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Review Article

Challenging diagnostic for open artery ischemia

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ABSTRACT

Ischemic heart disease has traditionally been linked to obstructive coronary artery disease. However, a significant subset of patients presents with ischemic symptoms despite having non-obstructive coronary arteries—a condition termed Open Artery Ischemia (OAI). This encompasses entities like ANOCA(angina with no obstructive coronary arteries), INOCA(ischemia with nonobstructive coronary arteries), and MINOCA(myocardial infarction with nonobstructive coronary arteries), which challenge conventional diagnostic paradigms. Patients with OAI often experience persistent chest discomfort and demonstrable ischemia, yet their angiograms reveal no significant epicardial blockage. These individuals, frequently women in midlife, endure considerable morbidity, including diminished quality of life and recurrent hospitalizations. Underlying mechanisms such as microvascular dysfunction, vasospasm, and systemic inflammation contribute to their symptoms. This review aims to elucidate the clinical features, pathophysiological mechanisms, and diagnostic challenges of OAI. By highlighting the importance of advanced diagnostic tools and a patient-centered approach, we advocate for increased awareness and better management strategies for this often-overlooked condition.

Keywords: Open artery ischemia, Non-obstructive Coronary Artery Disease, Chest Pain with Normal Angiogram

1. Introduction

Ischemic heart disease is one of the leading causes of death and is one of the factors for disability (decreased quality of life) in developed countries, thus absorbing most of the health resources. For a century, ischemia has always been associated with obstructive atherosclerosis in large coronary arteries. However, in this era, different findings have been shown that occur without large coronary obstruction.[1,2]

A new term, OAI (Open Artery Ischemia), has emerged as an entity to describe ischemia with open large coronary blood vessels. This is divided into 3 main subgroups: ANOCA (angina with no obstructive coronary arteries), INOCA (ischemia with nonobstructive coronary arteries), and MINOCA (myocardial infarction with nonobstructive coronary arteries). In the supporting examination itself, biomarkers and Cardiac MRI(Magnetic Resonance Imaging) show that there is a lot of overlap between ANOCA, INOCA, and MINOCA. So, questions arise about the usefulness and separation of classifications for practical use.[1,3]

Theories supporting the potential mechanisms underlying OAI continue to emerge, including Coronary microvascular dysfunction (CMD), Epicardial or microvascular vasospasm, Non-obstructive atherosclerosis, Hypercoagulable state, and Predisposition to heart failure with preserved ejection fraction (HFpEF). Emphasis is also placed on the condition of CMD where the number of CMD is >50% in OAI and is associated with decreased quality of life, increased hospitalization rates, and cardiovascular death.[1]

2. Epidemiology

In this era, ANOCA, INOCA, and MINOCA are recognized as the most common phenotypes of non-obstructive ischemic heart disease. There are as many as 100 million people with clinical manifestations of angina pectoris, making angina pectoris the main clinical manifestation of ischemic myocardial disease. When distributed by gender, INOCA is experienced by around 47% of women and 30% of men with typical chest pain complaints originating from the cardiac region. While ANOCA and MINOCA generally occur in young to middle-aged women.[1,2]

Traditional and non-traditional factors also add to the differences in non-obstructive CAD(Coronary Artery Disease) with obstructive CAD. Usually, the incidence of diabetes and dyslipidemia is lower than obstructive CAD. However, other risk factors such as hypertension, insulin resistance, endothelial dysfunction, menopause, obesity, chronic autoimmune disease, smoking (strongly associated with epicardial spasm) still play a role in non-obstructive CAD.[1,2]

Specifically, in women Psychological stress, migraine, preeclampsia, depression, and anxiety disorders play a role in (M)INOCA in women. Where, Mental stress is more likely to trigger endothelial dysfunction and vasomotor disorders in women than in men. In East Asian ethnicity, there is a higher prevalence of coronary vasospasm compared to Caucasians.[1,2]

