From Anatomy to Physiology: Coronary Microvascular Dysfunction and the Emerging Role of Invasive Functional Testing in Vietnam

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ABSTRACT

Up to 40% of patients evaluated for angina/ischemia have non-obstructive coronary arteries, referred to as ANOCA when angina is the presenting symptom and INOCA when objective ischemia is documented. The 2024 ESC Chronic Coronary Syndromes guideline introduces a Class I, Level B recommendation for performing invasive coronary angiography when invasive functional assessments are available to confirm or exclude obstructive coronary artery disease or ANOCA/INOCA, even if non-invasive testing yields an uncertain diagnosis. Despite the absence of epicardial stenosis, these patients frequently suffer from recurrent angina, reduced quality of life, and excess cardiovascular risk. Coronary microvascular dysfunction and vasospastic angina are the two dominant endotypes. A comprehensive invasive coronary function testing protocol that combines fractional flow reserve or instantaneous wave-free ratio with coronary flow reserve, the index of microcirculatory resistance (bolus thermodilution), and the emerging minimal microvascular resistance (continuous thermodilution), allowing for detailed physiological characterization. This expanded diagnostic framework enables the subclassification of coronary microvascular dysfunction into structural and functional endotypes, thereby facilitating personalized therapy and enhancing prognostic accuracy. Acetylcholine provocation further identifies endothelial or vasospastic components, completing a precision endotyping approach that guides risk-stratified therapy.

This narrative review synthesizes global evidence and provides a pragmatic roadmap relevant to health systems such as Vietnam's, where anatomical strategies still predominate. We summarize epidemiology, pathophysiology, diagnostic algorithms,

therapeutic implications, and research priorities, highlighting future directions and collaborative opportunities to responsibly expand access to invasive coronary physiology while maintaining patient safety and scientific rigor.

Keywords: ANOCA; INOCA; coronary microvascular dysfunction; microvascular angina; vasospastic angina; coronary flow reserve; index of microvascular resistance; minimal microvascular resistance; acetylcholine testing; Vietnam.

1. INTRODUCTION

The historical paradigm of ischemic heart disease focused almost exclusively on epicardial coronary artery stenosis as the primary, if not the sole, cause of angina and cardiovascular events [1]. This anatomical approach, rooted in the success of revascularization for obstructive disease, shaped clinical practice for decades. However, contemporary series have consistently shown that approximately one-third of patients referred for angina or ischemia investigation by invasive coronary angiography or computed tomography angiography (CCTA) do not exhibit flow-limiting stenoses[2,3]. This population, now recognized as having angina with non-obstructive coronary arteries (ANOCA) or ischemia with non-obstructive coronary arteries (INOCA), represents 30-40% of those investigated for angina and imposes a substantial burden on healthcare systems worldwide [4, 5].

The long-held assumption that symptoms in these patients were of non-cardiac origin has been refuted by accumulating evidence. Longitudinal cohorts such as the Women's Ischemia Syndrome Evaluation (WISE) and European registries have demonstrated significantly higher rates of major adverse cardiovascular events (MACE), including cardiac death, nonfatal myocardial infarction, and recurrent hospitalization for unstable angina, compared with matched controls[6,7,8]. Beyond event risk, these patients experience a marked reduction in quality of life, increased healthcare utilization, and cycles of uncertain diagnoses and empiric therapies [9, 10].

This challenge is especially relevant in health systems like Vietnam's and other low- and middle-income regions, where invasive functional testing is not yet standard practice. The resulting diagnostic uncertainty and therapeutic inertia, compounded by "normal" angiograms, lead to suboptimal management and patient frustration [11,12]. The 2024 European Society of Cardiology (ESC) Chronic Coronary Syndromes guideline now addresses this gap by introducing, for the first time, a Class I, Level B recommendation for performing invasive coronary angiography with available functional assessment to confirm or exclude ANOCA/INOCA [13].

Two dominant endotypes characterize these syndromes: coronary microvascular dysfunction (CMD) and vasospastic angina (VSA). CMD reflects the inability of the small intramyocardial vessels (arterioles and capillaries) to dilate appropriately in response to increased oxygen demand, whereas VSA results from transient but significant spasm of the epicardial coronary arteries or, occasionally, the microvasculature itself [14,15].

Advances in invasive coronary physiology have enabled precise endotyping of CMD through quantitative indices. The coronary flow reserve (CFR) measures the ratio of hyperemic to resting coronary flow and integrates epicardial and microvascular contributions. The index of microcirculatory resistance (IMR), obtained by bolus thermodilution, quantifies minimal microvascular resistance under maximal hyperemia and serves as a direct marker of structural microvascular impairment. The hyperemic microvascular resistance (HMR), derived from simultaneous Doppler flow velocity and distal coronary pressure, provides an alternative estimate of microvascular resistance when thermodilution is not available [15,16].

More recently, the minimal microvascular resistance (MMR) value, from which the microvascular resistance reserve (MRR) is derived, has been determined using continuous thermodilution rather than the bolus-based IMR method. The MRR is the ratio of resting to hyperemic microvascular resistance, providing a flow- and pressure-independent index of the vasodilatory capacity of the coronary microcirculation. Because it isolates microvascular function from epicardial influences, MRR has shown greater reproducibility and stronger correlation with clinical outcomes in recent studies [16].

