associated with transient 2-mm ST elevation in leads II, III, and aVF [...]."[1]

The clinical case demonstrates that two distinct coronary ischemic mechanisms involving two separate segments of the ventricular wall were present in the same patient. This conclusion was supported by the response to the provocative stressors dipyridamole and methylergometrine. Microvascular dysfunction was the cause of anterior wall ischemia and coronary spasm was the cause of inferior wall ischemia/necrosis confirming that different mechanisms may elicitate the ischemic event even in the same patients.

INTRODUCTION

Ischemic heart disease (IHD) concept has continued to evolve challenging the previous concept of "critical coronary stenosis." In fact, in 1974 Gould and Lipscomb described the effects of progressive coronary artery narrowing on resting and maximal coronary blood flow. A

reduction in coronary artery diameter of >50% limited maximal coronary vasodilative capacity and a reduction of >85% limited resting coronary blood flow.[2] These laboratory findings were soon transposed into the clinical setting introducing the definition of hemodynamically significant coronary stenosis, for stenosis >50%, and the concept of critical coronary stenosis in presence of stenosis of >85%. The concept of "critical coronary stenosis" was then further transmuted into "ischemia-causing stenosis." Based on this chain of postulates, coronary stenosis, and therefore atherosclerotic obstructions, gained increasing recognition as a consistent cause of IHD. Thus, when a relatively simple percutaneous technique that could reduce the atherosclerotic obstruction was introduced,[3] the cardiology community reacted with great enthusiasm and promptly endorsed the method. Gould's hypothesis of obstructive coronary artery disease (CAD), as the prevalent pathogenetic mechanism of myocardial ischemia, is now being reconsidered in the context of other mechanisms that can precipitate myocardial ischemia acting in isolation or in combination with anatomically obstructive CAD.[4] Furthermore, according to a wide range of evidence latest evidence obstructive CAD may not lead to symptomatic ischemia; and, conversely, the latter can occur in the absence of obstructive CAD.

♥ ANGINA AND MYOCARDIAL ISCHEMIA

Angina derives from the Latin *angere* ("to strangle") and *pectus* ("chest") and can therefore be translated as "a strangling feeling in the chest." In 1772 William Heberden's published the classic description of angina: "[...] but there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it and the sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris [...]."[5] In 1953 the Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels published the first description of angina describing features that were the same as those described by Heberden[6] The mechanism that initiates the syndrome was not clear and 200 years later from first description, Osler noticed that in the dog, ligation of one of the large coronary branches produces, within a minute, a condition of arrhythmia, and within two minutes the heart ceases contractions in diastole. "These experiments, however, do not throw much light upon the aetiology of angina pectoris." In 1983 Osler declared the divorce between myocardial ischemia and coronary stenosis: "in human being extreme sclerosis of the coronary arteries is common, and a large majority of the cases present no symptoms of angina. Even in the cases of sudden death due to blocking of an artery, particularly the anterior branch of the coronary artery, there is usually no great pain either before or during the attack."[7] A series of evidence, centuries later, confirmed the Osler's hypothesis, the relatively low prevalence of obstructive CAD in patients with established IHD. In a large observational study by Patel *et al.*, comprising 398.978 subjects undergoing invasive coronary angiography (ICA), stratified for symptoms characteristics and results of functional tests, only 40% to 53% of the patients with typical angina had obstructive CAD,

a prevalence only slightly higher than that of subjects with no symptoms (32-43%) or atypical symptoms (18-27%). It is also interesting to note that in this registry, the prevalence of obstructive stenoses in patients with a test positive for ischemia was not markedly different from that of those with a negative test.[8] The Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter (CONFIRM) registry based on a sample of 17,793 patients, all with suspected CAD, the prevalence of stenoses >50% was 50% in male patients, and 30% in female patients.[9] In addition, 38.2% of patients who underwent ICA for angina resistant to medical therapy had normal coronary arteries or non-obstructive CAD, suggesting that resistance to medical therapy does not necessarily imply severe underlying atherosclerosis. 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.[10] Based on registry data obstructive atherosclerotic lesions are absent in more than half of patients presenting with typical angina and/or myocardial ischemia. Data from published randomized clinical trials are not far from real life examples. The FAME study (fractional flow reserve *versus* angiography for guiding percutaneous coronary intervention), randomized 1005 to percutaneous coronary intervention (PCI) guided by fractional flow reserve (FFR) or by angiography. The primary end point (composite of major cardiac events) at 1 year occurred in significantly fewer patients in the FFR-guided group than in the angiography-guided group (13.2% *versus* 18.3%, P=0.02).[11] However, on the basis of FAME I study, De Bruyne *et al.* hypothesized that in patients with stable coronary artery disease and epicardial coronary stenosis, PCI performed on the basis of the FFR would be superior to optimal medical therapy (OMT). The 2-year follow-up of FAME 2 trial (Fractional Flow Reserve-Guided PCI for Stable Coronary Artery Disease), reported that the benefit of FFR-guided PCI was a decrease in urgent revascularization at the expense of 351 more revascularizations in PCI group when compared with OMT group, without an effect on death or MI. Moreover still 10% of patients in PCI group have angina at 6-month follow-up despite optimal revascularization and 332 subjects (27%) had a fractional flow reserve (FFR)>0.80. Patients included in the registry group (patients without significant stenosis) of the FAME 2 trial had the same clinical presentation despite absence of the significant stenosis.[12] Interestingly, the recent ORBITA trial, the first blinded placebo-controlled trial in the history of PCI, showed that when the efficacy of invasive procedures is assessed in a double-blind, placebo-controlled trial, PCI does not improve symptoms and exercise capacity, evaluated with Canadian Cardiovascular Society angina grading, Seattle Angina Questionnaire and EQ-5D-5L questionnaire, by more than the effect of a placebo procedure, despite the patients having ischemic symptoms and severe coronary stenosis both anatomically and hemodynamically.[13]