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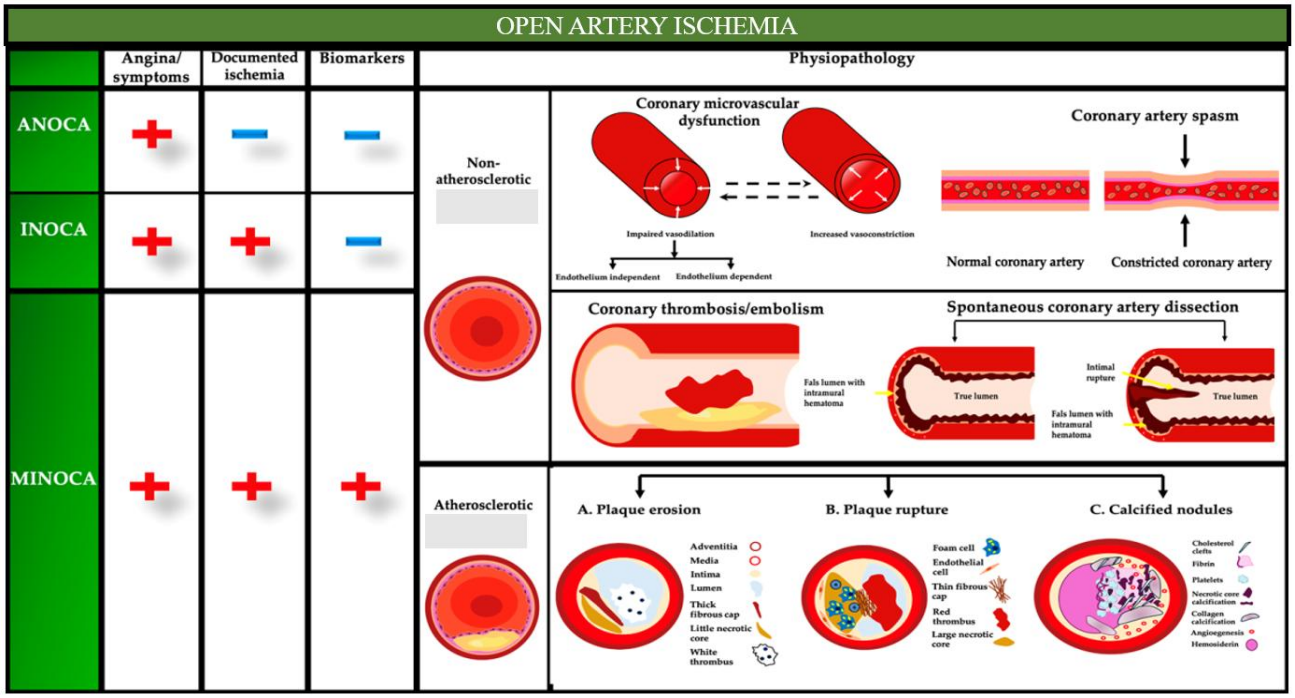

Figure 1. Physiopathology of non-obstructive coronary artery disease. ANOCA, angina with no obstructive coronary artery disease; INOCA, ischemia with no obstructive coronary artery disease; MINOCA, myocardial infarction with no obstructive coronary arteries.[1,2]

3. Distinguishing OAI

Differentiating OAI subgroups is a term that encompasses three important clinical entities, namely ANOCA, INOCA, and MINOCA. All three show symptoms or evidence of myocardial ischemia without significant (>50%) obstruction in the epicardial coronary arteries. Although they have similar angiographic characteristics (no obstruction), each has fundamental differences in terms of clinical manifestations, biomarkers, and physiopathological mechanisms. Therefore, the diagnostic and therapeutic approach to these three conditions needs to be adjusted to the characteristics of each entity.[1,3,4]

ANOCA (Angina Without Obstructive Coronary Artery) is characterized by the presence of angina symptoms without objective evidence of ischemia or increased cardiac biomarkers. The main mechanisms underlying ANOCA are microvascular dysfunction and coronary artery spasm, which cause impaired myocardial perfusion even though the coronary vessels appear anatomically normal. This condition is more common in women and is associated with poor quality of life due to persistent angina complaints. Management of ANOCA requires an individual approach based on invasive or non-invasive coronary physiology evaluation.[1,3,4]

