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CASE REPORT

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Ischemia With No Obstructive Coronary Artery Disease

Are Misdiagnosis and Undertreatment Always Behind the Corner?

Giulia Ghizzoni, MD,[a,b,*] Giulia Botti,[a,b,*] Filippo Russo, MD,[a] Luca Ferri, MD,[a] Marco Ancona, MD,[a] Barbara Bellini, MD,[a] Ciro Vella, MD,[a] Domitilla Gentile, MD,[a,b] Matteo Montorfano, MD,[a,b] Alaide Chieffo, MD[a,b]

ABSTRACT

Ischemia with no obstructive coronary artery disease (INOCA) is not an uncommon diagnosis in patients presenting with chest pain who undergo clinically indicated coronary angiography. However, the symptoms reported by patients with INOCA may be heterogeneous, leading to misdiagnosis and undertreatment. Herein we report 3 clinical cases of INOCA misdiagnosis and describe how the cases were reinvestigated following the appropriate diagnostic pathway. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;22:101978) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Ischemia with no obstructive coronary artery disease (INOCA) is estimated to affect a significant proportion of patients presenting with chronic coronary syndrome who undergo coronary angiography and report no anatomically or functionally significant stenoses of the epicardial vessels.[1] According to the recent European Society of Cardiology Guidelines[1] and the European Association of Percutaneous Cardiovascular Interventions Expert Consensus Document,[2] if the clinical picture is suggestive of INOCA, a complete diagnostic workup should be performed to define the INOCA endotype and tailor the medical treatment. Such diagnostic algorithm requires invasive testing, with the assessment of the coronary flow reserve and the index of microvascular resistance (Class IIa, Level of Evidence: B), and with vasoreactivity testing (Class IIb, Level of Evidence: B).

Although expertise in diagnosis and management of the disease is spreading, INOCA is still underdiagnosed, leading to inappropriate medical therapy and poor quality of life.[3]

Herein, we describe 3 clinical cases of INOCA misdiagnosis that required a complete reevaluation with full invasive tests, which led to a significant change in the treatment strategy.

CASE 1

An 81-year-old woman presented to her cardiologist's private practice complaining of recurrent episodes of classic chest pain both on exertion and at rest; she had recently experienced a family bereavement. Her past medical history was not notable for significant cardiovascular events, she was an active smoker, and suffered from dyslipidemia. She was independent in

From the [a]Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; and the [b]University Vita-Salute San Raffaele, Milan, Italy. *Drs Ghizzoni and Botti contributed equally to this work.

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ABBREVIATIONS AND ACRONYMS

CMD = coronary microvascular dysfunction

INOCA = ischemia with no obstructive coronary artery disease

LAD = left anterior descending artery

MVA = microvascular angina

VSA = vasospastic angina

her daily actives and conducted a quite active life. Because the chest pain presented during the consultation, an electrocardiogram was immediately performed, showing transient T-wave inversion in lead III and alterations in aVF that reverted after spontaneous cessation of the pain (Figure 1); the transthoracic echocardiogram was normal. Considering her clinical history, vasospastic angina (VSA) was suspected by the referral cardiologist, who started the patient on diltiazem 60 mg twice a day and referred her to our inpatient cardiology service for further diagnostic assessment.

The patient underwent coronary angiography in pharmacological wash-out, which excluded the presence of obstructive coronary artery disease (Figure 2). Coronary functional test with systemic administration of adenosine was performed to assess the microvasculature. The results provided a diagnosis of coronary microvascular dysfunction (CMD) (Figure 2). Acetylcholine provocation test was negative for epicardial or microvascular spasm (Video 1). The patient was diagnosed with microvascular angina (MVA), therefore diltiazem was replaced with bisoprolol 2.5 mg/d and nitroglycerin 5 mg transdermal patch. At follow-up, the patient remained asymptomatic.

