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ISCHEMIC HEART DISEASE

CLINICAL CASE

Invasive Diagnosis of HFpEF and ANOCA in a Patient With Effort Dyspnea and Angina

Imma Forzano, MD, Giuseppe Gargiulo, MD, PhD, Lina Manzi, MD, Marisa Avvedimento, MD, PhD, Viviana Narciso, BSc, Luca Ciaramella, MD, Luigi Di Serafino, MD, PhD, Giovanni Esposito, MD, PhD

ABSTRACT

BACKGROUND Angina or ischemia with nonobstructive coronary arteries (ANOCA/INOCA) and heart failure with preserved ejection fraction (HFpEF) are increasingly recognized conditions that may present with similar clinical presentation. Their underlying mechanisms and interplay remain incompletely understood. This case highlights how ANOCA/INOCA and HFpEF can coexist and be simultaneously diagnosed through a single invasive assessment.

CASE SUMMARY A 63-year-old man presented with recurrent exertional angina and dyspnea despite optimal medical therapy. Noninvasive testing and prior angiography had shown nonobstructive coronary disease. A comprehensive invasive evaluation including coronary angiography, physiology testing (adenosine and acetylcholine), and right heart catheterization was performed in a single procedure, revealing both coronary microvascular dysfunction and HFpEF. Target therapy led to symptomatic improvement.

DISCUSSION This case illustrates the clinical overlap and potential coexistence of HFpEF and ANOCA/INOCA, emphasizing the value of integrated invasive testing to achieve accurate diagnosis and tailored treatment.

TAKE-HOME MESSAGE A comprehensive invasive evaluation can uncover concomitant HFpEF and ANOCA/INOCA, improving diagnostic accuracy and patient outcomes. (JACC Case Rep. 2026;31:106732) © 2026 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/).

Patients presenting with angina and/or dyspnea despite nonobstructive coronary artery disease (CAD) often remain without a definitive diagnosis and therefore receive suboptimal therapy and follow-up. While angina typically suggests obstructive CAD, it may also occur in conditions such as angina or ischemia with nonobstructive coronary arteries (ANOCA/INOCA). Conversely, dyspnea is often attributed to pulmonary diseases or heart failure, including heart failure with preserved ejection fraction (HFpEF).[1]

In the past decade, knowledge and understanding of ANOCA/INOCA and HFpEF have significantly improved, enabling more accurate diagnostic strategies and tailored management. This case illustrates how an integrated invasive approach can identify both conditions in a single procedure, leading to improved quality of life.

From the Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ANOCA = angina with nonobstructive coronary arteries

CAD = coronary artery disease

CFR = coronary flow reserve

HFpEF = heart failure with preserved ejection fraction

IMR = index of microcirculatory resistance

INOCA = ischemia with nonobstructive coronary arteries

LVEF = left ventricular ejection fraction

PCWP = pulmonary capillary wedge pressure

HISTORY OF PRESENTATION

A 63-year-old man with recurrent exertional angina and dyspnea despite medical therapy was referred to our cardiology department. Symptoms had persisted for >5 years, limiting his daily activities and prompting repeated medical evaluations. At admission, he had a blood pressure of 115/70 mm Hg, heart rate of 72 beats/min, oxygen saturation of 97%, and there were no signs of congestion or pulmonary rales.