INOCA (Ischemia with No Obstructive Coronary Arteries) is similar to ANOCA in that there is no coronary obstruction, but differs in that there is documented evidence of ischemia, such as by stress testing or CMR(Cardiac magnetic resonance). However, there is no elevation in cardiac biomarkers such as troponins. Microvascular dysfunction and arterial spasm remain the dominant causes, which in many cases are determined by invasive testing such as coronary flow reserve (CFR) or microvascular resistance index (IMR). INOCA can predominantly affect middle-aged women and be associated with an increased risk of hospitalization and later development of heart failure

MINOCA can be the most significant in angina symptoms, documented ischemia, and elevations in cardiac biomarkers, indicating myocardial infarction. Although no anatomic obstruction can be found, the underlying pathologic process is complex and can be atherosclerotic (such as plaque rupture or erosion) or non-atherosclerotic (such as spasm, spontaneous arterial dissection, or coronary embolism). The diagnosis of MINOCA needs advanced imaging, such as cardiac MRI and intravascular imaging OCT(Optical Coherence Tomography), to identify the specific mechanism. MINOCA patients are used to be younger and have similar long-term risks as patients with obstructive CAD infarction, thus requiring comprehensive management.[1,3-5]

4. Pathophysiology of OAI

Understanding the clinical entities of ANOCA, INOCA, and MINOCA reveals that non-obstructive coronary artery disease should no longer be considered a benign or homogeneous condition. Rather, these syndromes represent a heterogeneous spectrum of coronary disorders, underpinned by diverse pathophysiological mechanisms. Broadly, these mechanisms fall into two categories: atherosclerotic processes—such as plaque rupture, erosion, and calcified nodules—and non-atherosclerotic processes, including coronary artery spasm (CAS), CMD, coronary thrombosis or embolism, and spontaneous coronary artery dissection (SCAD).[3]

Plaque disruption plays a crucial role in MINOCA and includes rupture, erosion, and less commonly, calcified nodules. Plaque rupture, typically seen in older individuals, results from the breakdown of the fibrous cap and exposure of the thrombogenic core. In contrast, plaque erosion tends to occur in younger women and smokers and involves the detachment of endothelial cells from the extracellular matrix. Although rare, calcified nodules may provoke thrombosis by disrupting the luminal surface. Elevated levels of inflammatory markers, such as soluble VCAM-1 and CCL-21, in MINOCA patients suggest that microstructural changes in plaques and microcirculatory dysfunction contribute to disease progression. These findings support the routine use of statins, while emphasizing the need for individualized therapeutic strategies.[1,3]

Coronary artery spasm represents another important mechanism, particularly in ANOCA and INOCA. CAS is defined by transient, severe (>90%) constriction of the epicardial arteries, often resulting in chest pain and electrocardiographic changes. The underlying pathophysiology involves hyperreactivity of vascular smooth muscle cells and endothelial dysfunction, with key contributions from signaling pathways such as calcium/calmodulin-MLCK(Myosine light chain kinase) and Rho-kinase. Inflammation and oxidative stress further exacerbate vasoreactivity, as reflected by elevated biomarkers like high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6). CAS is strongly associated with smoking and, in younger individuals, may also be triggered by emotional stress or psychosomatic factors. The CorMicA study has demonstrated that a stratified therapeutic approach based on invasive coronary physiological testing significantly improves symptom control and clinical outcomes.[1,3,6]