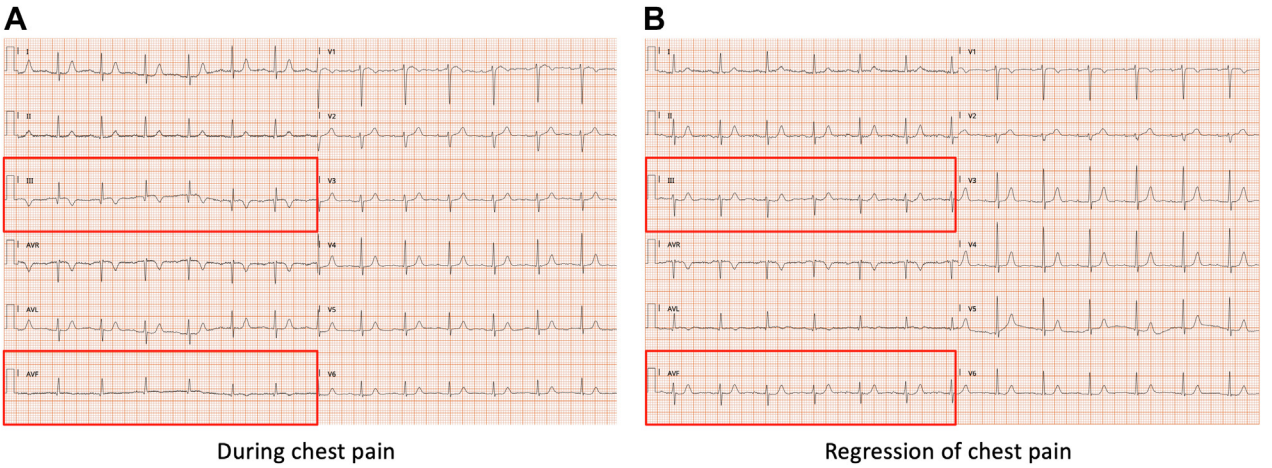
LEARNING OBJECTIVES

- To review the presentation of INOCA in a patient presenting with the typical risk factors and clinical picture.
- To understand the importance of a complete diagnostic assessment to identify the INOCA endotype and tailor the most appropriate treatment.
- To acknowledge the epidemiological variety of INOCA patients, which also includes young individuals of both sexes and with history of obstructive coronary artery disease.
- To consider the possibility that previous episodes might have been misdiagnosed and inadequately treated: past medical history should guide but not jeopardize following investigations.
- To understand that various etiologies of ischemic heart disease may coexist and should be individually but comprehensively managed.
- To avoid the temptation of using gender medicine to categorize our patients into fixed models and pursue a thoughtful and inclusive approach to angina symptoms in women.