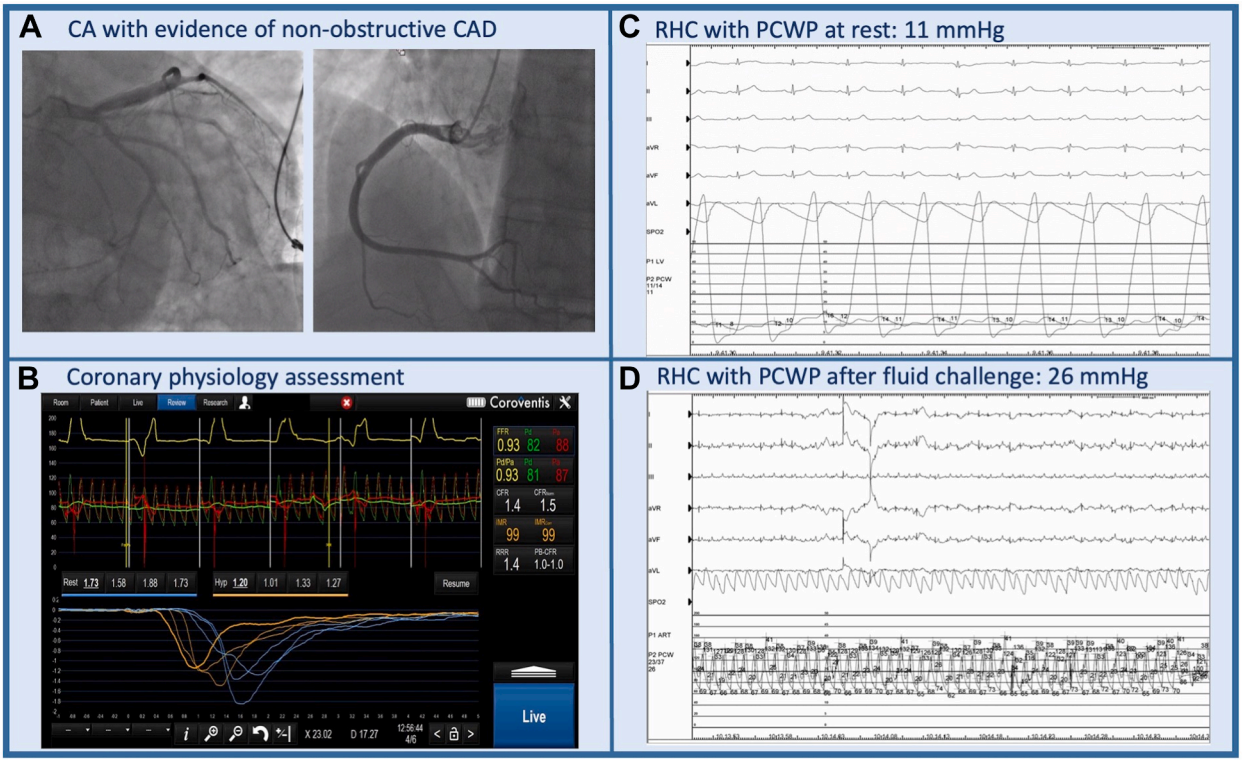
PAST MEDICAL HISTORY

Past medical history included hypertension, dyslipidemia, obesity (body mass index: 31.3 kg/m^2), paroxysmal atrial fibrillation, chronic obstructive pulmonary disease, and obstructive sleep apnea. His daily medications were omeprazole, bisoprolol, edoxaban, telmisartan, spironolactone, amlodipine, and atorvastatin.

TAKE-HOME MESSAGES

- A comprehensive invasive evaluation combining right heart catheterization and coronary physiology testing uncovered concomitant HFpEF and ANOCA/INOCA in a patient with persistent dyspnea and angina despite multiple previous tests.
- Identifying both pathophysiologic mechanisms in a single procedure enabled phenotype-guided therapy and improved patient outcomes and quality of life.

VISUAL SUMMARY **Comprehensive Invasive Evaluation of the Patient**



(A) Left: left coronary artery; right: right coronary artery. Evidence of nonobstructive CAD. (B) Results of coronary physiology test with adenosine indicated altered microcirculatory function (IMR: 99, normal values <25) and reduced CFR (1.8, normal values >2), with diagnosis of CMD. Acetylcholine test was negative (no symptoms and/or alterations at the electrocardiogram and/or evidence of coronary spasm). (C) Pressure waveforms of PCWP at rest: 11 mm Hg. (D) Pressure waveforms of PCWP after fluid challenge using 700 mL of NaCl 0.9% administered intravenously in 6 minutes: 26 mm Hg (normal values: <25 mm Hg). This finding confirmed the hemodynamic definition of HFpEF. CA = coronary angiography; CAD = coronary artery disease; CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; IMR = index of microcirculatory resistance; LAVi = left atrial volume index; LVEF = left ventricular ejection fraction; RHC = right heart catheterization; TRV = tricuspid regurgitation velocity.

