

Refractory Angina with Myocardial Ischemia in the Absence of Obstructive Coronary Artery Disease: A Case Report

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Introduction

Angina pectoris, the most common symptom of ischemic heart disease, affects approximately 112 million people globally.¹ A large proportion of patients (up to 70%) undergoing coronary angiography because of angina and evidence of myocardial ischemia do not have obstructive coronary arteries, a condition termed INOCA - ischemia with non-obstructive coronary arteries.²⁻⁴

Coronary microvascular dysfunction and epicardial vasospasm, alone or in combination with coronary artery disease (CAD), are adjunctive mechanisms of myocardial ischemia. Discrimination of epicardial coronary artery vasospasm from coronary microvascular dysfunction permits specific and distinct treatment and provides prognostic information to patients and their physicians.⁵

However, these conditions are rarely correctly diagnosed, resulting in the absence of customized therapy for these patients. As a consequence, they continue to experience recurrent angina with impaired quality of life, leading to repeated hospitalizations, unnecessary coronary angiography, and adverse cardiovascular outcomes in the short and long term.⁴⁻⁶

Case presentation

A 65-year-old man presented to the cardiology clinic with exertional angina despite optimal medical therapy. His medical history includes arterial hypertension, diabetes mellitus, dyslipidemia, active smoking, obesity, and a ST-elevation myocardial infarction.

His CAD manifested in 2022 when he experienced an acute myocardial infarction with ST-segment elevation. At that time, the electrocardiogram (ECG) showed ST-segment elevation in the inferior leads, the echocardiography demonstrated inferior wall hypokinesia with preserved left ventricular ejection fraction, and the coronary angiography

revealed an occlusion of the distal right coronary artery (RCA) and a 50% stenosis of the distal segment of the circumflex artery (Cx). Consequently, angioplasty of the RCA was performed with the implantation of a drug-eluting stent, with a good angiographic result.

In the following months, the patient complained of chest pain aggravated by exertion, consistent with typical angina grade II on the Canadian Cardiovascular Society (CCS) scale. At that time, his regular medication was bisoprolol, ramipril, and aspirin. In this context, diagnostic evaluation for myocardial ischemia was initiated.

The exercise ECG was clinically negative but electrically dubious for myocardial ischemia, and the exercise stress echocardiography showed extensive ischemia of the apex, mid-apical interventricular septum, apical anterior wall, and posterolateral wall. Despite this, a coronary angiography was performed, which did not reveal any new changes (RCA with no restenosis, distal Cx with 50% stenosis, and Fractional Flow Reserve (FFR) > 0.8) (Figure 1; Videos 1, 2, and 3).

Given this, the anti-ischemic therapy was optimized with the addition of lercanidipine and ranolazine; however, the patient continued to experience exertional angina.

Investigation and management

Considering refractory angina with normal coronary angiography, it was decided to proceed with invasive functional coronary assessment, including evaluation of microcirculation and vasoreactivity. The diagnostic algorithm and the cutoff values used are represented in Figure 2.^{7,8}

To evaluate the microcirculation, a diagnostic guidewire and adenosine test were used. This demonstrated a decrease in coronary flow reserve (CFR = 1.3) and an increase in the index of microcirculatory resistance (IMR = 28), consistent with microvascular angina (Figure 3).

Subsequently, the acetylcholine test for assessing vasoreactivity, with increasing doses of acetylcholine (2ug > 20ug > 100ug), showed significant epicardial vasoconstriction of Cx ($\geq 90\%$) with reproduction of the usual chest pain and ST-segment depression in the lateral leads, conditions that define the diagnosis of vasospastic angina (Figure 4; Videos 4, 5, 6, 7 and 8).

Given these results, the final diagnosis assumed was ischemia with non-obstructive coronary arteries resulting from both microvascular dysfunction and coronary vasospasm.

Due to the diagnosis of microvascular dysfunction and vasospastic angina, adjustments were made to the therapy. Bisoprolol was discontinued, as it is not recommended in

Keywords

Myocardial Ischemia; Microvascular Angina; Coronary Vasospasm.

