

# Coronary artery disease: two sides of the same coin

Paola Capozza and Giancarlo Todiere, Cardiovascular Medicine Division, Cardiac and Thoracic Department, University of Pisa, Fondazione Toscana "G. Monasterio", Pisa, Italy

Correspondence: Paola Capozza, Cardiovascular Medicine Division, Cardiac and Thoracic Department, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy  
Tel: 0039 050 995307, fax: 0039 050 995308  
e-mail: paola.cap@alice.it

## Abstract

A 48-year-old woman was admitted to our department with a diagnosis of acute coronary syndrome without persistent ST-segment elevation, and coronary angiography showed no significant atherosclerotic lesion, as documented by fractional flow reserve (FFR). On the same day we also admitted a 52-year-old man with chest pain at rest, an ECG showing downsloping ST-segment depression in anterolateral leads and a critical stenosis of a large marginal branch. In this case, FFR was pathologically low but also varied significantly with intracoronary nitrates. These examples demonstrate once again the complexity of ischemic heart disease in the acute setting of coronary syndromes. It is important to approach ischemic heart disease in a multipathological/factorial manner because the mechanisms underlying myocardial ischemia are extremely heterogeneous and do not merely depend on a fixed atherosclerotic coronary artery stenosis.

**Keywords:** Acute coronary syndrome; coronary angiography; fractional flow reserve

■ Heart Metab. (2013) 58:31–34

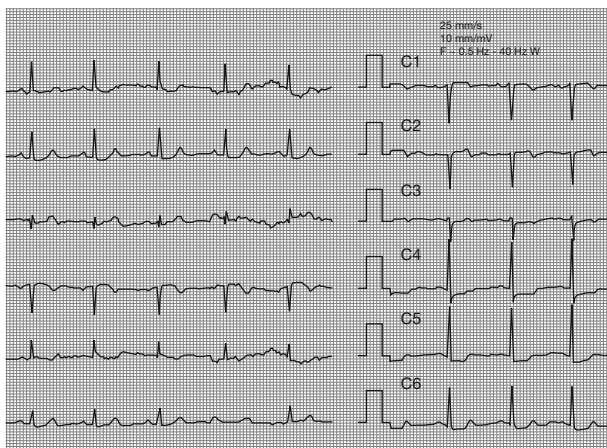
## History

### Patient 1

A 48-year-old woman was admitted to our department with a diagnosis of unstable angina.

Her cardiovascular risk profile was characterized by mild dyslipidemia and she was a cigar smoker.

In 2007 she underwent a left mastectomy with axillary lymphadenectomy for breast cancer, followed by chemotherapy for liver metastases (at the time of admission there was no evidence of new disease). At 08.00 hours on the day of admission, she had chest pain at rest radiating to arms and upper back, and associated with nausea and vomiting. In the emergency department (ED) she was asymptomatic for chest pain at arrival (11.05 hours). During observation in the ED she had a further episode of chest pain (relieved by sublingual nitrates) with downsloping ST-segment depression in leads V4–V6 (Fig. 1). Cardiac enzymes were negative. At physical examination she had blood pressure 120/75 mm Hg, pulse 75/minute, no heart murmurs, Killip class I. Echocardiography showed normal left ventricular volumes and ejection fraction (59%), without wall motion abnormalities. At coronary angiography a 50% diameter stenosis in the mid left anterior descending coronary artery was found (Fig. 2A); after intracoronary

