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Angina with non-obstructed coronary arteries

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Introduction

The term 'angina pectoris', proposed over 200 years ago, is generally considered synonymous with obstructive coronary artery disease (CAD). In recent years, however, it has become apparent that abnormalities of the coronary microcirculation (coronary microvascular dysfunction, CMD) play an additional pathogenic role in the pathogenesis of myocardial ischaemia and angina. Functional and structural mechanisms can affect the physiological function of the coronary microvasculature and lead to myocardial ischaemia in people without CAD. Abnormal dilatory responses of the coronary microvessels, coronary microvascular spasm, and increased extravascular compressive forces have been identified as pathogenic mechanisms.[1] The condition characterized by anginal symptoms and evidence of myocardial ischaemia triggered by CMD, in the absence of obstructive CAD, is known as 'microvascular angina' (MVA).

Case report

A 54-year-old woman has a family history of arterial hypertension and she never smoked. Hypertension diagnosed during pregnancy. Menopause since 7 years.

Starting 4–5 years ago she begun to complain of episodes of retrosternal pain with radiation to the left arm that occur during ordinary physical activity and are exacerbated by cold weather. During the episodes sometimes, she also experiences dyspnoea. Recently, she was admitted to hospital for a more prolonged episode of chest pain. Admission electrocardiogram showed ST depression on the precordial leads, and there was no evidence of necrosis biomarkers. Coronary angiography showed normal, smooth epicardial coronary arteries.

I saw this patient in the outpatient clinic. The physical examination was unremarkable except for the blood pressure that was not well controlled by treatment (atenolol 50 mg and hydrochlorothiazide 50 mg). I prescribe a positron emission tomography (PET) scan for measuring myocardial blood flow (MBF) and coronary flow reserve (CFR). The PET scan shows that maximum MBF is uniformly blunted and CFR is diffusely reduced (<2.5) (*Figure 1*). Thus according to the criteria proposed by the Coronary Vasomotion Disorders International Study Group (COVADIS), the diagnosis of MVA is confirmed[2] (*Table 1*). The patient begun treatment with the angiotensin converting enzyme (ACE) inhibitor perindopril 5 mg o.d. and diltiazem 120 mg b.i.d. with significant improvement of symptoms and good blood pressure control.

Discussion

The term CMD was coined to cover a large number of clinical scenarios characterized by evidence of a reduced CFR in the absence of obstructive CAD.[3] Several studies have demonstrated CMD in a large proportion of patients with non-obstructive CAD (30–50%) even after exclusion of epicardial spasm using provocative testing with acetylcholine.[2]

Patients with arterial hypertension often have symptoms and signs suggestive of myocardial ischaemia despite normal coronary arteries at angiography. Structural changes of the coronary microcirculation, unrelated to the degree of left ventricular hypertrophy have been demonstrated in these patients. These abnormalities can cause a reduction in maximum MBF and CFR, suggestive of CMD. These anatomical changes are due to remodelling of intramural coronary arterioles caused, at least in part, by excessive activation of the renin–angiotensin–aldosterone system and treatment with ACE inhibitors can induce reverse arteriolar remodelling while improving maximum MBF.[4]

No conclusive evidence is available to support a specific class of drugs for the treatment of MVA.[1,5] Calcium channel blockers are likely to represent first-line agents for patients with documented microvascular spasm or abnormal CFR whilst nitrates do not appear to have major beneficial effects. β-blockers are useful in patients with MVA with predominantly effort-induced myocardial ischaemia in whom a reduction in myocardial oxygen demand may increase exercise capacity although these drugs may increase

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Cardiac Positron Emission Tomography with ^{13}N-ammonia

SEGMENTS	MBF STRESS		MBF REST		CFR
	ml/min/g	SD%	ml/min/g	SD%	Stess/Rest
LDA	**2.190**		**1.103**		**1.985**
1. Basal anterior	2 .178	7.4	1.105	8.3	1.972
2. Basal Antero-Septal	2.370	5.1	1.230	5.7	1.926
7. Mid Anterior	2.217	7.0	1.055	6.4	2.101
8. Mid Antero-Septal	2.470	4.7	1.191	3.9	2.075
13. Apical Anterior	2.281	5.8	1.045	5.7	2.182
14. Apical Septal	1.735	6.6	0.947	7.9	1.831
17. Apex	1.837	7.7	1.028	8.9	1.786
CX	**2.623**		**1.229**		**2.134**
5. Basal Infero-Lateral	2.782	6.8	1.203	3.5	2.313
6. Basal Antero-Lateral	2.854	7.3	1.365	5.8	2.091
11. Mid Infero-Lateral	2.291	9.1	1.065	3.7	2.152
12. Mid Antero-Lateral	2.732	4.9	1.341	4.3	2.037
16. Apical Lateral	2.19 5	5.4	1.098	3.8	1.998
RCA	**1.880**		0.927		**2.028**
3. Basal Infero-Septal	2.173	9.5	1.024	11.3	2.123
4. Basal Inferior	1.596	9.3	0.888	6.0	1.798
9. Mid Infero-Septal	2.357	6.1	1.048	4.7	2.249
10. Mid Inferior	1.467	9.1	0.874	6.7	1.679
15. Apical Inferior	1.572	8.0	0.678	8.1	2.320
GLOBAL LV	**2.148**		**1.061**		**2.024**

Figure 1 Regional and global (left ventricle) myocardial blood flow measured at rest and during near maximal coronary vasodilatation following intravenous dipyridamole (0.56 mg/kg) and coronary flow reserve. In this patient, maximum myocardial blood flow (stress) is uniformly blunted and coronary flow reserve is diffusely reduced (<2.5). CX, circumflex coronary artery; LAD, left anterior descending coronary artery; LV, left ventricle; RCA, right coronary artery; SD%, standard deviation percent.

Table 1 Clinical criteria for suspecting microvascular angina

(1) Symptoms of myocardial ischaemia
  a. Effort and/or rest angina
  b. Angina equivalents (i.e. shortness of breath)
(2) Absence of obstructive CAD (<50% diameter reduction or FFR >0.80) by
  a. Coronary CTA
  b. Invasive coronary angiography
(3) Objective evidence of myocardial ischaemia
  a. Ischaemic ECG changes during an episode of chest pain
  b. Stress-induced chest pain and/or ischaemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
(4) Evidence of impaired coronary microvascular function
  a. Impaired coronary flow reserve (cut-off values depending on methodology used between ≤2.0 and ≤2.5)
  b. Abnormal coronary microvascular resistance indices (e.g. IMR >25)
  c. Coronary microvascular spasm, defined as reproduction of symptoms, ischaemic ECG shifts but no epicardial spasm during acetylcholine testing
  d. Coronary slow flow phenomenon, defined as TIMI frame count >25

CAD, coronary artery disease; CTA, computed tomography angiography; ECG, electrocardiogram; FFR, fractional flow reserve; IMR, index microvascular resistance; TIMI, thrombolysis in myocardial infarction. Adapted from Ong *et al.*[2]

coronary vasoconstriction by unmasking α-adrenoceptors in patients with microvascular spasm. Another agent that reduces myocardial oxygen demand through its bradycardic effects is ivabradine, but little information exists regarding its efficacy in patients with MVA. In small pilot studies in MVA, trimetazidine, a metabolic modulator that shifts cardiac metabolism away from fatty acid oxidation to improve myocardial metabolism during ischaemia, effectively improved symptoms and exercise capacity. Ranolazine, an inhibitor of the late sodium current, was shown to improve symptoms and CFR in women with MVA although other showed no beneficial effects.

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