In the published trials on acute coronary syndromes, the prevalence of normal or non-obstructive coronary arteries ranged from 8% to 27% in men and from 14% to 31% in women.[14] In the GUSTO IIb trial, 30.5% of women with unstable angina and 10.2% of women with STEMI had normal coronary arteries.[15] This large body of evidence confirms the inconsistency of the relationship between CAD and IHD. Obstructive CAD is neither necessary nor sufficient for the pathogenesis of IHD because: 1) many patients with IHD do not have obstructive CAD; and 2) most subjects with obstructive CAD do not have IHD.

THE FAILURE OF MYOCARDIAL REVASCULARIZATION

Randomized controlled trials (RCTs) in ischemic heart disease aimed to assess the PCI efficacy. In this setting numerous trials, since 1970 until now, failed to prove a prognostic benefit of PCI on top of medical therapy. Up to 2015, a total of 197,118 patients had been screened for enrollment in RCTs that compared PCI to OMT showing that 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.[16] One of the first trial that compared PCI *vs.* OMT was the Randomized Intervention Treatment of Angina Trial (RITA) that enrolled 1011 patients. The mortality rate in the RITA II trial was almost identical between the patients treated with PCI or OMT after an 8-year follow-up.[17] In the Medicine, Angioplasty, or Surgery Study (MASS II) and Asymptomatic Cardiac Ischemia Pilot (ACIP) trials no difference was reported in terms of reinfarction or mortality among patients treated with PCI or optimal medical therapy.[18, 19] However, the functional significance of coronary stenoses became more important only after the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) studies, which provided a clear demonstration that revascularizing anatomically significant coronary stenoses does not automatically confer a prognostic benefit.[11, 20] Results did not change between the pre- and post-ISCHEMIA era; 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.[21]

FROM SINGLE TO MULTIPLE MECHANISMS

Myocardial ischemia may be due to inadequate blood oxygen supply, impaired myocardial perfusion, reductions in blood oxygen content, increase in energy demand or impaired energetic metabolism; it may be transient, recurrent and/or sustained. This complex phenomenon may lead to electric, contractile, metabolic and/or structural consequences for the myocardium. Numerous reports have described the coronary and non-coronary functional alterations, other than the presence of coronary stenoses, leading to myocardial ischemia. Some of these include microvascular dysfunction, vasomotor disorders and endothelial or vascular smooth muscle dysfunction, that have been associated with increased risks for adverse outcomes. Microvascular dysfunction may include impaired vasodilator capacity, remodeling or rarefaction.[22] Vasomotor disorders include macrovascular and microvascular spasm, reflecting enhanced coronary reactivity due to an imbalance in vasodilator endothelial function and vasoconstrictor vascular smooth muscle cell tone. However, other than the mechanisms mentioned above, many other mechanisms may alter determinants of myocardial oxygen supply-demand with the potential to result in ischemia. In 2012 Pepine *et al.* elegantly proposed a classification of mechanisms that may cause ischemia. Authors divided the potential mechanisms into two compartments: vascular and non-vascular. The vascular section includes macrovascular (flow-limiting stenosis, endothelial dysfunction,

coronary spasm and vasomotion, inflammation, etc.) and microvascular circulation (microvascular dysfunction, endothelial dysfunction, microvascular spasm, etc.). The non-vascular compartment includes defects of transcellular and intracellular transport of oxygen, energy substrates and defects of mitochondrial energy production. It is important to highlight that symptoms due to myocardial ischemia may arise from a combination of these mechanisms that are not mutually exclusive, but frequently overlap each other.[4] Translating these evidence into practice: "coronary obstruction does not always imply the presence of ischemia and absence of obstruction does not always imply the absence of ischemia," meaning that a new multifactorial model could open novel pathways to the development of diagnostic and finally therapeutic approaches.

