Coronary microcirculation in effort ischemia: the roar of the rabbit

Paola Capozza and Enrico Orsini
Cardiovascular Medicine Division, Cardiac and Thoracic Department, University of Pisa, Pisa, Italy

Correspondence: Paola Capozza, Cardiovascular Medicine Division, Cardiac and Thoracic Department, Via Paradisa 2, 56124 Pisa, Italy. Tel: +39 050 995307; fax: +39 050 995308; e-mail: paola.cap@alice.it

Abstract

A 71-year-old man was admitted to our department with a history of effort angina, positive exercise stress test, and single photon emission computed tomography (SPECT) results indicative of reversible ischemia in the left anterior descending artery (LAD) territory. Coronary angiography showed no significant atherosclerotic lesions in either right or left coronary arteries. However, a relevant slow flow in the LAD artery was detected. In a traditional interpretation, the SPECT results would be seen as a false positive for coronary artery disease. In our opinion, the case is instead a true positive for coronary microcirculatory dysfunction. The pathophysiology of myocardial ischemia is not confined to the epicardial coronary level but globally involves coronary arteries, microcirculation, and myocardium.

Keywords: Coronary angiography, coronary slow flow, myocardial ischemia

History

A 71-year-old man was admitted to our department with a history of effort angina and a diagnosis of inducible ischemia. As coronary risk factors, he had essential hypertension and dyslipidemia.

In 2008, because of effort angina, he performed a treadmill exercise test that showed a significant ST-segment depression in V4-V6 leads, so he also underwent an exercise single photon emission computed tomography (SPECT). The examination detected a reversible perfusion defect in the inferior septum with a normal left ventricular ejection fraction (LVEF). Coronary angiography showed a 50% diameter stenosis in the mid left anterior descending coronary artery (LAD); this lesion was not treated with angioplasty because the fractional flow reserve (FFR) resulted in the normal range (0.87).

In October 2010, a few weeks before admission, the patient underwent a second exercise test for the persistence of effort angina despite medical treatment; the test was positive for inducible ischemia. He also repeated an exercise SPECT: the electrocardiogram (ECG) showed a downsloping ST-segment depression (2 mm) in V5-V6 leads (Figure 1), while the perfusion scan documented a moderate and reversible defect in the mid septum (Figure 2).

When the patient was admitted, he had a normal sinus rhythm. Echocardiography showed normal left ventricular volumes, wall thickness and LVEF (58%), without wall-motion abnormalities. Due to his high Framingham Risk Score and the positive SPECT results, we decided to perform a second coronary angiography. Coronary arteriography showed the absence of lesions in the right coronary and circumflex arteries and a non-critical stenosis (<50% luminal diameter narrowing) in the mid-LAD (Figure 3). The most important finding was the delayed progression of the contrast agent in the whole LAD artery that resulted in a Thrombolysis In Myocardial Infarction (TIMI) 2 flow (45 frames to opacify the distal vasculature, against 5 beats for the right coronary and circumflex artery). The corrected TIMI frame count for LAD (CTFC) was 26 [1]. The left ventriculography confirmed the absence of wall-motion abnormalities and a good LVEF (56%).
Discussion

We present a case report of ischemic heart disease (IHD) in the absence of epicardial coronary artery stenoses. Nearly 50 years after the introduction of coronary angiography, the anatomical approach to ischemic heart disease, directed to the coronary stenosis, remains the most popular way to manage such disease.

However, we know that atherosclerosis, traditionally considered a focal cholesterol storage disease, is instead a widespread inflammatory process, responsible for the development, evolution and complications of arterial lesions [2,3]. Furthermore, it is
now recognized that most atherosclerotic lesions grow outward, so a consistent burden of atherosclerosis can exist in the absence of stenoses. Finally, in the setting of acute coronary syndromes (ACS), Riofol et al demonstrated that vulnerable plaques are present throughout the coronary tree, regardless of the culprit lesion [4].

In reality, the pathophysiology of ischemic heart disease is not confined to epicardial coronary stenosis, but is much more complicated and invariably involves both coronary microcirculation and the myocardium.

