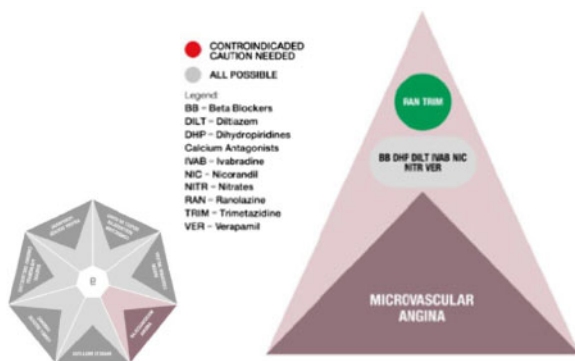


# Angina due to microvascular dysfunction with severe heart failure

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The patient is a 67-year-old woman, with a family history of ischaemic heart disease. In 2000, due to effort angina, she performed a treadmill exercise test that was positive for inducible ischaemia (ST-segment depression at a high threshold). In order to confirm the presence of inducible myocardial ischaemia, she was also referred for a dipyridamole stress echo that was negative for abnormal wall motion, but induced electrocardiogram changes and typical angina symptoms. The patient was put on beta-blockers (metoprolol 50 mg b.i.d.) and referred for coronary angiography, which showed the absence of significant stenosis in the epicardial coronary artery. The patient, then, was discharged on beta-blockers and cardioaspirin.

In October 2013, the patient was referred for a new cardiological evaluation as she reported recurrence of effort angina associated with dyspnoea on exertion and syncopal episode (electrocardiogram not available) despite confirming that she had continued to take the drugs as initially prescribed. At this point, the ambulatory Holter monitoring exam results were within normal limits. The echocardiogram showed moderate-to-severe left ventricular systolic dysfunction (ejection fraction 35%) with global hypokinesis

(not previously reported) (Figure 1). Cardiac magnetic resonance was also performed, confirming severe left ventricular dysfunction (ejection fraction 26%) with an area of late gadolinium enhancement with an intramyocardial pattern at the level of the interventricular septum.

Repeat coronary arteriography showed an absence of significant stenosis of the epicardial coronary arteries (Figure 2), with a depressed left ventricular ejection fraction (32%) at ventriculography. She was prescribed therapy that, on top of the beta-blocker included an angiotensin-converting enzyme inhibitor, digitalis, trimetazidine, and nitrates.

At the 6-month follow-up visit, the patient reported marked improvement in the symptoms, complete remission of exertional angina, and improved left ventricular function at transthoracic echocardiography (ejection fraction 40%).

## Discussion

This is a case of ischaemic heart disease in the absence of epicardial coronary artery stenoses. It is possible that a larger number of patients with symptoms and evidence of

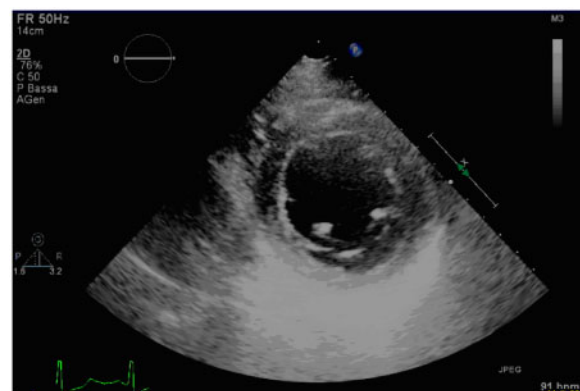


Figure 1 Transthoracic echocardiography showing a dilated left ventricle with global systolic dysfunction.

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**Figure 2** Coronary angiography showing no significant stenoses of the left coronary artery.

myocardial ischaemia at non-invasive stress tests have a normal coronary angiogram. The CASS study (Coronary Artery Surgery Study) involving 21 487 coronary arteriographies, showed that 18.8% of patients have non-obstructive coronary heart disease<sup>1</sup> and, among women, this percentage increases up to 50%, as documented by the WISE study (Women's ischaemia Syndrome Evaluation) study.<sup>2</sup> In the FAME-2 trial (Fractional flow reserve vs. Angiography for Multivessel Evaluation),<sup>3</sup> 27% of patients had no significant stenosis.

Initially, our patient presented with effort angina and evidence of inducible myocardial ischaemia so the clinician's attention was focused on detecting obstructive coronary artery disease. In the absence of a significant stenosis, her treating clinician correctly hypothesized that there was a microvascular aetiology, the so-called microvascular angina, previously known as Cardiac Syndrome X. This condition is attributed to small-vessel disease and vascular endothelial abnormalities, including small-vessel wall thickening,<sup>4</sup> patchy fibrosis,<sup>5</sup> and impaired endothelial release of nitric oxide.<sup>6</sup> This endothelial and microvascular dysfunction challenges and maintains myocardial ischaemia. At this stage, in the absence of a preferred therapy, a beta-blocker was prescribed, at least to reduce oxygen consumption and, therefore, the ischaemic burden.

The peculiarities of this case, however, are the progressive impairment in left ventricular function, leading to heart failure, and the persistence of angina despite

anti-ischaemic therapy. In microvascular angina, several drugs have been proposed, including ranolazine, ivabradine, angiotensin-converting enzyme inhibitors, xanthine derivatives, nicorandil, statins,  $\alpha$ -blockers, and, in perimenopausal women, oestrogens.<sup>7</sup> In this case, considering the left ventricular dysfunction and based on our previous experience, trimetazidine was considered to be particularly indicated. As a result, complete remission of the symptomatology was obtained together with some recovery of left ventricular systolic function.

## Conclusions

In the new understanding of myocardial ischaemia as a multifactorial condition, an effort should be made in each patient to choose the antianginal agent based on the clinical characteristics of the symptoms and the associated cardiac and extracardiac abnormalities.

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