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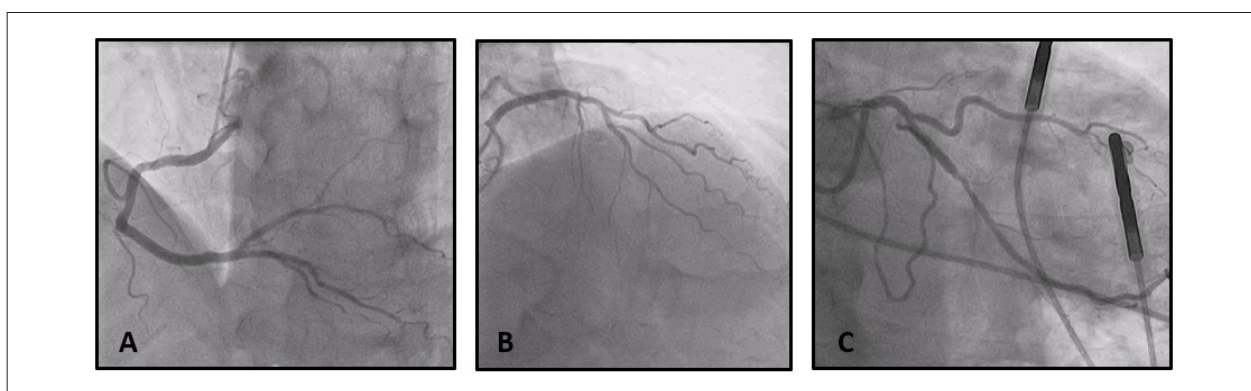


Figure 1 – Diagnostic Coronary Angiography: A) Dominant right coronary artery without lesions, B) Anterior descending artery with irregularities, C) Circumflex artery with 50% stenosis in the distal segment (FFR > 0,8).

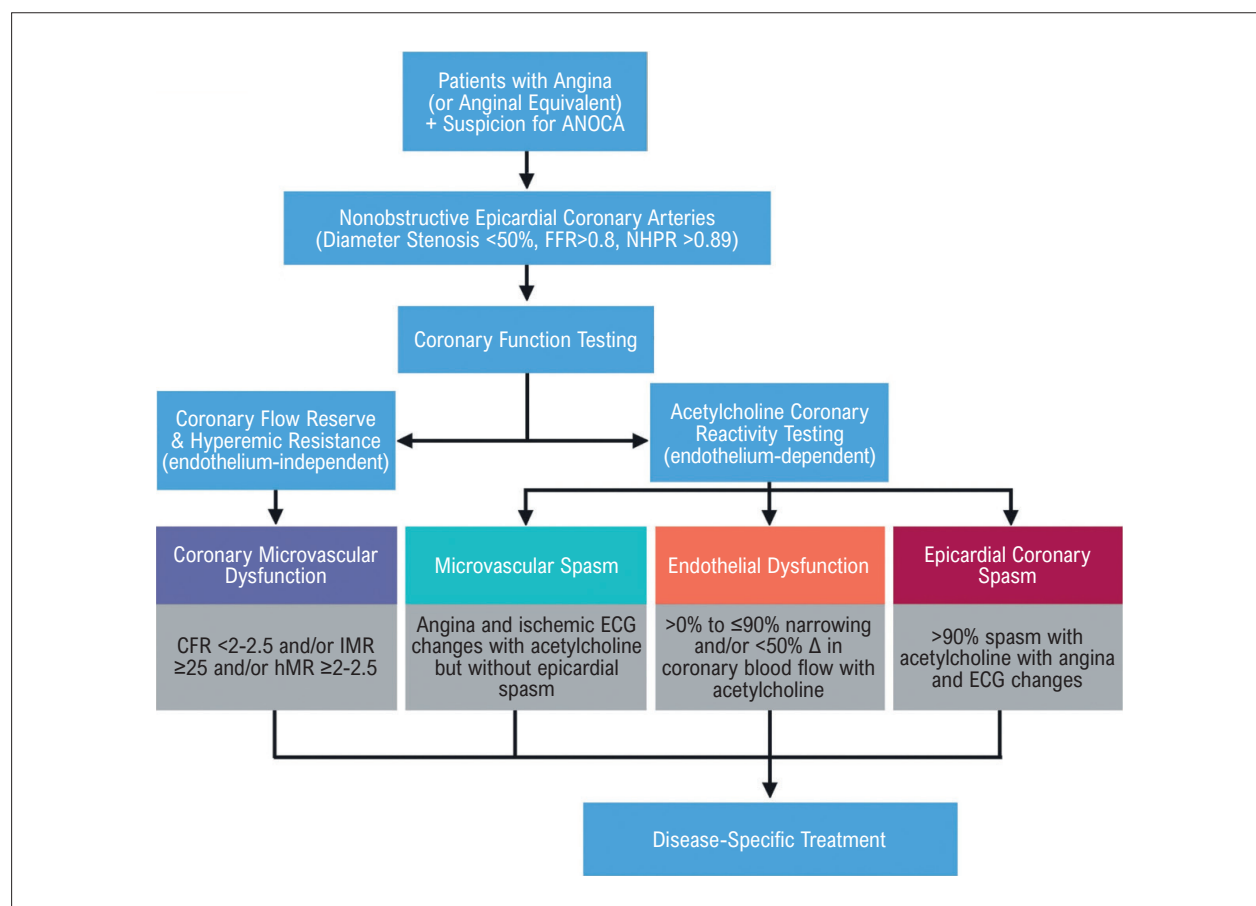


Figure 2 – Algorithm for the investigation of INOCA. ANOCA: Angina with Non-Obstructive Coronary Arteries; CFR: coronary flow reserve; IMR: index of microcirculatory resistance; hMR: hyperaemic microvascular resistance.

vasospastic angina; the doses of lercanidipine and ranolazine were increased, and verapamil was initiated. It should be noted that the patient did not tolerate nitrate therapy due to headaches. This management is consistent with guidelines recommending calcium channel blockers for vasospastic angina while avoiding β -blockers. The patient was also

encouraged to participate in a cardiac rehabilitation program and to be assessed in a smoking cessation consultation.