♥ CURRENT MANAGEMENT AND FUTURE PERSPECTIVE

In patients with suspected chronic coronary syndromes (CCS), current guidelines recommend the assessment of the pretest probability (PTP) to choose the appropriate diagnostic tests. When the PTP is intermediate, either the assessment of vessel anatomy through coronary computed tomography angiography (CCTA) and/or of inducible myocardial ischemia, through a functional stress testing, is advised. According to the current guidelines, CCTA should be preferred when the PTP is low-to-intermediate, and functional testing when the PTP is intermediate-to-high. A functional imaging test is also recommended when CCTA results are non-diagnostic, and *vice versa*.[23] However, the prevalence of coronary artery disease is approximately 18% in healthy men and 11% in healthy women >65 years of age, increasing to 19% and 16%, respectively, at >75 years.[24] Therefore, detection of anatomic CAD with anatomic imaging test, may risk the attribution of atypical symptoms to "incidental" CAD. In the absence of corroborative functional testing, detection of significant anatomic disease does not necessarily incriminate CAD as the source of the patient's symptoms. Moreover, patients with nonobstructive-CAD may thus be downplayed, missing therapeutic opportunities and perpetuating symptoms.[25] The Coronary Microvascular Angina (CorMicA) randomized-controlled trial recently demonstrated that a comprehensive approach at the time of ICA for the assessment of microvascular dysfunction and vasospastic angina (interventional diagnostic procedure [IDP]), linked to stratified medicine, in patients with non-obstructive CAD, is superior to usual care in improving quality of life.[12] In this study, Ford *et al.* enrolled 391 patients with angina undergoing invasive coronary angiography. Patients without obstructive CAD were immediately randomized 1:1 to the intervention group (IDP and stratified medical therapy) or the control group (standard care, IDP sham procedure). The IDP consisted of guidewire-based assessment of coronary flow reserve, index of microcirculatory resistance, fractional flow reserve, followed by vasoreactivity testing with acetylcholine. The primary endpoint was the mean difference in angina severity at 6 months (assessed by the Seattle Angina Questionnaire summary score). The intervention resulted in a mean improvement of 11.7 U in the Seattle Angina Questionnaire summary score at 6 months (95% confidence interval [CI]: 5.0-18.4; P=0.001). In addition, the intervention led to improvements in the mean quality-of-life score (EQ-5D Index: 0.10 U; 95% CI: 0.01-0.18; P=0.024). However, it is interesting to note that even in patients as extensively investigated as in the CorMicA trial, 11% of subjects with angina did not have a positive response to

any of the provocative tests. Although not all possible mechanisms underlying angina have been investigated in the trial, this condition was identified as "non anginal pain."[26]

Available evidence strongly encourages to recognize the importance of many causes of myocardial ischemia supporting the more inclusive definition of "myocardial ischemic syndromes." This new perception of myocardial ischemia is expected to give more attention to the alternative mechanisms of ischemia. The identification of these precipitating mechanisms(s) 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.

REFERENCES

1. Magnoni M, Esposito A, Coli S, *et al.* IMAGE CARDIO MED: Two different mechanisms of myocardial ischemia involving 2 separate myocardial segments in a patient with normal coronary angiography. Circulation 2010;121:e1–3.
2. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. Am J Cardiol 1974;34:48–55.
3. Gruntzig A, Hirzel H, Goebel N, *et al.* [Percutaneous transluminal dilatation of chronic coronary stenoses. First experiences]. Schweiz Med Wochenschr 1978;108:1721–3. [German].
4. Pepine CJ, Douglas PS. Rethinking stable ischemic heart disease: is this the beginning of a new era? J Am Coll Cardiol 2012;60:957–9.
5. Heberden W. Some account of a disorder of the breast. Medical Transactions. London: The Royal College of Physicians of London; 1772.
6. Nomenclature and Criteria of Diseases of the Heart and Blood Vessels. Fifth Edition. New York, NY: New York Heart Association, Inc.; 1953. p.77.
7. Osler W. The Principles and Practice of Medi-cine. New York, NY: D. Appleton & Company; 1893. p. 656.
8. Patel MR, Peterson ED, Dai D, *et al.* Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–95.
9. Hadamitzky M, Achenbach S, Al-Mallah M, *et al.* Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry). J Am Coll Cardiol 2013;62:468–76.
10. Shaw LJ, Shaw RE, Merz CN, *et al.* Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. Circulation 2008;117:1787–801.
11. Tonino PA, De Bruyne B, Pijls NH, *et al.* Fractional flow reserve *versus* angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
12. Morrone D, Marzilli M, Panico RA, *et al.* A narrative overview: Have clinical trials of PCI vs medical therapy addressed the right question? Int J Cardiol 2018;267:35–40.
13. Al-Lamee R, Thompson D, Dehbi HM, *et al.* Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. Lancet 2018;391:31–40.

