

## Microvascular angina and hypertension: a case report

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### Abstract

Angina pectoris is one of the most frequent reasons for presentation in the emergency department worldwide and in half of these patients, especially in the young ones, coronary arteries are normal or have non-obstructive stenoses. First described as a clinical entity in 1988, microvascular angina now has precise criteria of diagnosis: symptoms of myocardial ischemia, absence of obstructive coronary artery disease and impaired coronary microvascular function (reduced coronary flow reserve, coronary microvascular spasm, increased microvascular resistance and/or coronary “slow flow” phenomenon). It is frequently associated with cardiovascular risk factors, including arterial hypertension, even in the absence of overt atherosclerotic disease. We present a case of a young female with typical rest angina; electrocardiogram changes are suggestive of myocardial ischemia and normal epicardial coronary arteries in the context of untreated hypertension. She received guideline medical treatment and we presented the patient’s in-hospital evolution and at 6-month follow-up visit. Current recommendations for diagnosis, treatment and prognosis of microvascular angina are also discussed.

**Keywords:** microvascular angina, arterial hypertension, angina pectoris.

### Introduction

Angina pectoris is one of the most frequent reasons for presentation in the emergency department worldwide and in half of these patients, coronary catheterization or non-invasive tests show normal coronary arteries or non-obstructive stenoses [1, 2].

The diagnosis criteria of microvascular angina (term first used by Cannon and Epstein in 1988) are: symptoms of myocardial ischemia, absence of obstructive coronary artery disease, objective evidence of myocardial ischemia (electrocardiogram changes during angina or induced by stress testing) and impaired coronary microvascular function defined by either reduced coronary flow reserve, coronary microvascular spasm, increased microvascular resistance and/or coronary “slow flow” phenomenon [3, 4]. Microvascular angina (MVA) may be a consequence of atherosclerotic disease but frequently is associated with other cardiovascular risk factors like hypertension, insulin resistance and diabetes, metabolic syndrome or obesity in the absence of obstructive coronary artery disease; however, it is still uncertain

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whether MVA is a cause or a consequence of the underlying myocardial disease in these patients [1, 5–7]. The prognosis of microvascular angina is not benign; there are studies reporting an increase in cardiovascular events (death, myocardial infarction, stroke or hospitalization for heart failure) in women with microvascular angina and decreased coronary flow reserve [4, 8].

## Case report

A 52-year-old female patient is admitted to our cardiology department for episodes of chest pain, which appear at rest, with progressively increasing frequency and duration in the last 48 hours before admission. The chest pain has the clinical character of typical angina, it first appeared 1 year ago, usually at rest or in the context of psycho-emotional stress, less than 10 minutes in duration and it subsided spontaneously. The patient classified these chest pains as “panic attacks” and she did not seek medical evaluation for them.

The patient’s medical history reveals only elevated systolic blood pressure of 150–160 mmHg for about 3 years which she did not investigate, considering it to be the consequence of increased stress (she is divorced and a lawyer working in a large company). She is sedentary, non-smoker, does not consume alcohol, has a regular menstrual cycle, and is not taking any medication. She had 2 uncomplicated pregnancies 22 and 25 years ago. The family medical history is unremarkable.

The clinical examination at the time of admission reveals an overweight patient (BMI 28 kg/m<sup>2</sup>), afebrile, no peripheral adenopathy, no edema, without changes in the respiratory exam, with rhythmic heart sounds, without gallop, no cardiac or vascular murmurs, symmetrical bilateral peripheral pulse, BP=162/92 mmHg, respectively 156/90 mmHg (orthostatism), AV 78/min, no palpable liver and spleen, normal focused neurological exam.

The investigations done in the emergency department were nonspecific: the initial electrocardiogram (ECG), performed after the angina remission, was normal – sinus rhythm, AV 74 bpm, normal morphology and ST-T interval, without criteria for left ventricle hypertrophy (LVH); chest x-ray – no changes that could explain the patient’s symptoms, first set of myocardial necrosis enzymes (troponin I 0.2 ng/ml, CK 120 UI/l, CK-Mb 15 UI/l) with normal values (the first determination, approximately 1 hour after the last chest pain); the rest of the biological screening being also unremarkable (leucocytes 7090/ml, hemoglobin 13.2 g/dl, platelet 182000/ml, C reactive protein 1.36 mg/l, fibrinogen 243 mg/dl, blood glucose 128 mg/dl, creatinine 0.76 mg/dl, GOT/GPT 15/8u/l). Because of