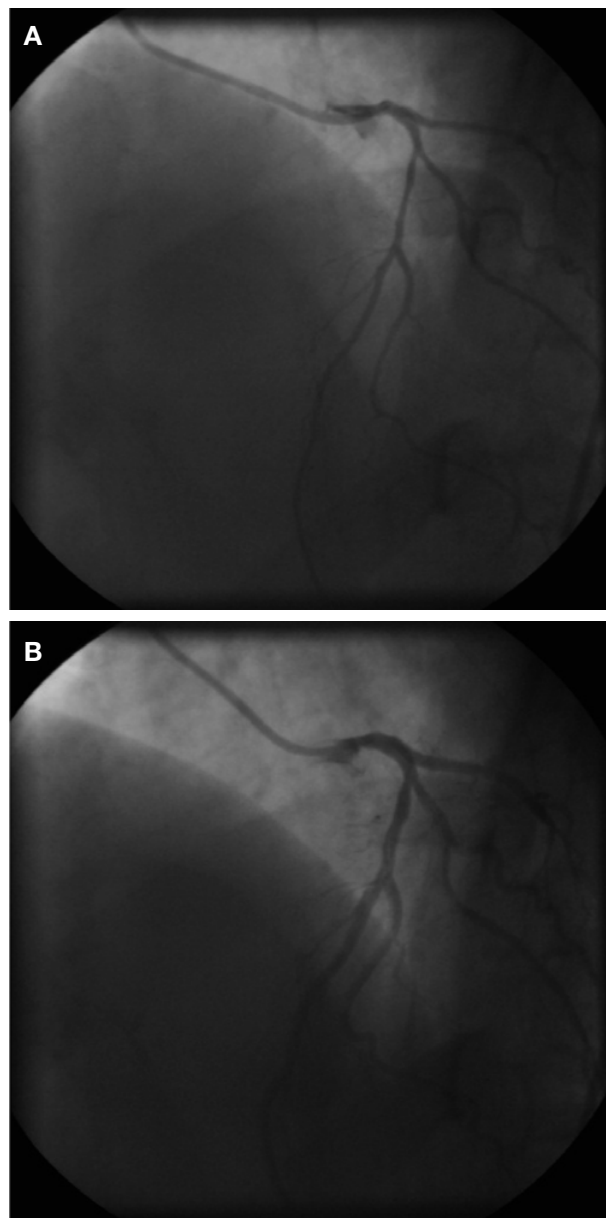


**Fig. 1** The ECG during chest pain revealed ST-segment down-sloping in anterolateral leads.

nitrates the epicardial vessels were dilated and the stenosis disappeared (Fig. 2B). This lesion was not treated with angioplasty because the fractional flow reserve (FFR) was in the normal range (0.88, normal value  $>0.80$ ) (Fig. 3). The patient started a tailored therapy with nitrates and verapamil and she was free from angina and events during the follow-up.

## Patient 2

On the same day as patient 1, we admitted to the cardiology unit a 52-year-old man with chest pain at rest. His cardiovascular risk profile was characterized by dyslipidemia, smoking and arterial hypertension. In the past he had a gastric ulcer. He described new onset angina ( $<2$  weeks) with a severe episode on the morning of admission. The ECG in the ED showed sinus rhythm with left anterior hemiblock, while echocardiography showed normal left ventricular volumes and ejection fraction (56%), with hypokinesia of the mid apical segments of the lateral and inferior walls. Troponin I was elevated (12.4 ng/mL) and during the ED stay he had episodes of complete atrioventricular block. In our department he was asymptomatic. On physical examination he had blood pressure 135/85 mm Hg, pulse 60/min, an apical systolic murmur, Killip class I. At coronary angiography a large marginal branch showed an eccentric plaque, determining a critical stenosis of 80–90% (Fig. 4), as documented by FFR (0.67). In this case nitrates allowed only a minimum increase in flow (fractional flow 0.73) with no substantial change in stenosis severity (Fig. 5). The patient underwent percutaneous coronary intervention with stent implantation. He was discharged on double antiplatelet therapy,

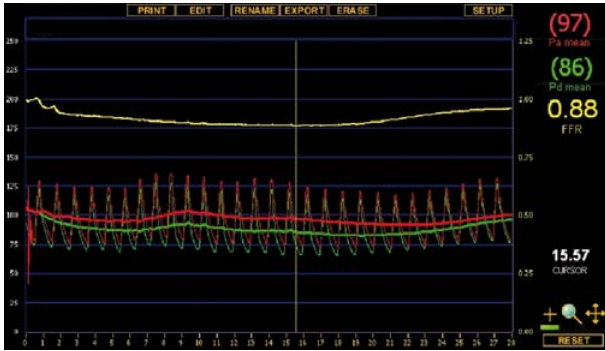


**Fig. 2** The picture shows two frames from the coronary angiography of patient 1. (A) A diffuse narrowed left anterior descending artery (LAD) with a stenosis of 50% in the mid tract. (B) The same angiographic view after the intracoronary administration of nitrates. Marked dilation of the vessel is clear.

