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Case report

Coronary Microvascular Dysfunction: A Case Report Emphasizing the Utility of Stress Echocardiography with Hyperventilation and Cardiac perfusion MRI

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Abstract

Introduction: Coronary microvascular dysfunction (CMD) causes angina in patients with non-obstructive coronary arteries (ANOCA) due to structural and functional microcirculation abnormalities. Although invasive testing is the gold standard, its use is limited. Non-invasive methods like hyperventilation combined with exercise stress echocardiography offer practical, accessible assessment of coronary vasomotor function and CMD detection.

Case report: We present a case of a 55-year-old woman with longstanding exertional chest pain, fatigue, and dyspnea, who remained undiagnosed despite normal findings on coronary CT and invasive angiography. Invasive testing with acetylcholine was not performed. Due to persistent symptoms, she underwent non-invasive evaluation using a combined hyperventilation and exercise stress echocardiography protocol. The test revealed a drop in coronary flow velocity after hyperventilation and inadequate coronary flow velocity reserve (CFVR <2) at peak exercise, with accompanying ST depression and subtle wall motion abnormalities—indicative of microvascular vasospasm. Cardiac magnetic resonance imaging (CMR) using adenosine and hyperventilation protocols confirmed widespread subendocardial perfusion defects, supporting a diagnosis of mixed-type CMD with both functional and structural components. Treatment with a calcium channel blocker, ranolazine, and statin led to marked symptom improvement.

Conclusion: This case highlights the diagnostic value of non-invasive methods—particularly hyperventilation stress echocardiographic test, further confirmed by CMR.

Key words Coronary microvascular dysfunction, Hyperventilation stress echocardiography, Microvascular vasospasm

Introduction

Coronary microvascular dysfunction (CMD)—particularly microvascular vasospasm—is a predominant but often unrecognized cause of anginal pain and physical limitation in patients with angina and non-obstructive coronary arteries (ANOCA). It can result from both structural and functional abnormalities of the coronary microcirculation. Structural mechanisms include inward remodeling of arterioles, capillary rarefaction, perivascular fibrosis, extramural compression and intravascular plugging. Functional mechanisms involve endothelial dysfunction, reduced nitric oxide bioavailability, impaired vasodilation, and enhanced vasoconstrictor response (due to increased sympathetic tone or microvascular spasm).[1,2]

The presence of multiple potential mechanisms underlying CMD makes its diagnosis particularly challenging. Although invasive functional testing is considered the gold standard, it is often difficult to implement in routine clinical practice.[3] Hirano et al. demonstrated that hyperventilation and cold pressor tests, when combined with stress echocardiography or angiography, can serve as non-invasive alternatives for provoking and diagnosing coronary vasospasm in patients with suspected vasospastic angina.[4] The aim of our case report is to present a patient in whom we diagnosed CMD using non-invasive diagnostic methods.

Case report

We report the case of a 55-year-old woman with a longstanding history of chest pain, fatigue, and occasional dyspnea, significantly impacting her quality of life. Her symptoms worsened with cold weather. At the time of presentation, she had already undergone coronary CT angiography and invasive coronary angiography, both showing no obstructive coronary artery disease. However, invasive functional testing with acetylcholine was not performed, reflecting a common limitation in routine clinical workflows.

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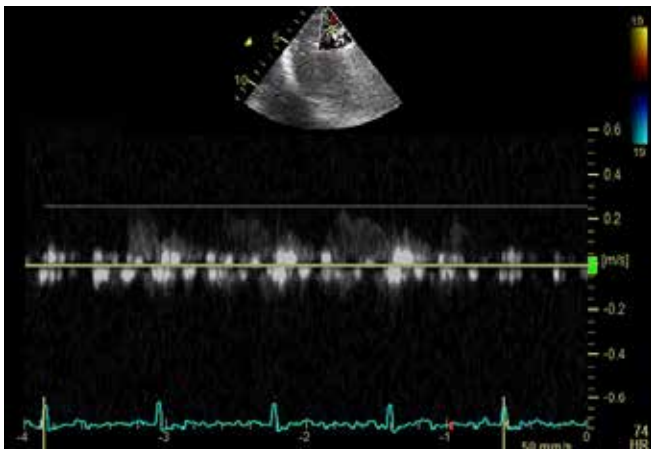