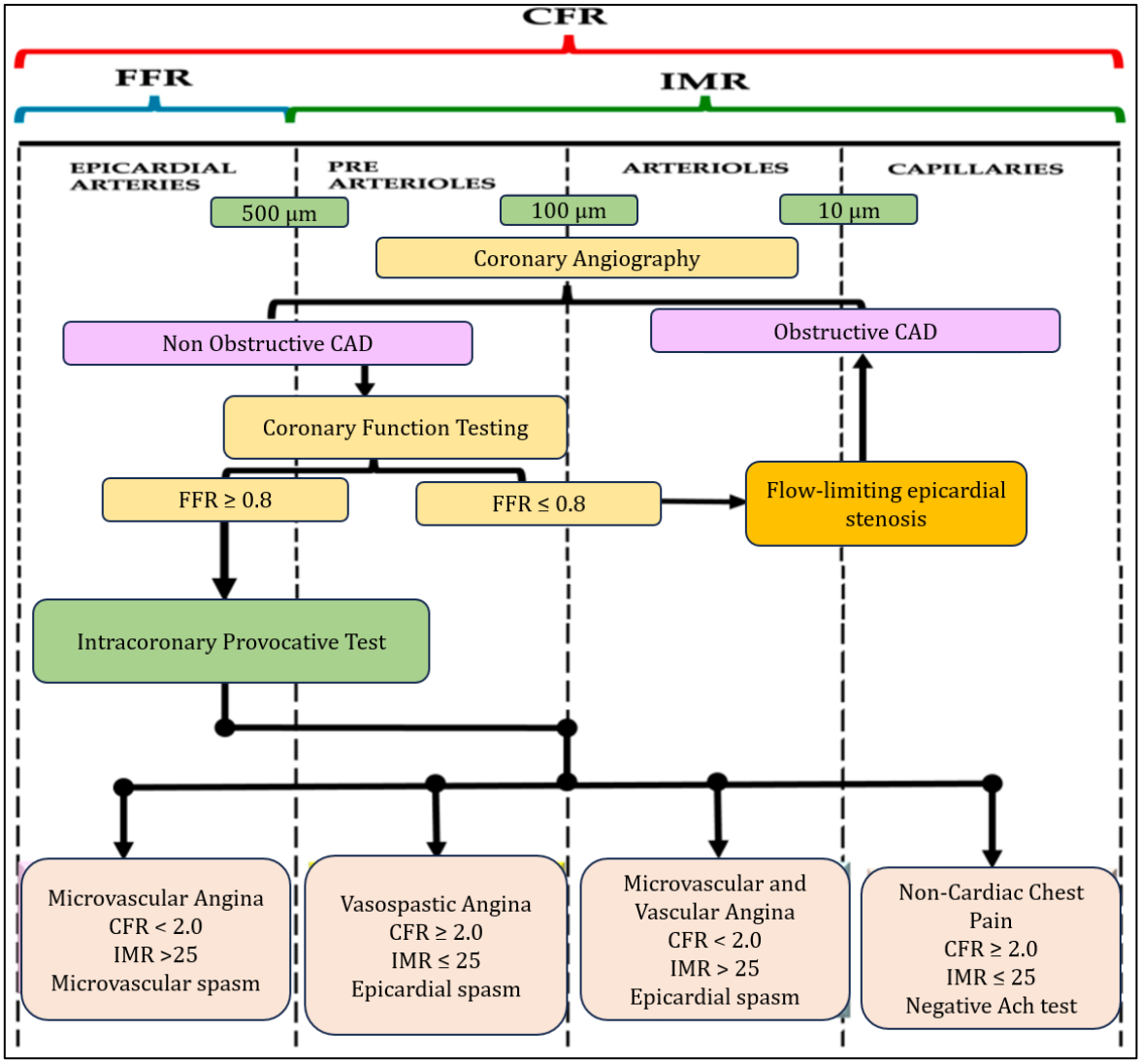

Figure 1. Diagnostic algorithm for invasive functional evaluation in patients with non-obstructive coronary artery disease. Ach—acetylcholine; CAD—coronary artery disease; CFR—coronary flow reserve; FFR—fractional flow reserve; IMR—index of microvascular resistance.[1,2]

Coronary microvascular dysfunction, meanwhile, is a predominant mechanism in both ANOCA and INOCA. CMD leads to impaired myocardial perfusion despite the absence of anatomical obstruction and is characterized by increased microvascular resistance driven by Rho-kinase activation, oxidative stress, and inflammatory mediators such as endothelin-1. CMD results in impaired vasodilation—both endothelium-dependent (e.g., nitric oxide, prostaglandins, EDHF) and independent. Factors like aging, oxidative damage, and platelet-endothelial interactions worsen microvascular inflammation. Notably, stress CMR imaging has revealed that approximately two-thirds of female MINOCA patients exhibit perfusion defects due to CMD, and endothelial dysfunction is observed in up to 50% of INOCA cases, correlating with persistent symptoms and heightened cardiovascular risk.[1,3,6]