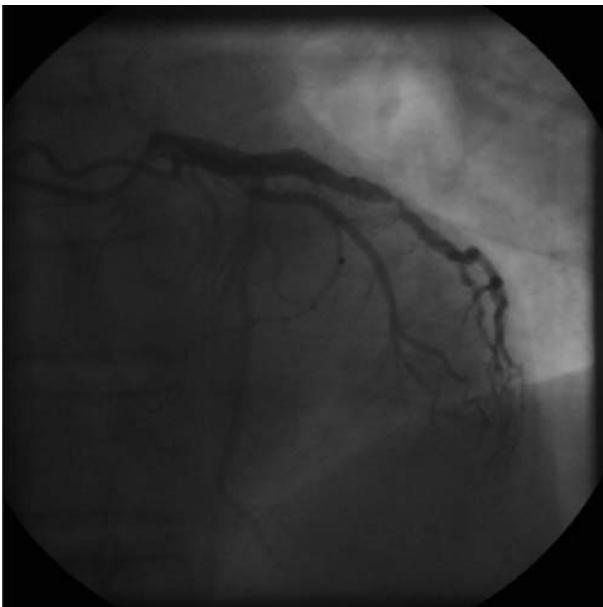
$\beta$ -blockers, a high dose of atorvastatin and an angiotensin-converting enzyme inhibitor. He was also free from cardiovascular events at follow-up.

## Discussion

We have presented two cases of acute coronary syndrome with similar clinical presentations but with very different pathogeneses of ischemia requiring tailored subsequent treatment. Patient 1 had unstable angina

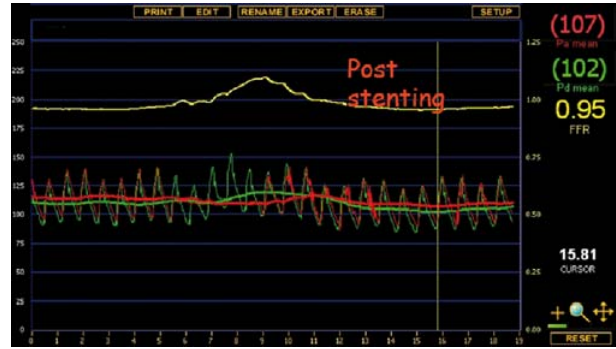
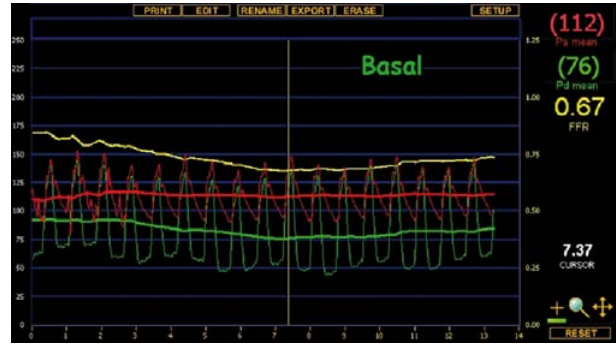


**Fig. 3** The functional evaluation of stenosis confirmed that the stenosis on the left anterior descending artery was not significant with a fractional flow reserve value after intracoronary adenosine of 0.88 (normal value >0.80).



**Fig. 4** The coronary angiography of patient 2 documented a tight stenosis in a very large marginal branch.

caused by diffuse coronary spasm, predominantly affecting the left anterior descending artery, but without a classic definite epicardial coronary stenosis. In contrast, a critical fixed stenosis was found in patient 2. Coronary vasomotion can thus be considered the leading pathology underlying the acute coronary syndrome in the first case. While in the second case, a classic plaque with a large atherosclerotic burden was the underlying cause. Therefore, these cases highlight two different pathologies, both leading to regional myocardial ischemia, and near identical presentations. Marzilli et al [1] recently published a review to explain the Copernican revolution, as the authors interpret the par-



**Fig. 5** The fractional flow reserve values recorded at baseline, after intracoronary administration of nitrates and after stenting were 0.67, 0.73 and 0.95, respectively. The first two values are pathological and confirmed the critical stenosis able to determine myocardial ischemia.

adigm of ischemic heart disease. The solar system of ischemic heart disease puts myocardial ischemia at the center, confining coronary stenosis on the side as one of many contributors to myocardial ischemia.