Figure 1. Coronary flow velocity at rest in LAD

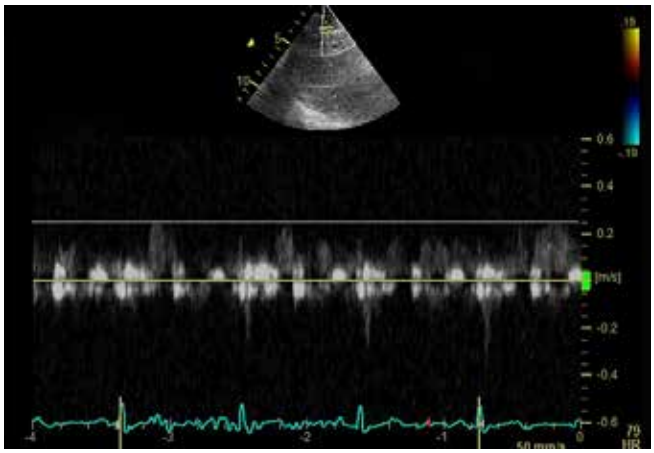

Figure 2. Coronary flow velocity after hyperventilation in LAD

Despite multiple specialist consultations, the patient remained without a definitive diagnosis and continued to experience symptoms despite treatment with beta-blockers and trimetazidine. She was referred for further non-invasive evaluation due to suspected CMD.

Her clinical examination was unremarkable, with a normal BMI. She was a former tennis player, a non-smoker, had two children, and no family history of cardiovascular disease. Laboratory tests showed elevated lipid levels (total cholesterol: 5.78 mmol/L; LDL: 3.80 mmol/L; HDL: 1.80 mmol/L), with normal BNP, NT-proBNP, renal and liver function, and blood count.

Resting ECG revealed discrete ST-segment depression in leads II, III, aVF, and V3–V6, with biphasic T waves in lead V2. Transthoracic echocardiography was within normal limits, with only trivial aortic and mitral regurgitation.

To evaluate for coronary vasospasm, we performed a combined hyperventilation and exercise stress echocardiography protocol. This included five minutes of hyperventilation (≥30 breaths/min), followed by semi-supine bicycle exercise to the target heart rate. Left ventricular function, wall motion, and ECG changes were assessed throughout. Coronary flow velocity reserve (CFVR) was measured using transthoracic Doppler echocardiography at rest, after hyperventilation, and at peak exercise. Impaired responses were defined as reduced coronary flow velocity post-hyperventilation and inadequate

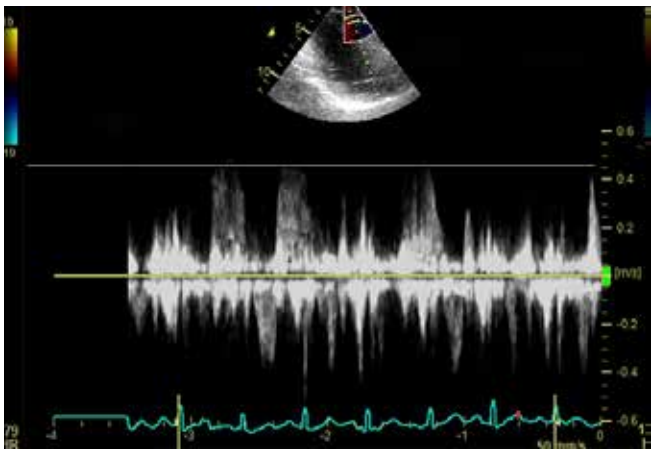

Figure 3. Coronary flow velocity at peak stress in LAD

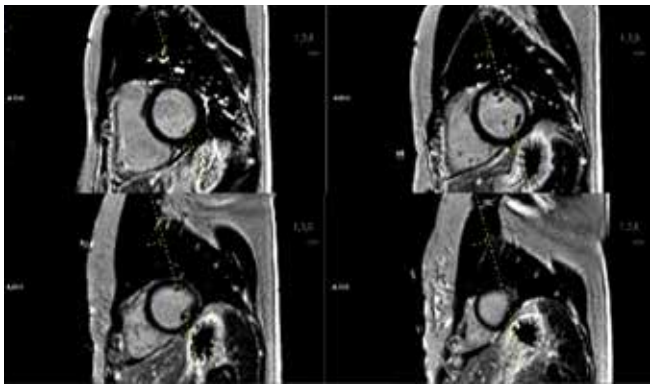

Figure 4. LGE PSIR sequence, short axis: Without areas of LGE phenomenon

CFVR (CFVR <2) during peak exercise—indicative of microvascular vasospasm.