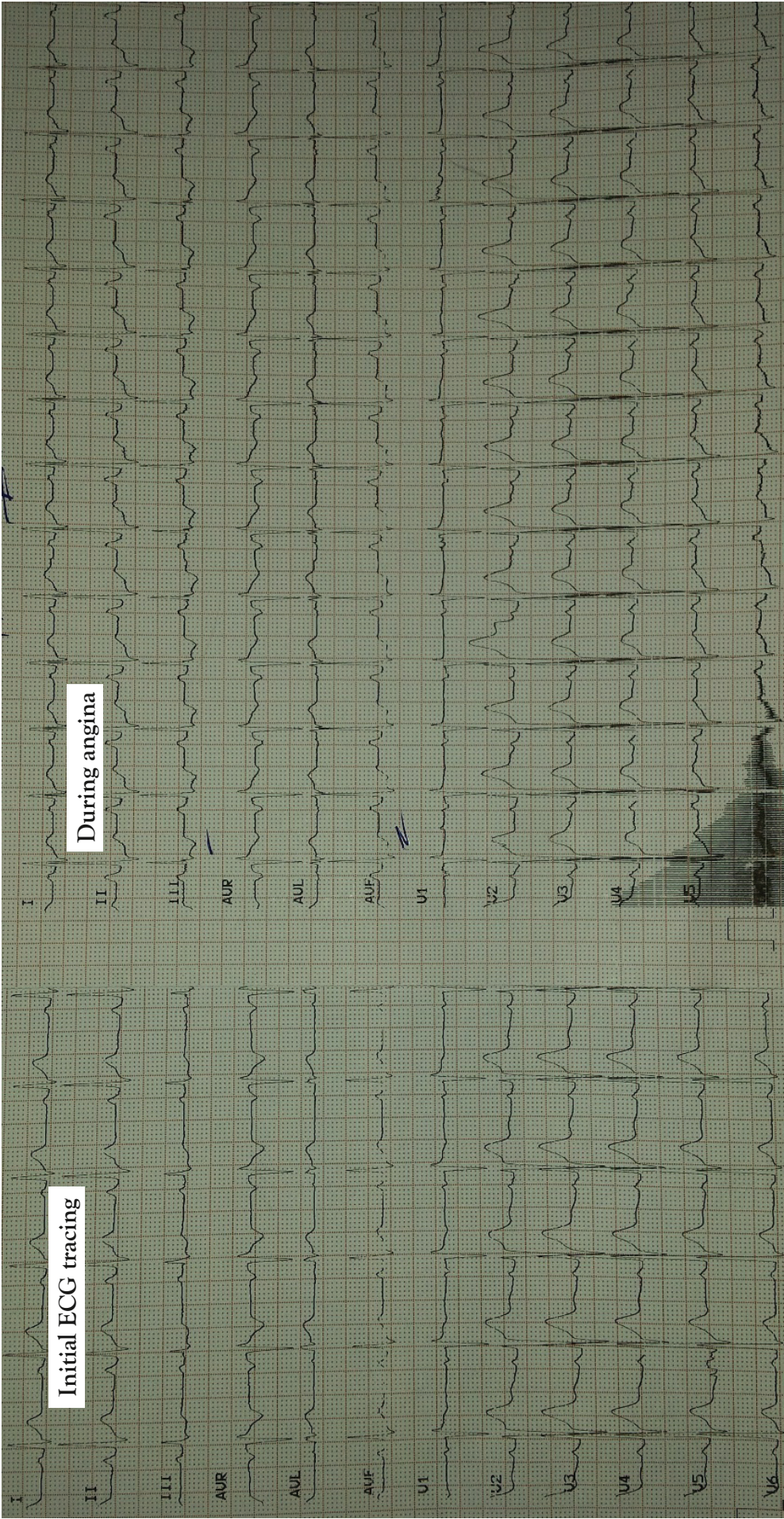
the high clinical suspicion of unstable angina in an untreated hypertensive patient, she was admitted to the cardiology department for further evaluation – to establish the cause of the chest pain (acute coronary syndrome or noncardiac) and the cardiovascular risk profile of the patient and to screen for hypertension-mediated organ damage (HMOD).

The patient had serial troponin I (0.2 ng/ml), CK (160 UI/l) and CK-MB (21 UI/l) measurements that were within normal limits, ruling out acute myocardial necrosis. However, the ECG recorded during an angina episode revealed significant changes in inferolateral subendocardial ischemia (Figure 1).