FIGURE 1 Scores for Assessing Diagnostic Probability of HFpEF

H_2FPEF

	Definition	Pts
Heavy	BMI >30 kg/m²	2
Hypertension	≥2 antihypertensive medicines	1
AF	Any history	3
PH	*PAPs >35 mmHg	1
Elder	>60 y	1
Filling Pressure	*E/e' >9 ratio	1

HFA-PEFF

Domain	Major Criteria - Max 2 pts per category	Minor Criteria - Max 1 pt per category
Functional	• Average E/e' ≥15 • Septal e' <7 cm/s • Lateral e' <10 cm/s • TRv >2.8 m/s	• Average E/e' ratio 9-15 • GLS <16%
Morphological	• LAVi >34 mL/m² • LV mass index >149/122 g/m² and RWT >0.42	• LAVi 29-34 mL/m² • LV mass index >115/95 g/m² • RWT >0.42 • LV wall thickness ≥12
Biomarker (sinus rhythm)	• NT-pro-BNP >220 pg/mL • BNP >80 pg/mL	• NT-pro-BNP 125-220pg/mL • BNP 35-80 pg/mL
Biomarker (AF)	• NT-pro-BNP >660 pg/mL • BNP >240 pg/mL	• NT-pro-BNP 365-660 pg/mL • BNP 105-240 pg/mL

H_2FPEF 0-1 HFA-PEFF 0-1	H_2FPEF 2-5 HFA-PEFF 2-4	H_2FPEF 6-9 HFA-PEFF 5-6
Low probability score / Unlikely HFpEF	Intermediate probability score	High probability score / Likely HFpEF

Considering the H_2FPEF score, our patient had 8 points (obesity, hypertension, atrial fibrillation, elderly, filling pressure). Considering the HFA-PEFF score, our patient had 5 points (septal e' <7 cm/s, lateral e' <10 cm/s, NT-proBNP >220 pg/mL, average E/e' ratio 9-15, LAVi 29-34 mL/m^2). These scores indicated he had a high probability/likelihood of HFpEF. AF = atrial fibrillation; BMI = body mass index; GLS = global longitudinal strain; HFpEF = heart failure with preserved ejection fraction; LAVi = left atrial volume index; LV = left ventricle; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAP = pulmonary artery systolic pressure; PH = pulmonary hypertension; RWT = relative wall thickness; TRv = tricuspid regurgitation velocity.

DIFFERENTIAL DIAGNOSIS

Initial differential diagnoses included obstructive CAD, ANOCA/INOCA, HFpEF, pulmonary disease, and structural cardiomyopathies (eg, hypertrophic or infiltrative). No clinical, anamnestic, or echocardiographic features supported alternative diagnoses.