CASE 2

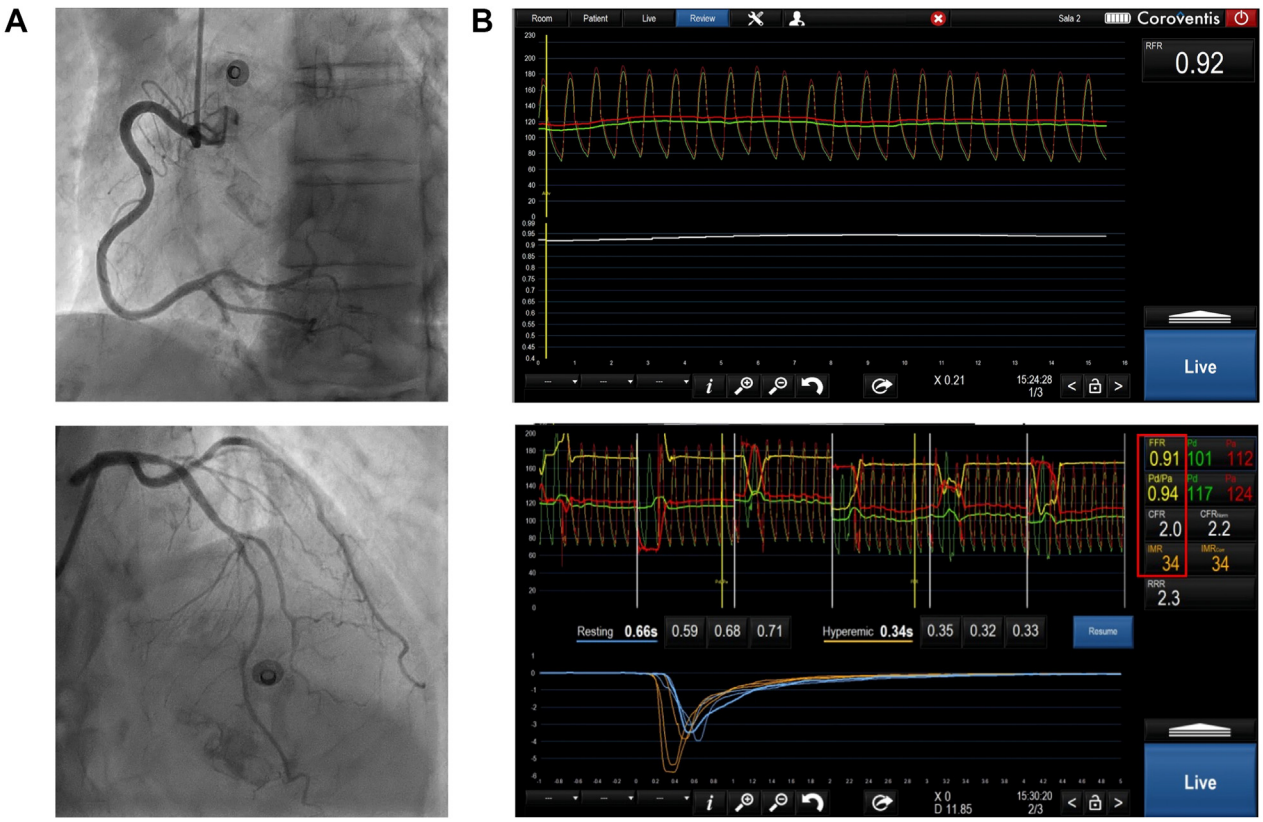
A 36-year-old man was referred to our cardiology service due to worsening chest pain; he was overweight, a former smoker, dyslipidemic, and his past medical history was notable for 2 episodes of non-ST-segment elevation myocardial infarction, both treated with percutaneous coronary intervention and stenting of the left anterior descending

FIGURE 1 Case 1: Electrocardiograms at Attending Cardiologist's Practice



Upon the onset of chest pain, the electrocardiogram showed inverted T waves in lead III and alterations in aVF, highlighted in **red (A)**, which rapidly reversed at cessation of symptoms **(B)**.

FIGURE 2 **Case 1: Basal Coronary Angiography and Coronary Functional Testing**



(A) Absence of obstructive coronary artery disease at coronary angiography. **(B)** Absence of functionally significant left anterior descending artery stenoses: RFR = 0.92 (n.v. >0.9), FFR = 0.91 (n.v. >0.8). Coronary functional testing, highlighted in **red**, was positive for microvascular dysfunction: CFR = 2.0 (n.v. >2.0), IMR = 34 (n.v. <25). CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microvascular resistance; n.v. = normal value; RFR = resting full-cycle ratio.