Together, these invasive indices allow subclassification of CMD into structural forms (characterized by increased microvascular resistance and impaired CFR) and functional forms (marked by preserved resistance but abnormal vasomotor reactivity). This mechanistic framework enables tailored therapy and improves diagnostic and prognostic precision beyond the traditional anatomical paradigm [17].

The objective of this narrative review is threefold: first, to detail the pathophysiology and invasive diagnostic algorithms for CMD and vasospasm; second, to synthesize evidence supporting endotype-guided management; and third, to provide a pragmatic roadmap for integrating invasive coronary physiology into transitioning health systems such as Vietnam's. By moving from an anatomy-based to a physiology-based diagnostic strategy, clinicians can improve accuracy, optimize treatment, and ultimately enhance long-term outcomes for this large but often underrecognized patient population.

2. PATHOPHYSIOLOGY AND ENDOTYPES OF ANOCA/INOCA

The modern understanding of ANOCA/INOCA is based on the differentiation of its underlying mechanisms. The goal of invasive functional testing is to dissect the problem in the catheterization lab to identify which component of the coronary circuit (epicardial or microvascular) is responsible for ischemia [17,18].

2.1. Coronary Microvascular Dysfunction (Structural and Functional Endotypes)

CMD is defined as the impairment of the coronary circulation capacity to increase blood flow in response to increased myocardial demand (exercise or pharmacological stress). These conditions lead to a failure in the CFR. CMD is the most common endotype, affecting approximately two-thirds of patients with

ANOCA/INOCA [17]. CMD is generally classified according to its primary mechanism:

- Functional/Endothelial Dysfunction: Involves altered production or reduced action of endogenous vasodilators (mainly endothelium-mediated nitric oxide) or increased release of vasoconstrictors. Traditional risk factors (diabetes, hypertension, dyslipidemia, smoking) contribute to endothelial dysfunction by increasing oxidative stress and inflammation [19,20]. Functional dysfunction can be transient and reversible with aggressive risk factor modification therapies.

- Structural Dysfunction: Involves fixed anatomical changes in the microvessels. These include thickening of the medial wall of the arterioles, perivascular fibrosis, and capillary rarefaction (loss of capillary density)[21]. This type of CMD, often in patients with long-standing hypertension or advanced diabetes, imposes a physical limit on maximal vasodilatory capacity, resulting in persistently elevated microvascular resistance (as measured by the Index of Microvascular Resistance [17, 22].

- Mixed or Extravascular CMD: The disease can be a combination of both types. Additionally, conditions that increase left ventricular end-diastolic pressure, such as heart failure with preserved ejection fraction (HFpEF), can compress microvessels extravascular, increase resistance, and often coexist with CMD [22, 23].

Measuring CFR and IMR is crucial for sub-classifying CMD. The COVADIS Consensus (Coronary Vasomotion Disorders International Study Group) objectively classifies CMD by reduced CFR and/or elevated IMR. Structural CMD: CFR <2.5 and IMR ≥25 (or HMR ≥2.5) and MRR <2.6 and Functional CMD: CFR <2.5 and IMR <25 (or HMR <2.5) and MRR ≥2.6 [24,25].

2.2. Endothelium-dependent. Vasospastic Angina (VSA)

Vasoreactivity testing evaluates endothelium-dependent mechanisms of CMD and abnormalities in epicardial and microvascular vasomotor tone. Intracoronary acetylcholine remains the most established method, although alternative agents such as ergonovine have been explored. The core pathophysiological substrate is heightened by smooth muscle hyperreactivity, in which angiographically normal vessels exhibit an exaggerated constrictive response to stimuli such as acetylcholine, histamine, or catecholamines. Like CMD, vasospastic angina frequently arises on a background of endothelial dysfunction, characterized by impaired nitric oxide bioavailability and a relative predominance of contractile mediators, such as endothelin-1 [26, 27].

Spasm can be:

Epicardial vasospasm: Total or subtotal occlusion of an epicardial vessel (≥90%) that reproduces symptoms and ST-segment changes on the ECG. Known as Prinzmetal's angina, it is a primary vasoreactivity disorder characterized by transient but severe spasms of the epicardial coronary arteries that induce myocardial ischemia [28]. It is particularly prevalent in Asian populations, including Japan and Korea, making its diagnosis essential in the context of Vietnam [18,29].

Microvascular vasospasm (Microvascular

Spasm Angina): Spasm occurring predominantly in microcirculation without epicardial spasm (defined as an ACh-induced increase in microvascular resistance that reproduces angina and ECG changes, often with preserved CFR under basal conditions) [28].

Patients with VSA often have symptoms at rest, particularly during nighttime or morning hours, and may manifest severe ventricular arrhythmias or even sudden death during spasm episodes [30,31]. Given the frequency of mixed endotypes (CMD and VSA), invasive functional assessment requires a dual approach to identify both mechanisms [32].