Given this diverse pathophysiology, accurate identification of the underlying mechanism is essential for guiding effective treatment. Invasive functional assessment is key in patients without obstructive coronary disease on angiography. While coronary angiography remains the initial step to exclude significant epicardial obstruction, further physiological evaluation is crucial in selected cases. Measurements such as fractional flow reserve (FFR ≤ 0.80) suggest flow-limiting lesions, while a CFR < 2.0 and an index of microvascular resistance (IMR) ≥ 25 are indicative of CMD. Acetylcholine provocation testing can diagnose both epicardial and microvascular spasm. These tests are instrumental in distinguishing between angina due to vasospasm, microvascular dysfunction, or non-cardiac causes.[1,3,6]

Each syndrome presents with unique clinical and physiological profiles. In ANOCA, patients experience typical anginal symptoms in the absence of obstructive coronary lesions, often attributable to CMD, epicardial spasm, or a combination of both. Observational studies report that nearly a quarter of these patients have microvascular dysfunction, while a similar proportion demonstrate microvascular or macrovascular spasm. INOCA is defined by objective evidence of myocardial ischemia without obstructive coronary artery disease, with CMD and CAS as leading contributors. In a large cohort, CMD was identified in 12% of patients, CAS in 33.2%, and a combination in 18.6%, highlighting the value of invasive functional testing in guiding diagnosis and avoiding mismanagement. MINOCA, on the other hand, encompasses a broader range of etiologies, including plaque disruption, CAS, CMD, thrombosis, embolism, and SCAD. OCT and CMR imaging have revealed that epicardial spasm is present in over 60% of MINOCA patients, with nearly half exhibiting plaque disruption and a subset demonstrating non-ischemic conditions such as myocarditis or Takotsubo syndrome.[1,3,6,7]

5. Clinical implications

The clinical implications of OAI, particularly those caused by CMD, require a more targeted approach to the underlying pathophysiology. Current therapies focus on modifying traditional risk factors and addressing endothelial dysfunction and chronic inflammatory processes. Given that CMD is an entity that cannot be detected by conventional angiography alone, therapeutic strategies need to consider the role of microinflammation, oxidative stress, and vasomotor pathway dysregulation in maintaining microcirculatory function. Therefore, pharmacological interventions targeting these pathways are a major focus in therapeutic development.[1]