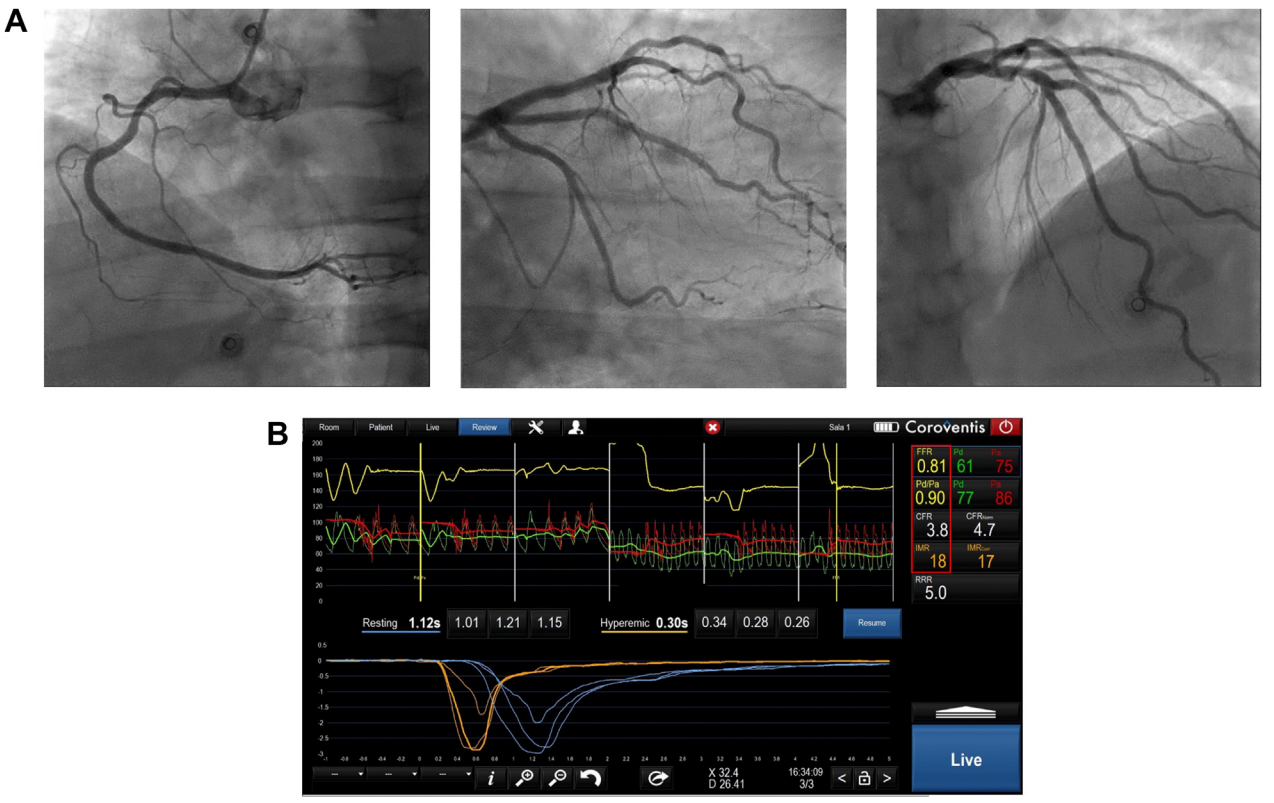
artery (LAD) and diagonal branch. The patient's pharmacological therapy included dual antiplatelet therapy and bisoprolol 2.5 mg/d.

At coronary angiogram, the previously stented vessels were patent and the coronary tree was overall free from obstructive coronary artery disease. The presence of a myocardial bridge was evident in the mid-distal LAD. Coronary physiology testing was negative for CMD (Figure 3). Vasoreactivity testing with intracoronary administration of four increasing doses of acetylcholine (2-20-100-200 μg) was positive for significant epicardial spasm of the mid-distal segment of the LAD, with concomitant occurrence of anginous symptoms and electrocardiogram alterations (negative T waves in the anterolateral leads). This picture promptly regressed after intracoronary administration of nitroglycerin (Figures 4 and 5, Video 2). The patient was diagnosed with VSA and started on diltiazem 120 mg twice a day. To date, the patient remained asymptomatic.