In our patient, the test revealed a significant drop in coronary flow velocity after hyperventilation and inadequate CFVR at peak exercise, accompanied by ST-segment depression and subtle regional wall motion abnormalities—findings consistent with microvascular vasospasm. (Figures 1, 2, 3)

In differential diagnosis epicardial spasm was excluded based on the absence of ST elevation, arrhythmias, or severe chest pain.

To confirm CMD, the patient underwent cardiac perfusion MRI (CMR). Perfusion imaging was performed using both adenosine and hyperventilation protocols. Adenosine stress revealed circumferential subendocardial perfusion defects in all mid-ventricular segments and the apical anterior/septal segments. Hyperventilation provoked perfusion defects in the basal, mid, and apical septal segments. These findings supported the diagnosis of CMD with both vasospastic and impaired vasodilatory components—indicating a mixed functional and structural microvascular abnormality. (Figure 4, 5)

Therapy was escalated to include a calcium channel blocker, ranolazine, and rosuvastatin, with discontinuation of beta-blockers. The patient reported marked symptomatic improvement.

At 6-month and 1-year follow-ups, she remained significantly better, demonstrating the value of targeted therapy and the accuracy of our diagnostic approach.

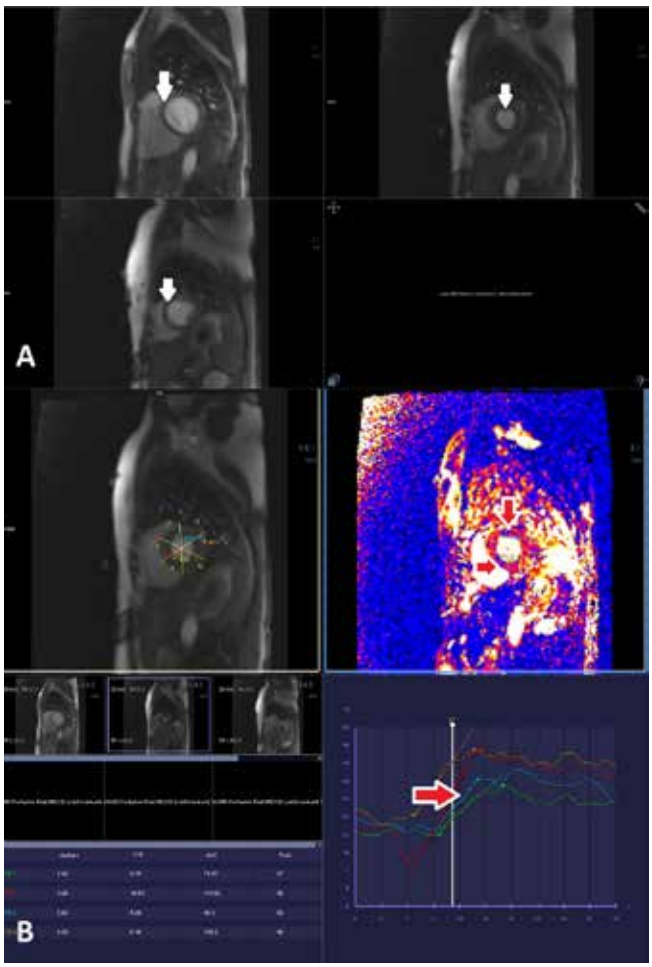

Figure 5. Qualitative (A) and semiquantitative (B) evaluation of CMR hyperventilation test: Diffuse subendocardial defect in perfusion after the hyperventilation test.