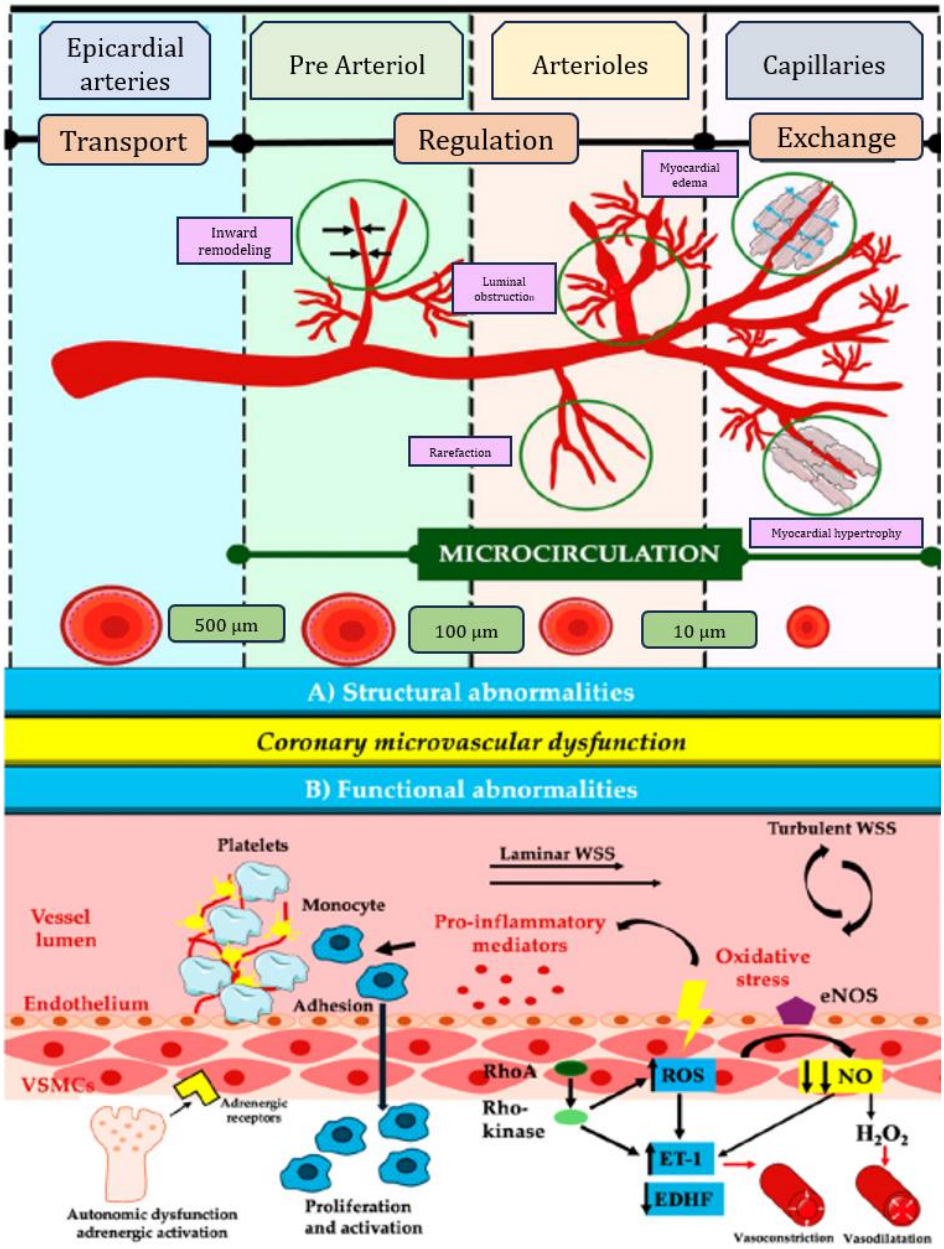

Figure 2. Physiopathology of coronary artery spasm. Ach—acetylcholine; CaM—calmodulin; ET-1—endothelin-1; NO—nitric oxide; MLC—myosin light chain; MLCK—myosin light chain kinase; PLC—phospholipase C; PKC—protein kinase C; ROS—reactive oxygen species; RhoA—Ras homolog gene member A; VSMCs—vascular smooth muscle cells.[1,2]