CASE 3

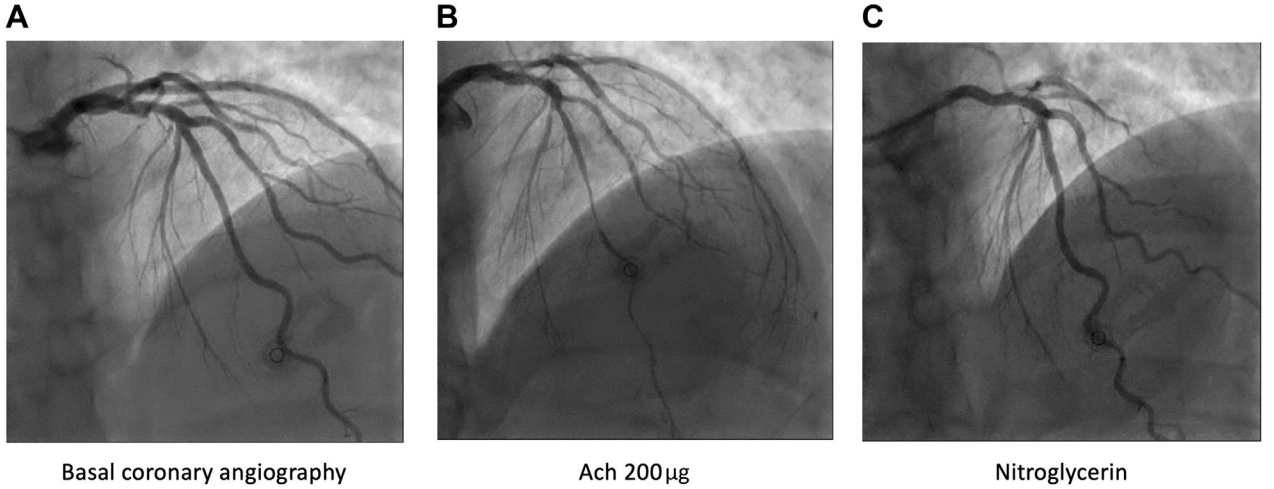
A 51-year-old woman was referred to our inpatient cardiology service due to worsening chest pain following mild exertion (Canadian Cardiovascular Society Angina Score III), despite optimal medical therapy. Her past medical history was notable for Takayasu arteritis, now clinically stable under treatment with azathioprine and tocilizumab. Her cardiovascular risk factors included active smoking, arterial hypertension, and familial hypercholesterolemia treated with the PCSK9-inhibitor evolocumab. She had been experiencing classic exertional chest pain for several years (Table 1). A first diagnostic workup was performed and cardiac computed tomography showed nonobstructive atherosclerosis with <50% stenoses in the major epicardial vessels. Stress echocardiography induced typical angina and electrocardiographic abnormalities, but no regional wall motion abnormalities were reported. A reduced value of

FIGURE 3 **Case 2: Basal Coronary Angiography and Coronary Functional Testing**



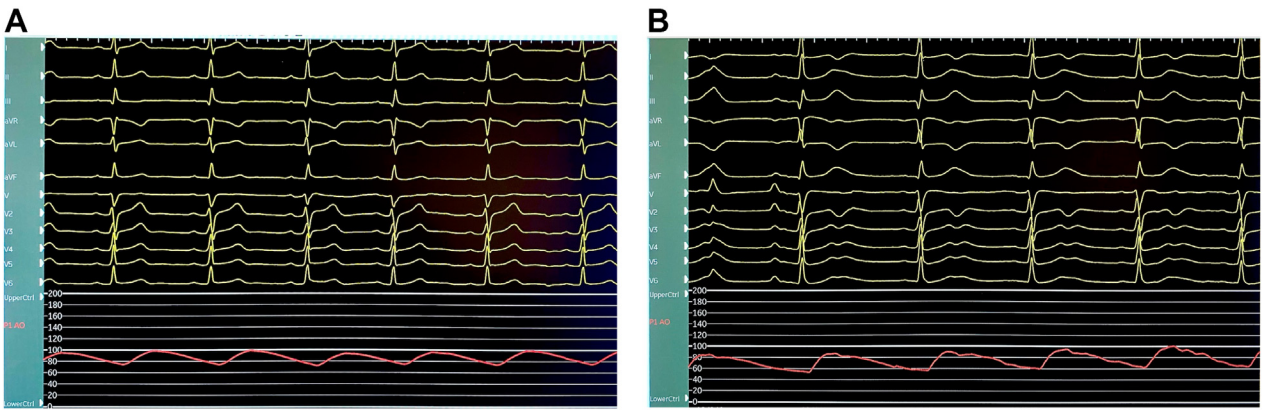
(A) Absence of obstructive coronary artery disease at coronary angiography. **(B)** Absence of functionally severe left anterior descending artery stenoses: FFR = 0.81 (n.v. >0.8). Coronary functional testing, highlighted in red, was negative for microvascular dysfunction: CFR = 3.8 (n.v. >2.0), IMR = 18 (n.v. <25). CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microvascular resistance; n.v. = normal value.