14. Crea F, Bairey Merz CN, Beltrame JF, *et al.* Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization. Eur Heart J 2019;40:2455–62.

15. Orsini E, Marzilli M, Zito GB, *et al.* Clinical outcomes of newly diagnosed, stable angina patients managed according to current guidelines. The ARCA (Arca Registry for Chronic Angina) Registry: A prospective, observational, nationwide study. Int J Cardiol 2022;352:9–18.

16. Morrone D, Marzilli M, Kolm P, *et al.* Do clinical trials in ischemic heart disease meet the needs of those with ischemia? J Am Coll Cardiol 2015;65:1596–8.

17. Coronary angioplasty *versus* medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. Lancet 1997;350:461–8.

18. Hueb WA, Bellotti G, de Oliveira SA, *et al.* The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. J Am Coll Cardiol 1995;26:1600–5.

19. Davies RF, Goldberg AD, Forman S, *et al.* Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy *versus* revascularization. Circulation 1997;95:2037–43.

20. Boden WE, O'Rourke RA, Teo KK, *et al.* Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.

21. Maron DJ, Hochman JS, Reynolds HR, *et al.* Initial Invasive or Conservative Strategy for Stable Coronary Disease. N Engl J Med 2020;382:1395–407.

22. Rahman H, Demir OM, Khan F, *et al.* Physiological Stratification of Patients With Angina Due to Coronary Microvascular Dysfunction. J Am Coll Cardiol 2020;75:2538–49.

23. Gulati M, Levy PD, Mukherjee D, *et al.* 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;144:e368–e454.

24. Cheng VY, Berman DS, Rozanski A, *et al.* Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation 2011;124:2423–32, 1–8.

25. Kunadian V, Chieffo A, Camici PG, *et al.* An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur Heart J 2020;41:3504–20.

26. Ford TJ, Stanley B, Good R, *et al.* Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. J Am Coll Cardiol 2018;72:2841–55.

2 Transferring new concepts from theory to practice

Enrico Orsini

INTRODUCTION

For nearly 50 years, the management of stable ischemic heart disease (SIHD) has been dictated by the "open artery principle," with surgical or percutaneous revascularization being the preferred treatment for most patients. It is remarkable that this approach is still commonly practiced nowadays, despite being supported only by old experimental and clinical evidence dating back to the 1970s and by uncontrolled, observational studies.

From a pathophysiological point of view, the pioneering experimental evidence of a direct and predictable relationship between the degree of coronary artery narrowing and the impairment of coronary flow, obtained by Gould and Lipscomb in the dog,[1] had been immediately translated in the clinical setting, warranting invasive and surgical procedures targeted at removing or bypassing atherosclerotic coronary stenoses.

A pivotal meta-analysis of seven randomized clinical trials conducted between 1972 and 1979, comparing medical therapy to coronary artery bypass graft (CABG) in patients with SIHD, showed a significant reduction of mortality favoring revascularization.[2]

The open artery principle has been strongly reinforced among the cardiology community by the development, starting from the 1970s of coronary angioplasty (PCI).[3] The availability of a "simple, effective and safe" technique, capable of reopening blocked coronary arteries, prompted the execution of hundred of thousands procedures around the world, without a rigorous assessment of its benefits on the outcomes.

Investigations from the 70s had shown the predictive power of an abnormal exercise stress test.[4] More recent observational studies confirmed the prognostic value of inducible ischemia, showing that the extent and severity of myocardial ischemia evaluated by stress perfusion single photon emission computed tomography (SPECT) was predictive of the outcome benefits of revascularization over medical therapy, with the survival curves crossing in favor of revascularization for an extension of ischemia ≥10% of the left ventricle.[5, 6]

This old body of evidence, however, has not been confirmed in recent years in randomized trials provided with a rigorous methodological design and comparing revascularization with the modern optimal medical therapy (OMT). The OMT today includes statins, RAAS-inhibitors and antiplatelet agents, drugs unavailable in the 70s, and able to positively modify the prognosis of cardiovascular disease. When PCI has been compared with OMT, in five trials conducted between 2004 and 2018 and enrolling patients with stable angina and documented