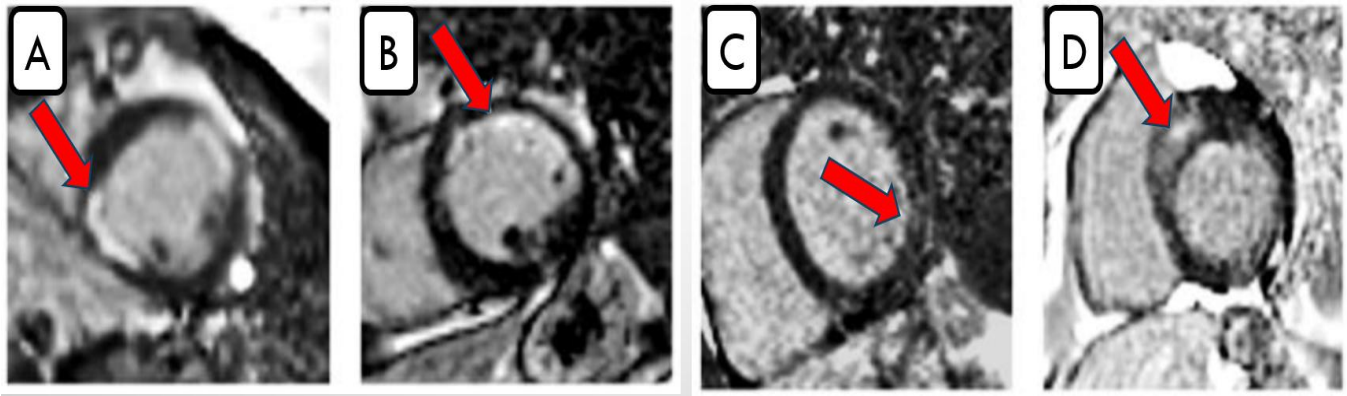

Figure 4. Representative cases of Late Gadolinium Enhancement (LGE) in key cardiac conditions: (A): A patient with prior ST-elevation myocardial infarctions affecting the anterior and inferolateral walls, showing LGE involving more than 50% of the myocardial wall thickness. ; (B): A patient with a history of non-ST-elevation myocardial infarction in the anterior region, exhibiting subendocardial LGE involving less than 50% of the myocardial wall thickness. ; (C): A patient diagnosed with viral myocarditis, demonstrating patchy LGE in the lateral wall. ; (D): A patient with hypertrophic cardiomyopathy (HCM), showing septal LGE located in the region with the most pronounced hypertrophy.[8]

Table 1. This table summarizes the key imaging findings on CCTA, CMR, PET, and SPECT that help differentiate ANOCA, INOCA, and MINOCA based on the presence of obstructive lesions, ischemia, and microvascular dysfunction.[1,2]

Criteria	ANOCA	INOCA	MINOCA
CCTA (Coronary CT Angio)	Coronary arteries appear normal / no significant stenosis	No significant stenosis; possible microvascular dysfunction	No significant lesion, but dissection, plaque erosion, or embolism must be ruled out
CMR (Cardiac MRI)	No edema / no ischemic late gadolinium enhancement (LGE)	No ischemic LGE; may show edema or delayed perfusion	May show myocardial edema and/or LGE consistent with non-transmural infarction
PET	Reduced flow reserve indicates microvascular dysfunction	Reduced flow reserve → indicates microvascular dysfunction	Flow reserve is usually normal unless microvascular disease is present
SPECT	Normal or mild reversible defect (false positive non-obstructive angina)	Reversible defect without obstructive coronary lesion	Ischemic defect corresponding to area of non-obstructive infarction

One of promising therapies is the use of SGLT2 inhibitors, which have been shown to improve microvascular function in animal models by reducing free radical (ROS) production and increasing nitric oxide (NO) bioavailability. Statins is a mainstay of therapy due to their anti-inflammatory and anti-oxidative effects, as well as their ability to increase CFR. However, a study in female patients with INOCA presented statin administration for six months was not enough to significantly improve the microvascular resistance index (IMR). This proposes microcirculatory improvement may require a more complex combination of therapies and a longer duration.[1,7]

Inflammatory biomarkers also possess an important role in the prediction and monitoring of patients with CMD. High-sensitivity C-reactive protein (hsCRP) has conjunction with high troponin levels and as a predictor of ischemic events, suggesting the involvement of inflammation in microcirculatory damage. Interleukin-6 (IL-6), which is found to be elevated in patients with CMD and coronary artery spasm, has been proposed as a predictive biomarker for MINOCA. However, clinical trials with IL-6 receptor antagonists such as tocilizumab did not present improvement in microvascular function in patients with NSTEMI, indicating the demands or a more selective approach to cytokine-based therapy.[1,3,7]

Recent experimental studies have also highlighted several other potential therapeutic targets that could be utilized to inhibit vascular inflammation. Inhibitors of the enzyme myeloperoxidase (MPO) have been shown to improve inflammation-induced endothelial dysfunction. In addition, the use of TNF-α inhibitors in patients with autoimmune diseases such as psoriasis has been shown to indirectly benefit cardioprotection through increased CFR and decreased systemic inflammatory biomarkers. Other targets under investigation include cholesterol metabolism pathways, fatty acid mediators, and autophagy-lysosome mechanisms that may play a role in vascular regeneration and homeostasis. Furthermore, immunological therapeutic approaches are at the forefront of microvascular disease treatment strategies. Cytokines such as IL-1β and IL-6 have been identified as key drivers of chronic cardiovascular inflammation. Agents such as colchicine, although still investigational, show promise in suppressing these inflammatory pathways. In addition, novel biomarkers such as visfatin and placental growth factor (PlGF) are being studied for their potential in assessing risk and targeting therapy. Fractalkine, in particular, is known to activate the NF-κB pathway, which may worsen microvascular dysfunction through increased leukocyte adhesion and endothelial activation.[1,3,7]

6. Integration of Multimodal Imaging.

Cardiac imaging is central to the diagnosis and management of OAI, a spectrum of ischemic heart disease that includes ANOCA, INOCA, and MINOCA, all characterized by evidence of myocardial ischemia without obstructive coronary arteries (typically <50% stenosis on angiography). Since traditional angiography cannot detect the full range of functional or microvascular abnormalities, a multimodal imaging approach is essential.