FIGURE 4 **Case 2: Vasoreactivity Test With Intracoronary Administration of Four Increasing Doses of Acetylcholine (2-20-100-200 μg)**



(A) Basal coronary angiography. **(B)** The intracoronary administration of 200 μg of acetylcholine induced significant epicardial spasm of the mid-distal segment of the left anterior descending artery, with concomitant occurrence of anginous symptoms and electrocardiographic alterations. **(C)** Epicardial spasm promptly regressed after intracoronary administration of nitroglycerin.

FIGURE 5 Case 2: ECG Alterations During Vasoreactivity Test



(A) Basal electrocardiogram (ECG). **(B)** After intracoronary administration of acetylcholine, ECG showed transitory T-wave inversion in the anterolateral leads.

coronary flow reserve (1.6) was detected using pulsed-wave Doppler on the LAD suggesting CMD, and the patient was therefore diagnosed with MVA and started on ivabradine, ramipril, and rosuvastatin. However, because of the persistence of anginous symptoms, stress myocardial computed tomography perfusion was performed, exacerbating typical symptoms and revealing diffused reduction of myocardial perfusion in the antero-septal mid-basal region, in the anterior mid-apical region, and in the inferior mid-basal region, with myocardial blood flow values of 100 mL/g/min (normal values >91 mL/g/min) during hyperemia and, more significantly, a ratio of 0.6 between hypoperfused areas and normally vascularized areas. Thus, the diagnosis of CMD was reconfirmed and the patient remained medically managed. Despite regular cardiological follow-up and up-titration of the medical therapy with the addition of ranolazine, symptom relief was never fully obtained, and the patient was admitted to our center for in-depth investigation of the clinical picture. Coronary angiogram showed a diffused, calcific, angiographically intermediate lesion of the proximal and mid LAD, and functional assessment revealed a pathological fractional flow reserve value of 0.71, which indicates functional relevance of the coronary artery stenoses. Intravascular ultrasound showed a significant reduction of the lumen with a minimal lumen area of 3.82 mm^2 on the proximal LAD and was used to plan and guide the percutaneous coronary intervention (**Figure 6**) that was successfully carried out with implantation of 2 overlapping drug-eluting stents (**Figure 7**). The patient was discharged the day after on her anti-anginal medication. Since then, she remained asymptomatic.