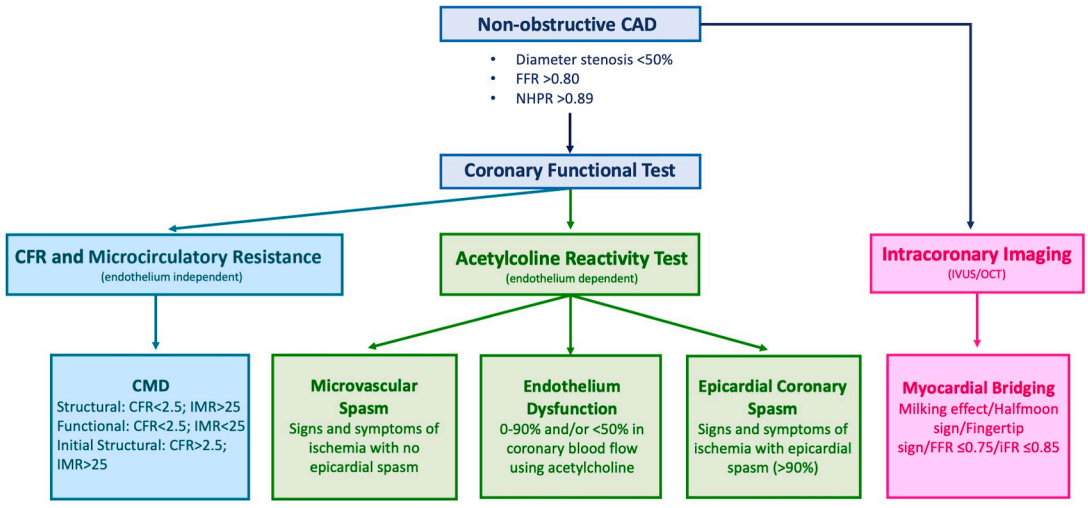
INVESTIGATIONS

Five years earlier, myocardial perfusion single-photon emission computed tomography had demonstrated mild (5%) inferior ischemia, with subsequent coronary angiography excluding obstructive CAD. Despite repeated medical visits and emergency room access over the following years, his symptoms persisted.

During a recent evaluation, the electrocardiogram was unremarkable, echocardiography showed preserved left ventricular ejection fraction (LVEF), and serial troponins were within normal limits, while N-terminal pro-B-type natriuretic peptide was elevated (952 pg/mL). The patient was discharged after exclusion of acute coronary syndrome and acute pulmonary diseases, with a recommendation for repeat noninvasive ischemia testing. Repeat single-photon emission computed tomography showed mild inferolateral ischemia (5%). Angina significantly impaired his quality of life, as reflected by a Seattle Angina Questionnaire-7 score of 56.

Given the persistence of symptoms, the patient was hospitalized for a comprehensive reassessment (**Figures 1 and 2**). Both the H_2FPEF and HFA-PEFF (Heart Failure Association-Pretest assessment, Echocardiography and natriuretic peptide, Functional testing, Final etiology) score indicated a high probability of HFpEF (**Figure 1**).[2] Other potential causes of elevated filling pressures (hypertrophic, infiltrative, or restrictive cardiomyopathies) were excluded on clinical, echocardiographic, and laboratory grounds. Echocardiography showed preserved LVEF (59%) and volumes (end-diastolic volume/body surface area: 69 mL/m^2), with normal relative wall thickness (0.4), left ventricle mass (106 g/m^2), and left atrial volume index (32 mL/m^2). Doppler indices were consistent with grade I diastolic dysfunction (septal e': 5 cm/s, lateral e': 7 cm/s, E/e': 10.8,

FIGURE 2 ANOCA/INOCA Diagnosis



Once obstructive CAD is excluded with coronary angiography, a coronary functional test is needed to point out the exact ANOCA/INOCA phenotype. ANOCA/INOCA = angina and ischemia with nonobstructive coronary arteries; CAD = coronary artery disease; CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; FFR = fractional flow reserve; iFR = instantaneous free wave ratio; IMR = index of microcirculatory resistance; IVUS = intravascular ultrasound; NHPR = nonhyperemic pressure ratio; OCT = optical coherence tomography.

tricuspid regurgitation velocity: 2.82 m/s) (Table 1, Figure 3).