Coronary Anatomy Assessment

Invasive Coronary Angiography (ICA):

The gold standard for ruling out obstructive CAD. All patients with suspected OAI must first undergo ICA to confirm non-obstructive status.

Coronary CT Angiography (CCTA):

A non-invasive alternative with high negative predictive value. CCTA helps detect high-risk plaque features and may aid in risk stratification, particularly in women with INOCA, as shown in the WARRIOR trial.[6]

Functional Ischemia Assessment

Stress Echocardiography:

Detects inducible wall motion abnormalities during exercise or pharmacological stress.

Single Photon Emission Computed Tomography (SPECT):

Assesses myocardial perfusion but is limited in spatial resolution and quantification.

Positron Emission Tomography (PET):

Gold standard for evaluating myocardial blood flow (MBF) and myocardial flow reserve (MFR). An MFR <1.5 is diagnostic for coronary microvascular dysfunction (CMD) and predictive of major adverse cardiovascular events (MACE).

Stress Cardiac Magnetic Resonance Imaging (Stress-CMR):

Utilizes vasodilator stress and gadolinium contrast to detect perfusion defects. CMR-derived Myocardial Perfusion Reserve Index (MPRI) provides a quantitative assessment of CMD, especially valuable in INOCA and female-predominant presentations.[6]

Structural and Tissue Characterization

Cardiac MRI (Non-Stress Protocol):

Late Gadolinium Enhancement (LGE): Identifies fibrosis or infarction; essential in evaluating MINOCA.

T2 Mapping and T2-weighted Imaging: Visualizes myocardial edema, indicating acute injury.

T1 Mappin: Assesses diffuse myocardial inflammation or fibrosis, especially useful in autoimmune-related or inflammatory OAI.[6]

Coronary Microvascular Dysfunction (CMD) Evaluation

Invasive Coronary Functional Testing:
CFR <2.0 and IMR ≥25 define CMD.

Non-Invasive Alternatives:
PET/CMR: Quantitative MBF and MPR estimation, especially valuable when invasive access is limited.[6]

Vasospasm Provocation

Acetylcholine Provocation Testing (Invasive):

Directly induces and diagnoses epicardial or microvascular spasm in patients with resting angina and unobstructed coronaries.

Non-invasive alternatives:

Still limited; ambulatory ECG or Holter may detect transient ischemic ST changes but lacks specificity.[6]

7. Conclusion

Open Artery Ischemia (OAI), consisting of ANOCA, INOCA, and MINOCA, is defined a clinical entity that is increasingly recognized as an important cause of myocardial ischemia without epicardial coronary artery obstruction. Despite the absence of significant occlusion, patients with OAI remain at risk for decreasing quality of life, recurrent hospitalizations, and even cardiovascular death.[1,3,4,7]

The underlying mechanisms of OAI have complex and involve microvascular dysfunction, coronary spasm, plaque disruption, and chronic, hidden inflammatory processes. These explain the importance of a multimodal diagnostic approach and the use of invasive physiological tests to accurately identify the disease endotype.[1,3,4,7]

Getting the right diagnosis means more than just guiding treatment — it means giving patients the clarity they've longed for, and the hope they may have started to lose.Therefore, understanding and managing OAI must be a priority in modern cardiology practice, so that we not only open arteries, but also open our eyes to clinical realities that have been hidden.[1,3,4,7]

8 . Declaration

8.1 Ethics Approval and Consent to participate
Not applicable.

8.2. Consent for publication
Not applicable.

8.3 Availibility of data and materials
Data used in our study were presented in the main text.

8.4 Competing interests
Not applicable.

8.5 Funding Source
Not applicable.

8.6 Authors contributions
Idea/concept: ARA. Design: ARA. Control/supervision: AFR. Data collection/processing: ARA, AFR. Analysis/interpretation: ARA, AFR. Literature review: ARA, AFR. Writing the article: ARA. Critical review: AFR. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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