Fortunately, after several months, the patient's symptoms improved with a combination of anti-ischemic drugs, lifestyle changes, and control of modifiable cardiovascular risk factors.

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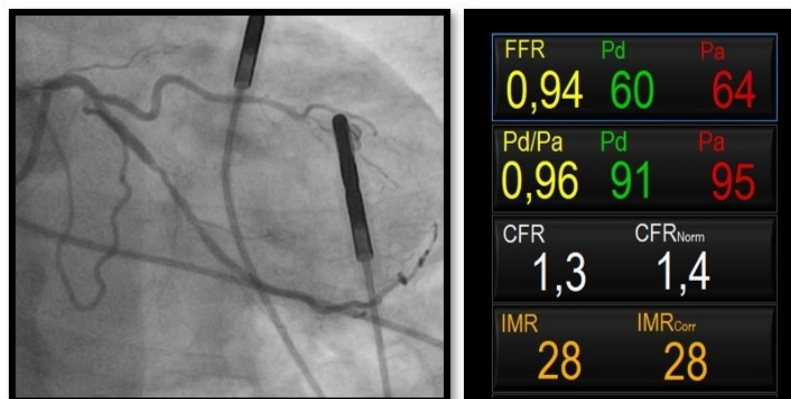


Figure 3 – Diagnostic Guidewire and Adenosine test. Study of microcirculation compatible with coronary microvascular dysfunction.

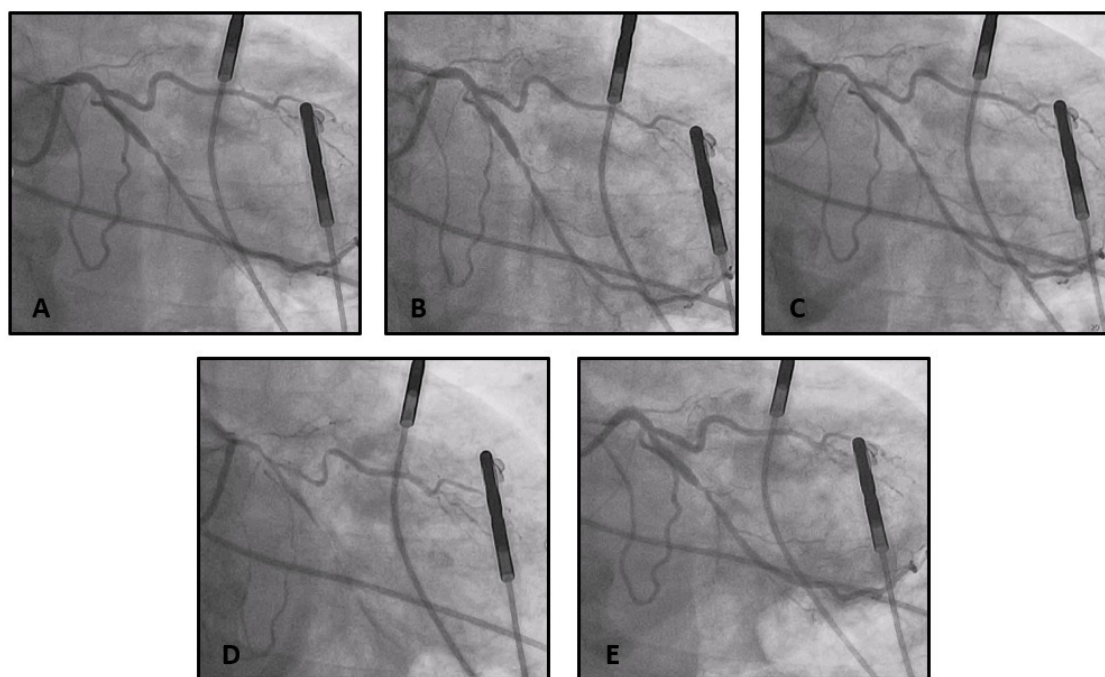


Figure 4 – Vasoreactivity Assessment - Test with increasing doses of Acetylcholine (ACh), A- Basal, B- 2µg ACh, C- 20µg ACh, D- 100µg ACh, E- After-coronary nitrate.