We know that atherosclerosis, traditionally considered a focal cholesterol storage disease, is now viewed as a widespread inflammatory process, responsible for the development, evolution and complications of arterial lesions [2, 3]. It is now recognized that most atherosclerotic lesions grow outward, but a consistent burden of atherosclerosis can exist in the absence of stenosis. In the setting of acute coronary syndrome (ACS), Rioufol et al [4] demonstrated that vulnerable plaques were

present throughout the coronary tree, regardless of the culprit lesion.

So the pathophysiology of ischemic heart disease seems to be heterogeneous and more complicated.

Several published series have demonstrated that a number of patients with symptoms and signs of ischemic heart disease had no stenosis at coronary angiography, both in stable and acute scenarios. In ACS, the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial demonstrated that approximately 30% of patients had no culprit lesion [5]; the same result was confirmed recently by the Coronary Artery Spasm in Patients With Acute Coronary Syndrome (CASPAR) study, which also documented that epicardial coronary vasospasm was responsible for the ACS in half of the cases [6].

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

Likoff et al [9] and Kemp et al [10] reported two studies in which patients, despite normal coronary angiography, presented with ECG changes (ST-segment depression or T wave inversion) at rest that were accentuated during exercise. 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]. So the general effort of the cardiological community must be to direct cardiac investigations to the study of ischemic heart disease beyond the search for coronary obstruction, but towards the ultimate goal of investigating a dynamic system that encompasses several pathophysiological mechanisms. Coronary atherosclerosis and vasospasm are the most common pathways, but many other contemporary mechanisms are involved.

### Conclusion

Our cases highlight myocardial ischemia at the center of acute syndromes, representing the central sun of an ideal solar system in which many orbiting planets/players are involved. These planets/players include

atherosclerosis and vasospasm (the two examples of our report), but also microvascular dysfunction, inflammation, endothelial dysfunction, platelet activation and coagulation. In daily practice, this different approach can be useful in obtaining a deeper understanding of the mechanisms underlying ischemia, offering the opportunity to tailor treatment in a specific patient or to develop strategies that can protect myocytes from ischemic damage. Such personalized medicine should be our ultimate goal. •

### References

1. Marzilli M, Bairey Merz CN, et al (2012) Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link! *JACC* 60:951–956
2. Orsini E, Zito GB (2010) Matching pathophysiology and evidence-based medicine for optimal management of ischemic heart disease. *J Cardiovasc Med (Hagerstown)* 11:469–479
3. Falk E (2006) Pathogenesis of atherosclerosis. *J Am Coll Cardiol* 47(8 Suppl):C7–12
4. Rioufol G, Finet G, Ginon I, et al (2002) Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study. *Circulation* 106: 804–808
5. Hochman JS, Tamis JE, Thompson TD, et al (1999) Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. *N Engl J Med* 341:226–232
6. Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M, Sechtem U (2008) Coronary artery spasm as a frequent cause of acute coronary syndrome: The CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) Study. *J Am Coll Cardiol* 52:523–527
7. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL (1986) Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *J Am Coll Cardiol* 7:479–483
8. Pepine CJ, Anderson RD, Sharaf BL, et al (2010) Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. *J Am Coll Cardiol* 55: 2825–2832
9. Likoff W, Segal BL, Kasparian H (1967) Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. *N Engl J Med* 276:1063–1066
10. Kemp HG, Elliott WC, Gorlin R (1967) The anginal syndrome with normal coronary arteriography. *Trans Assoc Am Physicians* 80:59–70
11. Cannon RO (1993) Chest pain with normal coronary angiograms. *N Engl J Med* 328: 1706–1708
12. Cannon RO (1998) The conundrum of cardiovascular syndrome X. *Cardiol Rev* 6:213–220