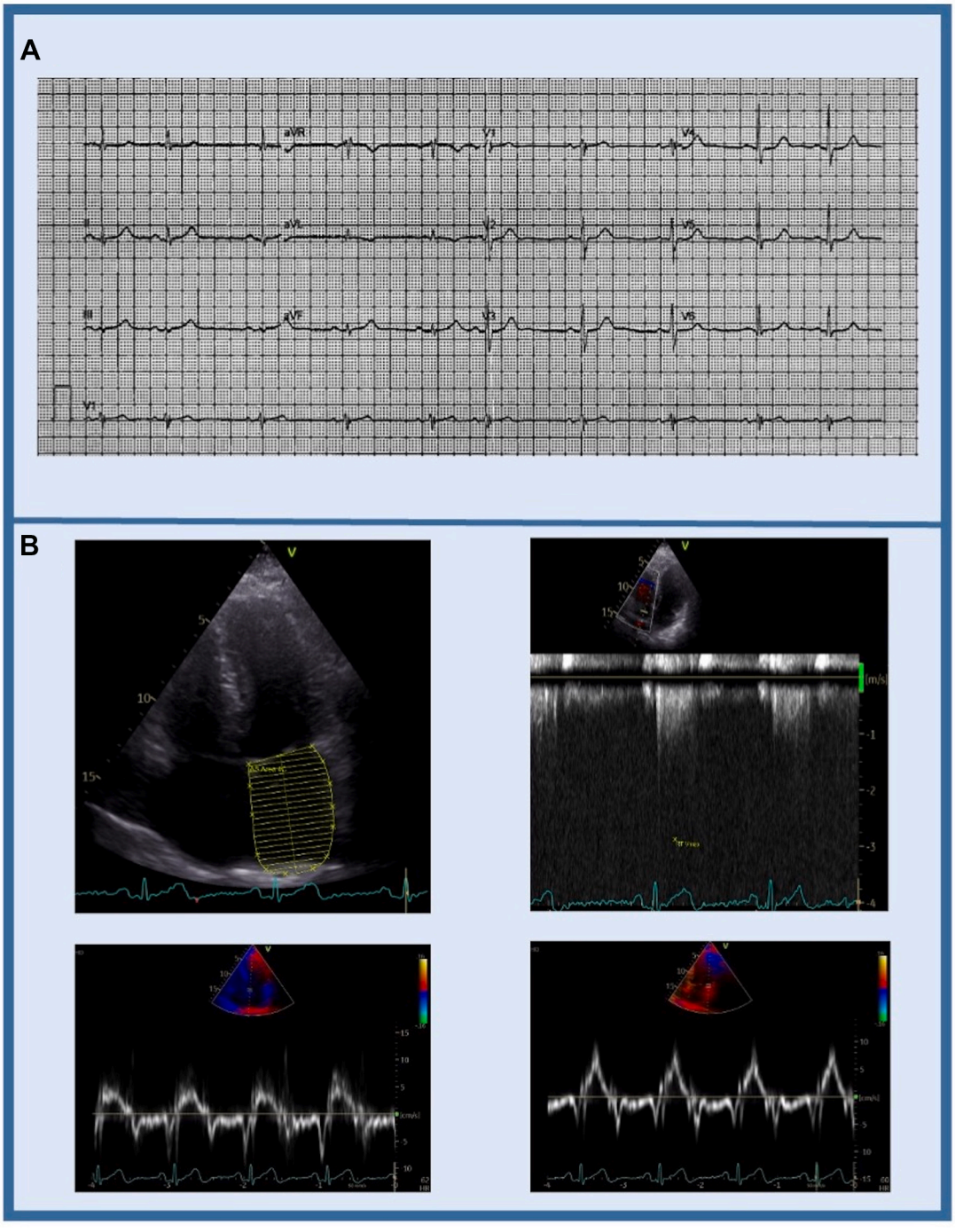
Coronary angiography excluded significant epicardial stenosis. A comprehensive coronary functional assessment was then performed, starting with adenosine and followed by acetylcholine testing. An EBU 4.0, 6-F guiding catheter was engaged in the left main ostium, and a pressure and temperature wire (Pressure Wire X, Abbott) was positioned distally in the left anterior descending artery. Bolus-