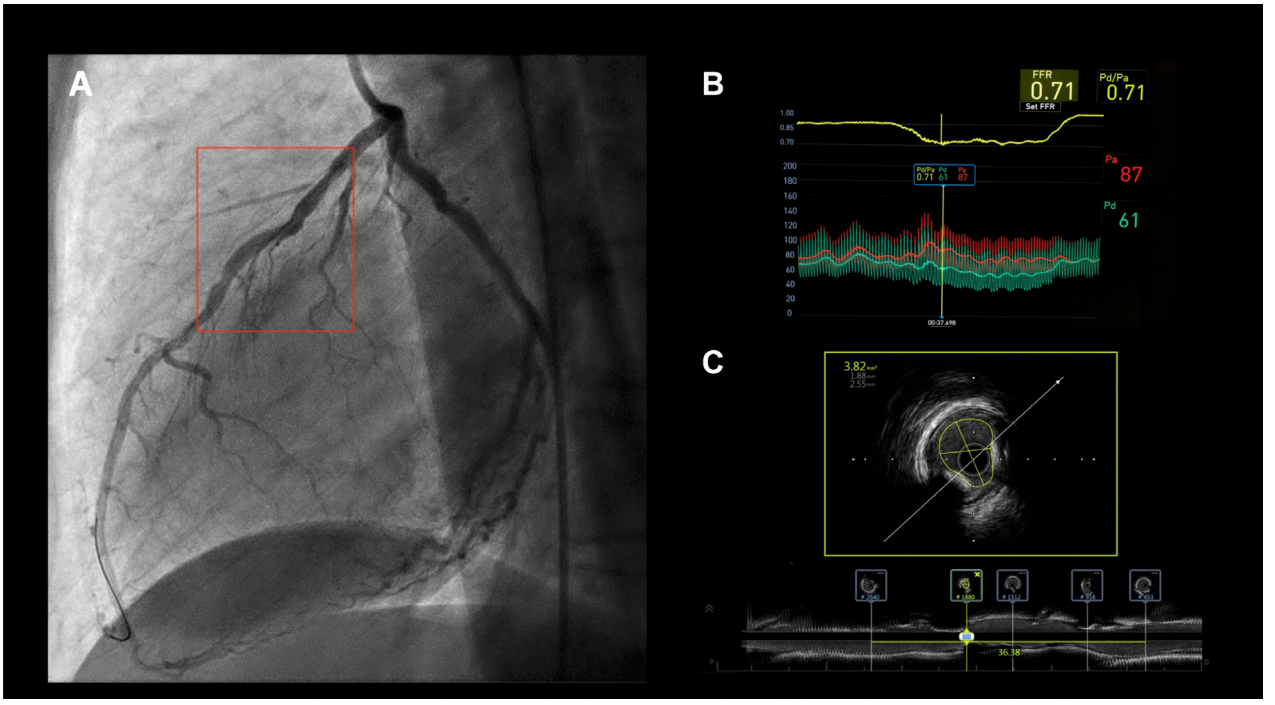
DISCUSSION

INOCA is being progressively acknowledged as one of the pathophysiological mechanisms of chronic coronary syndrome in an increasingly wide range of clinical pictures.[2] It must be highlighted that INOCA is not a benign condition: affected patients usually experience a significant impairment of their quality of life and are exposed to increased risk of cardiovascular events and rehospitalizations.[4] Therefore, a prompt diagnosis and adequate tailored therapy are pivotal in the management of these patients; however, the disease remains a clinical challenge, especially if not thoroughly investigated.

TABLE 1 Case 3: Timeline of Clinical Events

7 y before admission	First reported episodes of recurrent typical angina; diagnosis of microvascular angina and medical therapy prescription.
7 to 1 y before admission	Progressive up-titration of medical therapy to obtain symptom relief.
8 mo before admission	Onset of increasingly severe typical angina, despite optimal medical therapy. Unremarkable ECG and echocardiography. Dynamic cardiac computed tomography stress perfusion imaging showing inducible myocardial ischemia, with calcific nonobstructive coronary artery disease.
Upon admission	Unremarkable physical examination; normal ECG and laboratory testing. Coronary angiogram showing angiographically intermediate calcific stenosis of the left anterior descending artery. Functional assessment with fractional flow reserve revealing an ischemia-inducing lesion, and intravascular ultrasound documenting reduction of lumen. Percutaneous coronary intervention with positioning of 2 drug-eluting stents.
1-d post-admission	Discharge from hospital.
1-mo post-discharge	Patient asymptomatic.

FIGURE 6 **Case 3: Invasive Diagnostic Workup**



(A) Angiographic documentation of intermediate, diffused calcific stenosis of the left anterior descending (LAD) artery. **(B)** Functional assessment of the LAD lesion with pathological values of fractional flow reserve (FFR) (FFR = 0.71, n.v. >0.8). **(C)** Intravascular ultrasound showing pathological values of minimum lumen area on the proximal segment of the LAD artery (minimum lumen area = 3.82 mm ^{2}). n.v. = normal value.