Echocardiography has a class I indication in the acute coronary syndrome workup and also in the evaluation of any hypertensive patient, regardless of the severity and age of hypertension [9]. In our patient, it was performed in the first 24 hours of presentation and showed: concentric remodeling of the left ventricle [LV (LV mass index 86 g/m<sup>2</sup>, relative wall thickness RWT 0.54)], normal regional and global LV systolic function (LVEF 62%), first-degree diastolic dysfunction with normal filling pressures (E/A 0.7, EDT 226ms, E/E1 7.4, left atrium volume of 26 ml/m<sup>2</sup>), without any changes suggesting pericarditis, myocarditis, valvulopathies or right cavities overload. The diameters and 2D appearance of the aorta were also normal, excluding an aortic dissection. The laboratory investigations showed: mixed dyslipidemia (total cholesterol 198 mg/dl, LDL-cholesterol 127 mg/dl, HDL-cholesterol 38 mg/dl, triglycerides 164 mg/dl), mild hyperuricemia (6.4 mg/dl), normal fasting glucose (95 mg/dl) and glycated hemoglobin (5.8 g/dl). The renal function (GFR MDRD 86 ml/min/1.73 m<sup>2</sup>) and the albumin/creatinine level (22 mg/g) were also normal. There was no clinical suspicion of secondary hypertension and the lab tests for thyroid function (TSH 2.23 mcUI/ml, T4 119 mcg/dl), cortisol (246 nmol/l) and serum potassium (3.99 mmol/l), urinary metanephrines (164.6 mcg/24h) were within normal limits.

In conclusion, it was a case of unstable angina with significant ST depression in a young hypertensive and dyslipidemic female patient. The initial treatment consisted of double antiplatelet therapy (aspirin 75 mg qd, clopidogrel 75 mg qd), fractionated heparin (sc enoxaparin 80 mg bid), beta-blocker (metoprolol succinate 50 mg bid), statin (atorvastatin 80 mg qd), angiotensin-converting enzyme inhibitor (perindopril 10 mg qd) as well as IV nitrate. Optimal control of BP and heart rate was achieved, but the symptoms persisted. The patient repeated 3–4 angina per day without any increase of the CKMB and troponin I under maximal medical treatment, which is why she was referred for an emergency coronary angiography. The result was: normal epicardial coronary arteries without invasive criteria for coronary vasospasm at the acetylcholine test. Unfortunately, the coronary flow reserve (CFR) and index of microvascular resistance (IMR) were





**Figure 1.** Initial Electrocardiogram – sinus rhythm, HR 62 bpm, normal QRS axis and duration, no LVH criteria and normal ST-T morphology; Electrocardiogram during angina – sinus rhythm, HR 102 bpm, significant ST depression in DII, DIII, avF, V5-V6.



not measured because the pressure- and temperature-sensitive diagnostic guidewire was unavailable.

After the intervention, the patient's assessment of HMOD was continued. The carotid-vertebral axis ultrasound revealed an intima-media index at the upper limit of normal (0.9/0.84 mm) but without plaques or flow disturbances. At the abdominal ultrasound, the kidneys were of normal size and structure, without renal arteries stenoses. The fundoscopy revealed I-II degree hypertensive retinopathy.

After coronarography, the patient continued the treatment with antiplatelets, beta-blocker, statin, converting enzyme inhibitor, prolonged-release nitrate and trimetazidine were added with favorable clinical outcomes.

At discharge, the patient received recommendations that comply with current guideline indications [2, 9]. As in obstructive coronary atherosclerosis, in the case of microvascular angina in an overweight, hypertensive and dyslipidemic patient, rigorous and optimal control of cardiovascular risk factors is required. The patient received lifestyle modification recommendations; she was encouraged to lose weight through an adapted, low-sodium, hypolipemic and hypocaloric diet rich in vegetables, fruits, fish and low-fat dairy products. Because the patient is sedentary, physical activity should be initiated progressively in terms of duration and intensity up to a target of at least 30 minutes a day.

The medication consisted of carvedilol 12.5 mg bid, clopidogrel 75 mg qd, atorvastatin 40 mg qd with LDL-cholesterol target below 70 mg/dl, isosorbide mononitrate 40 mg qd, trimetazidine 35 mg bid as well as perindopril 10 mg qd with the target of a systolic BP $\leq$ 130 and diastolic BP $<$ 80 mmHg1.

The patient had a follow-up visit at 6 months after discharge. The angina episodes decreased in frequency, appearing only in the context of intense emotional stress and subsiding after one puff of nitroglycerin or even spontaneously. She started practicing yoga regularly with good exertion tolerance and is following the recommended treatment. The physical exam was normal, with a weight loss of 6kg, BP at rest of 128/82 mmHg and HR of 62/min; the electrocardiogram with sinus rhythm, no LVH criteria and normal ST-T interval; the echocardiography showed no changes compared to the index examination.