TABLE 1 Timeline of the Case With Clinical and Test Findings

Time	Symptoms	Test Findings	Echocardiography Findings
Year 1	Angina and dyspnea	• Myocardial perfusion SPECT: 5% of inducible ischemia • Coronary angiography: nonobstructive CAD	–
Year 2	Angina and dyspnea	• Emergency room access: no ACS • Myocardial injury biomarkers (troponin): negative	LVEF: 55%
Year 3	Angina and dyspnea	–	–
Year 4	Angina and dyspnea	• Emergency room access: no ACS • Myocardial injury biomarkers (troponin): negative • NT-proBNP: 952 pg/mL • Myocardial perfusion SPECT: 5% of inducible ischemia	LVEF: 55%
Year 5	Angina and dyspnea	• Cardiology unit visit for indication to hospitalization: no obstructive CAD, CMD, HFpEF • Coronary angiography, coronary functional test with adenosine and acetylcholine, RHC: modification of therapy	LVEF: 59%, dD: 54 mm, EDV: 152 mL, EDV/BSA: 69 mL/m^2, RWT: 0.4, mass/BSA: 106 g/m^2, LAVi: 32 mL/m^2, TRV: 2,82 m/s, septal e′: 5 cm/s, lateral e′: 7 cm/s, E/e′: 10.8
Follow-up 30 d	Improvement of symptoms	• Cardiology unit visit: NT-proBNP 350 pg/mL	–
Follow-up 6 mo	No symptoms	• Cardiology unit visit: NT-proBNP 175 pg/mL	–
Follow-up 18 mo	No symptoms	• Cardiology unit visit: NT-proBNP 140 pg/mL	–

ACS = acute coronary syndrome; BSA = body surface area; CAD = coronary artery disease; CMD = coronary microvascular dysfunction; dD = diastolic diameter; EDV = end diastolic volume; HFpEF = heart failure with preserved ejection fraction; LAVi = left atrial volume index; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RHC = right heart catheterization; RWT = relative wall thickness; SPECT = single-Photon emission computed tomography; TRV = tricuspid regurgitation velocity.

FIGURE 3 **Patient Evaluation**



(A) Electrocardiogram showing sinus rhythm at 66 beats/min, with no specific anomalies. (B) Echocardiography demonstrated LVEF 59%, LAVi 32 mL/m^2, TRV 2.82 m/s, septal e′ 5 cm/s, lateral e′ 7 cm/s, and E/e′ 10.8. LAVi = left atrial volume index; LVEF = left ventricular ejection fraction; TRV = tricuspid regurgitation velocity.

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thermodilution was used to derive coronary flow reserve (CFR) and index of microcirculatory resistance (IMR), yielding CFR 1.4 and IMR 99, consistent with structural coronary microvascular dysfunction. An acetylcholine provocation test (incremental doses of 20-50-100-200 μg) did not induce symptoms, electrocardiographic changes, or angiographic spasm, ruling out epicardial or microvascular vasospasm. A pigtail catheter was advanced into the left ventricle, showing a normal end-diastolic pressure (7 mm Hg). Subsequently, right heart catheterization with a Swan-Ganz catheter was performed to assess hemodynamics at rest and after fluid challenge (700 mL of NaCl 0.9% administered intravenously over 6 minutes). At rest, pulmonary capillary wedge pressure (PCWP) was 11 mm Hg, right atrial pressure 3 mm Hg, and cardiac index 3.56 L/min/m^2. After the fluid challenge, PCWP rose to 26 mm Hg, confirming the hemodynamic diagnosis of HFpEF. These findings established 2 concomitant diagnoses (coronary microvascular dysfunction and HFpEF), explaining the overlapping presentation of exertional angina and dyspnea.

MANAGEMENT

Pharmacotherapy was optimized according to the dual diagnosis. The patient was discharged on nebivolol 5 mg once daily, ranolazine 375 mg twice daily, empagliflozin 10 mg once daily, pantoprazole 20 mg once daily, telmisartan 80 mg once daily, edoxaban 60 mg once daily, eplerenone 50 mg once daily, atorvastatin 80 mg once daily, and ezetimibe 10 mg once daily.

OUTCOME AND FOLLOW-UP

At the 30-day, 6-month, and 18-month follow-ups, the patient remained in sinus rhythm with progressive symptom improvement (Seattle Angina Questionnaire-7 scores: 68, 78, and 81, respectively) and decreased N-terminal pro-B-type natriuretic peptide (350, 175, and 140 pg/mL, respectively). Medical therapy remained unchanged with the exception of an increase in ranolazine dosage to 500 mg twice daily. He reported normal exercise tolerance, without angina or dyspnea. At follow-up, the patient said, “I was scared to perform an additional invasive assessment and required more than 1 month to accept to do it. Today, after several years of living with effort symptoms and limitations, I am happy to have accepted the risk because I reached specific diagnoses and treatments and most of all mental and physical health.”