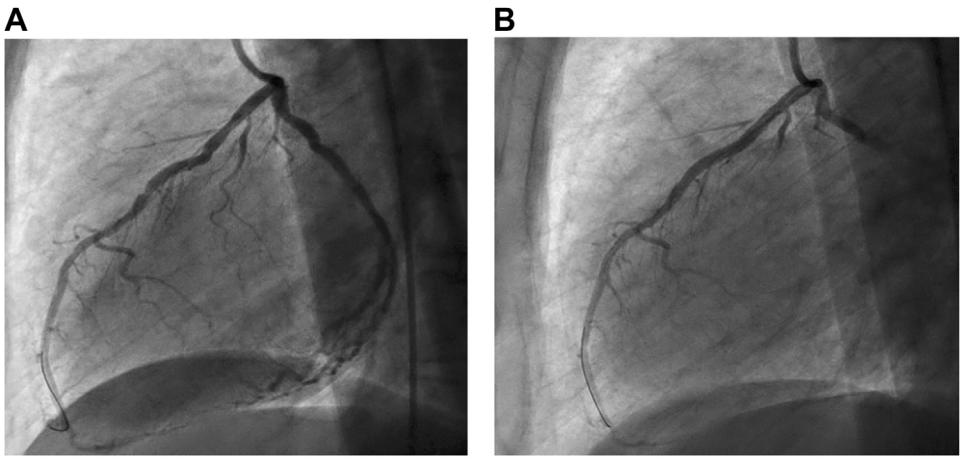
In this perspective, Case 1 is emblematic, as the patient had been correctly diagnosed with INOCA, but the assumption of the wrong endotype led to the choice of an inadequate medication: VSA was suspected, and diltiazem was empirically started. However, this was not the first-line treatment for the patient's endotype (CMD), therefore she would have likely had to bear the side effects of high-dose calcium channel blockers, without receiving any clinical benefit from the medication.

Furthermore, avoiding stigmatization of epidemiological features may also increase the rate of INOCA diagnosis, as depicted in Case 2. This disease is usually expected in middle-aged women after menopause; however, it cannot be excluded a priori in a young man.[5] Case 2 also offers the opportunity to reflect on the eventuality of misdiagnosis of previous conditions: the patient who was diagnosed with VSA had undergone percutaneous coronary intervention and coronary stenting twice, but the persistence of symptoms, together with the evidence of little to no calcific disease at the coronary angiography and the novel VSA diagnosis after vasoreactivity test, cannot exclude that a nonobstructive coronary artery disease prone to vasospasm might have been stented in previous procedures. The patient also presents a myocardial bridge in the mid-distal segment of the LAD; however, because the fractional flow reserve on the segment is negative, it was not considered ischemia-generating.

Conversely, Case 3 aims at shedding light on the issue of gender-biased diagnosis and treatment in cardiovascular disease: the patient represented the ideal phenotype of CMD, presenting epidemiological features, predisposing factors, and most of the disease-defining criteria of MVA.[6] Therefore, based on this assumption, she was initially denied further invasive testing, whereas the persistence of typical angina with nonobstructive atherosclerosis and positive myocardial perfusion imaging would have most probably led to invasive coronary angiography, had the patient been male. This case also highlights that atherosclerosis is a dynamic process, and that CMD and epicardial coronary artery disease may coexist and simultaneously progress as part of the wide spectrum of the same disease.

Currently different observational studies are ongoing to better understand the real prevalence of

FIGURE 7 Case 3: Coronary Angiography Before and After LAD PCI



(A) Basal coronary angiography. **(B)** Coronary angiography after left anterior descending artery (LAD) percutaneous coronary intervention (PCI) with implantation of 2 overlapping drug-eluting stents.

INOCA in different geographies and if a tailored therapy based on the INOCA endotype diagnosis through invasive testing can affect the patient's quality of life and outcomes. In this regard, INOCA-IT Registry RF-2019-12369486 (Ischemia in patients with Non-Obstructive Coronary Artery disease in ITaly INOCA-IT Multicenter Registry; NCT05164640) is currently enrolling patients with suspected INOCA in Italy.

CONCLUSIONS

INOCA is a common clinical picture, with a defined diagnostic pathway and specific medical therapy. However, misdiagnosis in nonobstructive and obstructive coronary artery disease can occur at different stages of the process and hamper the effectiveness of treatment, often leaving the patients with an impaired quality of life.

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ADDRESS FOR CORRESPONDENCE: Prof Alaide Chieffo, University Vita-Salute San Raffaele, IRCSS Ospedale San Raffaele, Via Olgettina, 60, 20132 Milan, Italy. E-mail: Chieffo.alaide@hsr.it. @alaide_chief.

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KEY WORDS INOCA, misdiagnosis, tailored therapy

APPENDIX For supplemental videos, please see the online version of this paper.