Discussion

The 2024 Guidelines for Chronic Coronary Syndromes recommend invasive functional testing in the catheterization laboratory for diagnosis. However, in busy clinical settings, these recommendations are rarely implemented. While not currently included in clinical guidelines, hyperventilation and cold pressor tests are acknowledged in the literature and cardiology textbooks as potential non-invasive methods for evaluating coronary vasomotor function.[4] These simpler provocative tests have historically been used for this purpose, yet they are often overlooked in contemporary clinical practice despite their simplicity, safety, and accessibility. Recently, however, there has been renewed interest in their diagnostic value. A study conducted by our department demonstrated that hyperventilation testing may serve as a useful non-invasive tool in the assessment of coronary microvascular dysfunction, underscoring its potential role in everyday clinical evaluation.[5]

The ESC Guidelines support CMR as a promising non-invasive tool for detecting myocardial ischemia and subendocardial perfusion defects suggestive of CMD. CMR offers high spatial resolution and the ability to detect subtle subendocardial perfusion defects, which are often indicative of CMD.[6] We used CMR to test endothelium-dependent function, using hyperventilation as the trigger. This approach enhances the differentiation of CMD from other underlying causes of myocardial ischemia, including ischemic injury, inflammatory conditions, and infiltrative cardiomyopathies.

The combination of hyperventilation testing, stress echocardiography, and cardiac magnetic resonance imaging (CMR) may represent a practical and effective diagnostic approach in settings where invasive functional testing is either not feasible or not readily available.

Conclusion

CMD is an important contributor to angina and ischemia in patients with INOCA. Timely diagnosis is essential for symptom control and potentially reducing long-term cardiovascular risk. Although invasive coronary reactivity testing remains the gold standard, non-invasive evaluation—particularly in experienced centers—is a valuable and underutilized tool, neglected in the latest 2024 Guidelines for CCS.

This case illustrates the utility of hyperventilation stress echocardiography as a practical, non-invasive method for detecting CMD, especially microvascular vasospasm. By combining provocative testing with coronary flow measurements, clinicians can gain meaningful insight into coronary physiology. Our findings were validated by perfusion CMR, reinforcing the clinical relevance of a comprehensive, non-invasive diagnostic strategy in CMD.

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Sažetak

Disfunkcija koronarne mikrocirkulacije: Prikaz slučaja koji ističe korisnost stres-ehokardiografije sa testom hiperventilacije i perfuzionom magnentnom rezonancom srca

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Uvod: *Koronarna mikrovaskularna disfunkcija (CMD) je uzrok anginoznih tegoba kod bolesnika sa neokluzivnim koronarnom arterijskom bolešću (ANOCA) usled strukturnih i funkcionalnih poremećaja mikrocirkulacije. Iako invazivno funkcionalno testiranje predstavlja zlatni standard, njegova primena je ograničena. Neinvazivne metode, kao što je kombinacija hiperventilacije i ergometrijskog stres ehokardiografskog testiranja, nude praktičnu i dostupnu procenu koronarne vazomotorne funkcije i detekciju CMD.*
Prikaz slučaja: *Prikazujemo slučaj 55-godišnje žene sa dugotrajnim bolom u grudima provociranim naporom, umorom i dispnejom, kod koje nije postavljena dijagnoza uprkos normalnim nalazima na koronarnom CT-u i invazivnoj angiografiji. Invazivno testiranje acetilholinom nije sprovedeno. Zbog perzistentnih simptoma, izvršena je neinvazivna evaluacija korišćenjem kombinovanog protokola hiperventilacije i stres ehokardiografije. Test je pokazao pad brzine protoka kroz koronarne arterije nakon hiperventilacije i nedovoljnu koronarnu rezervu protoka (CFVR <2) pri najvećem naporu, uz pridruženu ST depresiju i diskretne promene segmentne kinetike — što ukazuje na mikrovaskularni vazospazam. Magnetna rezonanca srca (CMR) sa adenozinskim i hiperventilacionim testom potvrdila je široko rasprostranjene subendokardijalne perfuzione defekte, što potvrđuje dijagnozu mešovitog tipa CMD sa funkcionalnim i strukturnim komponentama. Terapija blokatorom kalcijumskih kanala, ranolazinom i statinom dovela je do značajnog poboljšanja simptoma.*
Zaključak: *Ovaj slučaj ističe dijagnostičku vrednost neinvazivnih metoda — naročito hiperventilacioni stres ehokardiografski test, dalje potvrđen pomoću magnetne rezonance srca.*

Ključne reči: *Mikrovaskularna disfunkcija, vazospazam, hiperventilacija*