DISCUSSION

Angina is the hallmark symptom of CAD, yet up to 70% of patients presenting with angina and signs of ischemia have no angiographic evidence of obstructive disease. These cases, now recognized under the ANOCA/INOCA spectrum, include several phenotypes, such as coronary microvascular dysfunction, microvascular or epicardial spasm, endothelial dysfunction, and myocardial bridging.[1] Despite typical symptoms, these patients are often misdiagnosed or undertreated. Diagnosis requires invasive coronary physiology testing to exclude epicardial stenosis and identify the specific ANOCA/INOCA phenotype.[3] ANOCA/INOCA is associated with high morbidity and a greater risk of major adverse cardiovascular events, and accurate diagnosis and phenotype-driven therapy are essential to improve quality of life, although the condition remains often underdiagnosed.[4] According to guidelines, in patients with persistent angina and nonobstructive coronary arteries, coronary functional testing, including measurement of CFR, IMR, and acetylcholine provocation, is important to clarify the underlying pathophysiology and guide management.[1]

HFpEF, conversely, accounts for up to 50% of heart failure cases and represents a growing clinical challenge. It typically affects older, female, obese individuals and is characterized by dyspnea, fatigue, and exercise intolerance.[5] Despite its increasing prevalence (1.0%-1.5%) and high morbidity, effective therapies remain limited. Diagnosis of HFpEF requires symptoms and signs of heart failure, preserved LVEF (≥50%), and objective evidence of elevated left ventricular filling pressures, either invasively or not.[5] According to guidelines, right heart catheterization remains the gold standard for confirming increased filling pressures, particularly in patients with inconclusive noninvasive findings.[5] The diagnosis is confirmed by a PCWP of ≥15 mm Hg at rest or ≥25 mm Hg during exercise, or a left ventricular end-diastolic pressure of ≥16 mm Hg at rest.[6]

Invasive hemodynamic assessment is reasonable in patients with unexplained dyspnea when the diagnosis of HFpEF remains uncertain after noninvasive testing.[5] In the current case, right heart catheterization was performed because the patient was already undergoing cardiac catheterization, dyspnea could have multiple causes, and the diagnostic scores indicated a high probability but not certainty of HFpEF. While invasive testing carries procedural risks, it provides the most reliable hemodynamic confirmation of HFpEF. Exercise right heart

catheterization is considered the reference standard for stress evaluation but requires specialized equipment and expertise. When unavailable, alternative tests, such as fluid challenge, can be used. A PCWP of ≥18 mm Hg after volume loading supports the diagnosis of HFpEF, although further validation is warranted.[7-9]

Interestingly, coronary microvascular dysfunction has been variably reported in both ANOCA/INOCA and HFpEF.[7] Microvascular dysfunction may contribute to the development of heart failure, particularly HFpEF, suggesting that these conditions might represent a spectrum of a single disease process instead of 2 distinct entities. Nevertheless, the exact prevalence and causal relationship between coronary microvascular dysfunction and HFpEF remain to be further elucidated.

CONCLUSIONS

This case highlights the value of an integrated invasive diagnostic strategy combining right heart catheterization and coronary physiology testing in a patient with persistent dyspnea and angina despite nonobstructive CAD. After >5 years of persistent symptoms without specific diagnoses despite noninvasive and invasive tests, our comprehensive approach enabled the simultaneous identification of HFpEF and ANOCA/INOCA, guiding tailored therapy and improving the patient's quality of life. Despite growing awareness, diagnostic algorithms and treatment strategies for these overlapping conditions remain challenging. Further studies are needed to define standardized protocols and to evaluate the long-term benefits of phenotype-guided management.

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ADDRESS FOR CORRESPONDENCE: Prof Giuseppe Gargiulo, Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University of Naples, Via S. Pansini 5, Naples 80131, Italy. E-mail: peppegar83@libero.it OR giuseppe.gargiulo1@unina.it. X handle: @GargiuloG83.

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