Discussion

Patients with chest pain in the absence of obstructive CAD remain a challenge.

Ischemia with no obstructive arteries is defined as patients with evidence of ischemia but no obstructive CAD at coronary angiography. In INOCA, the discrepancy between the blood supply and the oxygen demand of the myocardium may result from either coronary microvascular

dysfunction or epicardial coronary artery spasm, particularly in cases of nonobstructive coronary atherosclerosis.^{3,7}

The prognosis of patients with INOCA is far from benign. Angina without obstructive CAD is associated with impaired quality of life for patients, a higher risk of disability, and a greater occurrence of adverse events, which include rises in mortality and morbidity, along with increased healthcare expenses, with higher recurrence

rates of hospital readmissions and repeated coronary angiograms.⁸⁻¹¹

Invasive approaches should be employed, utilizing coronary angiography along with interventional diagnostic procedures. These include a diagnostic guidewire, pressure and flow measurements, as well as pharmacological coronary reactivity testing performed in the catheterization laboratory. These strategies are essential for distinguishing between vasospastic angina, microvascular angina, and non-cardiac pain.³

The CorMicA trial — a cornerstone randomized study — demonstrated that in patients with angina and no obstructive CAD, invasive coronary function testing followed by mechanism-guided therapy significantly improves symptoms, quality of life, and diagnostic accuracy without increasing adverse events.⁵

Mileva et al. (2022) reported that approximately 23% of patients with non-obstructive coronary arteries have both coronary microvascular dysfunction and vasospastic angina.¹²

Furthermore, the very recently published ILIAS ANOCA trial (Eur Heart J. 2025) showed that approximately 20% of patients present a mixed pattern of vasospasm and microvascular dysfunction, and that those treated according to the Coronary Function Test experienced significant symptom improvement compared with standard care, highlighting the importance of physiological stratification in the management of these patients.¹³

The overlap between vasospasm and microvascular dysfunction presents a therapeutic challenge, as beta-blockers may exacerbate vasospasm while calcium channel blockers may not fully address microvascular dysfunction. This combination makes the case exceptionally rare, clinically intriguing, and notably challenging in terms of diagnosis and management.¹²

Recognizing INOCA as a valid clinical diagnosis is therefore essential, given its association with adverse outcomes, including an increased risk of major adverse cardiovascular events, and its significant implications for healthcare systems.⁷

Limitations

This case involves a single patient, which limits the ability to generalize the findings and provides no statistical power. In addition, the absence of objective post-treatment assessments, such as imaging studies or standardized clinical evaluations, restricts the capacity to conclusively determine the treatment's effectiveness.

Conclusions

A stratified approach for managing INOCA is necessary to effectively address the short- and long-term prognosis of these

patients. This approach should incorporate personalized counseling on lifestyle factors, management of risk factors according to cardiovascular disease prevention guidelines, and the use of pharmacotherapy to relieve ischemia and associated symptoms.

This case demonstrates the complexity of managing a patient with angina and highlights that clinicians and interventional cardiologists should adopt a systematic approach to diagnose and treat these patients. Given the lack of in-depth knowledge, further research is urgently needed to increase our mechanistic understanding, develop innovative therapies, and improve the management of this serious condition.

Author Contributions

Conception and design of the research, Acquisition of data, Writing of the manuscript and Critical revision of the manuscript for content: Vilela FS, Ferreira CO, Rocha B, Faria J, Fernandes AS, Dias M, Conde I, Gaspar A, Braga CG; Analysis and interpretation of the data: Ferreira CO, Rocha B, Faria J.

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The authors did not use any artificial intelligence tools in the development of this work.

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This article does not contain any studies with human participants or animals performed by any of the authors.

Data Availability Statement

All datasets supporting the results of this study are available upon request from the corresponding Author.

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*Supplemental Materials

Supplemental Video 1: Diagnostic Coronary Angiography. Dominant right coronary artery without lesions. To see, click here.

Supplemental Video 2: Diagnostic Coronary Angiography. Anterior descending artery with irregularities. To see, click here.

Supplemental Video 3: Diagnostic Coronary Angiography. Circumflex artery with 50% stenosis in the distal segment (Fractional Flow Reserve > 0.8). To see, click here.

Supplemental Video 4: Vasoreactivity test using increasing doses of acetylcholine. Basal. To see, click here.

Supplemental Video 5: Vasoreactivity test using increasing doses of acetylcholine. 2ug Acetylcholine. To see, click here.

Supplemental Video 6: Vasoreactivity test using increasing doses of acetylcholine. 20ug Acetylcholine. To see, click here.

Supplemental Video 7: Vasoreactivity test using increasing doses of acetylcholine. 100ug Acetylcholine. To see, click here.

Supplemental Video 8: Vasoreactivity test using increasing doses of acetylcholine. After intra-coronary nitrate. To see, click here.



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