## Discussion

This case has several peculiarities. It is about a young patient, apparently healthy until the time of admission, but in whom we highlighted the presence of elevated blood pressure values, a metabolic syndrome and microvascular angina (previously known as coronary X syndrome) without evidence of macrovascular atherosclerotic involvement of

the coronary and carotid arteries. However, investigations revealed cardiac and retinal changes secondary to HTN (concentric remodeling, diastolic dysfunction, hypertensive retinopathy). These findings place the patient in the high-risk group of second-stage hypertension even if the blood pressure values are only mildly elevated (grade 2 HTN).

Arterial hypertension is common in patients with angina and angiographically normal epicardial coronary arteries [1, 4, 7–11]. The coronary microvascular dysfunction is independent of the presence or severity of LV hypertrophy. Even though its mechanism is still incompletely understood, several pathophysiological abnormalities are involved: endothelial dysfunction, increased sympathetic tone, microvascular spasm, estrogen deficiency and even increased pain sensitivity. The consequence of coronary microvascular damage, with similar aspects in both hypertensives and diabetics, is a reduction in coronary flow reserve and, in evolution, interstitial and perivascular fibrosis that will result in cardiac remodeling and diastolic dysfunction [3, 10]. Some studies reported autonomic dysregulation as the cause of abnormal blood pressure and heart rate response to physical activity in patients with MVA [11].

In our patient, angina episodes associated with psycho-emotional stress and interventions to reduce it (yoga, alpha-beta blockers) may have significantly impacted symptom control.

The gold standard for diagnosis of microvascular angina is invasive testing of coronary artery function: after exclusion of significant epicardial stenosis, intracoronary administration of acetylcholine will assess the epicardial or microvascular spasm-induced myocardial ischemia; the impaired microvascular vasodilation is measured by thermodilution or intravascular Doppler after administration of adenosine [2, 3, 12].

Coronary microvascular dysfunction may be evaluated non-invasively by either transthoracic Doppler echocardiography, positron emission tomography, cardiac magnetic resonance or computed tomography using adenosine/dipyridamole or contrast agents with acceptable negative predictive value but limited specificity [3, 12]. In our patient, the coronary angiography excluded obstructive coronary artery disease and vasospasm, thus raising the suspicion of microvascular angina due to isolated impaired vasodilation.

The treatment of microvascular angina should be based on the mechanism suggested by the provocative tests. If the epicardial or microvascular spasm is diagnosed, then calcium channel blockers and long-acting nitrates are recommended [2]. In patients without abnormal coronary flow reserve, increased vascular resistance and negative acetylcholine test, as our patient is, beta-blockers, statins and ACE inhibitors, along with lifestyle changes and weight loss, are indicated by the current guidelines [2].

Microvascular angina currently has no specific treatment for pain relief. Beta-blockers have been

shown to be more effective than nitrates or calcium blockers in reducing symptoms in patients with coronary syndrome X [13]. We chose carvedilol because alpha-beta blockers may provide additional benefits through their ability to increase coronary flow reserve. Also, particularly in this patient, there was no excessive tachycardia during angina episodes, so the dose of 12.5 mg carvedilol bid provided good heart rate control both at rest and also with exertion.

Converting enzyme inhibitors (ACEIs) control blood pressure, improve endothelial dysfunction and have vascular anti-inflammatory effects [13]. In patients with microvascular angina, this class increased coronary flow reserve and reduced the frequency of angina attacks with increased exercise tolerance [8].

In a study [14] that evaluated patients with hypertensive heart disease and coronary microvascular damage using endomyocardial biopsy, the long-term administration of perindopril significantly reduced periarterial fibrosis and the coronary flow reserve increased by 67%, reaching normal values.

Besides the evidence of cardiovascular events prevention, in studies with patients with microvascular angina, the administration of clopidogrel improved microvascular endothelial dysfunction, independent of the antiplatelet action [15]. Statins also showed antianginal efficiency, probably through the same effect on the coronary endothelium [16].

Currently, the therapy used in microvascular angina may improve symptoms and quality of life but lacks evidence in major cardiovascular event prevention. Two outcome trials – the Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR) and the International Coronary Microvascular Angina Trial (iCorMicA) are currently underway [4].

## Conclusion

Chest pain in a hypertensive patient may be a consequence of myocardial ischemia regardless of the age or severity of the hypertension. Microvascular angina is more frequent in these patients and requires extensive, invasive or non-invasive testing to individualize treatment. Outcome trials in patients with microvascular angina are ongoing and will provide better insight into this syndrome. Whether to actively screen for coronary microvascular dysfunction in any asymptomatic hypertensive patient to further improve their prognosis remains an open question.

## Conflict of interest

The authors declare no conflict of interest.

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