Several published series have demonstrated that a large number of patients with symptoms and signs of ischemic heart disease have no stenoses at coronary angiography. In the setting of ACS, the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial demonstrated in a large cohort that about 30% of patients had no culprit lesions [5]. The same result was recently confirmed by the Coronary Artery Spasm in Patients With Acute Coronary Syndrome (CASPER) study, which also documented that epicardial coronary vasospasm was responsible of the ACS in the half of the cases [6].

As regards stable angina, the Coronary Artery Surgery Study (CASS), involving 21,487 angiograms, showed that 18.8% of patients had non-obstructive coronary artery disease [7] and, among women, this percentage raises up to 50%, as documented by the Women’s Ischemia Syndrome Evaluation (WISE) study [8].

Likoff et al [9] and Kemp [10] reported two studies in which patients with ST-segment depression or T-wave inversion at rest accentuated such ECG changes during exercise despite normal coronary angiography. Abnormalities in coronary flow and metabolic responses to stress were reported over the years by several groups, all findings consistent with a microvascular etiology for ischemia and symptoms [11,12], the so-called microvascular angina.

The coronary slow-flow phenomenon (CSFP), documented in our case report, is defined as an abnormal condition in which (micro)vascular resistances are inappropriately high, causing a slow anterograde progression of the contrast medium [13]. CSFP was widely recognized as a marker of myocardial ischemia [14]. The overall incidence of CSFP has been reported as 1% among patients undergoing coronary angiography, especially in patients presenting with acute coronary syndromes [15]. In the TIMI-IIIa study, the incidence of CSFP was approximately 4% among patients presenting with unstable angina and without significant epicardial coronary artery disease [16]. Myocardial perfusion scintigraphy shows reversible perfusion abnormalities in 28–75% of patients with CSFP [17,18].

Different theories have been postulated about the cause of small-vessel dysfunction, including microvascular tone alteration, small-vessel wall thickening [19], patchy fibrosis [20], and impaired endothelial release of nitric oxide (NO) [21]. In any case, structural or functional alterations of coronary microcirculation have been documented in several clinical conditions, such as stable and unstable angina [22–27]. In these conditions, endothelial and microvascular dysfunction play a pathophysiological role both in the precipitation and maintenance of myocardial ischemia, also in the absence of coronary atherosclerosis.

The discussion of our case report should focus on two main questions. The first issue is whether or not our patient suffered from IHD despite the absence of coronary artery disease (CAD). The second is the significance of a positive stress test in absence of CAD.

The answer to the first question is undoubtedly yes. Our patient had not only a long history of stable, reproducible, and typical angina on effort but also unequivocal signs of myocardial ischemia documented by both electrocardiographic and myocardial perfusion markers. The patient had moderate perfusion defects on stress imaging SPECT. We know that, regardless of the diagnostic approach, 5% or more of ischemic myocardium is an important measure of 2-year risk of death or MI [28].

Regarding the second issue, many stress tests have been evaluated to clarify their diagnostic and predictive accuracy [29,30]. In our case, the SPECT result would be conventionally rated as a false positive result for CAD, even in the presence of typical symptoms and other unequivocal signs of inducible ischemia. In reality, our case report demonstrates that exercise stress test and SPECT results must be regarded as a true positive result for coronary microcirculatory dysfunction and microvascular ischemia. Patel et al [31], in a recently published paper, show that, although a positive test is highly predictive of coronary obstructions, significant coronary stenoses are present in >30% of patients with negative exercise test, both symptomatic and asymptomatic. Therefore, CAD does not necessarily imply IHD, since ischemic syndromes often manifest in absence of coronary atherosclerosis and, vice versa, even a severe coronary atherosclerosis frequently occurs in the absence of documentable ischemia.

**Conclusion**

IHD is a multi-factorial syndrome, with a complex pathophysiology that goes far beyond coronary stenosis and involves both coronary microcirculation and the myocardium.
Case report

Coronary microcirculation in effort ischemia: the roar of the rabbit

References