***Table 1**. Coronary endotypes in ANOCA/INOCA*

Endothelium-dependent-ACh testing	Endothelium-independent-Adenosine-based CMD
Epicardial spasm (Vasospastic angina)	Structural CMD ⟶ CFR↓, IMR↑
Microvascular spasm (Microvascular angina)	Functional CMD ⟶ CFR↓, IMR normal
Equivocal response	No CMD ⟶ CFR normal, IMR normal

ACh = acetylcholine; CMD = coronary microvascular dysfunction; CFR = coronary flow reserve; IMR = index of microcirculatory resistance; ANOCA/INOCA = angina/ischemia with non-obstructive coronary arteries

Note: *Endothelial dysfunction (reduced vasodilatation to low-dose ACh) may coexist with any endothelium-dependent response and is not considered a separate diagnostic endotype.*

3. INVASIVE CORONARY FUNCTION TESTING: THE DIAGNOSTIC GOLD STANDARD

Invasive coronary function testing is now recognized as the gold standard for diagnosing and phenotyping ANOCA/INOCA because it provides a comprehensive assessment of both epicardial and microvascular physiology in a single procedure. Unlike angiography, which cannot evaluate vasomotor tone, endothelial function, or microvascular resistance, invasive testing integrates anatomical imaging with pressure-flow measurements and pharmacological vasoreactivity, offering superior diagnostic accuracy, therapeutic guidance, and prognostic value [13]. The CorMiCA trial demonstrated that a physiology-guided endotype-specific strategy improves angina, quality of life, and clinical outcomes, further establishing invasive testing as the preferred approach.

This tiered methodology comprises:

- **Assessment of epicardial stenosis** using FFR/iFR
- **Microcirculatory evaluation** with thermodilution (bolus or continuous) or Doppler
- **Vasomotor testing** with acetylcholine to detect endothelial dysfunction or coronary spasm.

3.1. Assessment of Epicardial Stenosis (FFR/iFR)

Before evaluating the microcirculation, it is crucial to confirm that there is no hemodynamically significant epicardial stenosis that would limit flow. Although angiography showed no obstruction, intermediate stenoses often require this

assessment [33]:

Fractional Flow Reserve (FFR): Measures the ratio of pressure distal to the stenotic vessel to aortic pressure during maximal hyperemia. An FFR value <0.80 indicates stenosis-limited ischemia.

Instantaneous Wave-Free Ratio (iFR): It is a resting measurement of the stenosis performed during the wave-free period in diastole. An iFR value of ≤0.89 is indicative of ischemia.

If FFR or iFR are normal (ruling out epicardial obstruction), the focus shifts entirely to microcirculation, which confirms the diagnosis of ANOCA/INOCA [34].

3.2. Assessment of the vasodilation capacity: CFR, Index of Microvascular Resistance (IMR), and Minimal Microvascular Resistance (MMR)

Evaluation of microvascular vasodilatory function requires integrating multiple hyperemic indices, as no single parameter fully captures the physiological complexity of the coronary microcirculation. In addition to CFR and IMR, MMR obtained by continuous thermodilution provides a more stable, load-independent measure of microvascular vasodilatory reserve and must be considered in contemporary assessment [17].

Coronary Flow Reserve (CFR)

CFR expresses the ratio between hyperemic and resting coronary blood flow and remains a global marker of vasodilatory capacity. However, its diagnostic specificity is limited because CFR integrates both epicardial and microvascular physiology and is strongly affected by resting hemodynamics, including preload, afterload, heart rate, autonomic tone, and anemia. Hyperemia induced by intracoronary adenosine is also dose- and territory-dependent, commonly ~200 µg in the left coronary system and ~100 µg in the RCA, while higher doses may be needed to reproduce intravenous hyperemia, at the expense of increased AV block. These sources of physiological and technical variability, combined with the intrinsic noise of bolus thermodilution transit times, reduce CFR's reliability as an isolated marker of structural microvascular disease. Consequently, a CFR <2.5 suggests impaired vasodilatory reserve but must always be interpreted in conjunction with resistance-based indices for accurate CMD phenotyping [5,29,35].

Index of Microvascular Resistance (IMR - Bolus Thermodilution)

IMR quantifies microvascular resistance during maximal hyperemia and is calculated as the product of distal coronary pressure and the mean transit time of a saline bolus. Hyperemia is typically induced with intracoronary adenosine, whose short-acting profile is well-suited to the rapid measurements required during bolus thermodilution. However, this approach is prone to variability: transit-time measurements depend on operator technique, are sensitive to hemodynamic fluctuations, and may be affected by submaximal hyperemia. These limitations partly explain why IMR can remain within normal ranges in early-stage or functional CMD, where abnormalities in resting tone predominate rather than structural increases in resistance. According to ESC CCS 2024 and EAPCI/COVADIS standards, IMR ≥25

is considered abnormal, while higher cutoffs (≥30) have been proposed to identify higher-risk phenotypes based on contemporary reference-interval and prognostic data [25,37].

Minimal Microvascular Resistance (MMR - Continuous Thermodilution)

Continuous thermodilution allows direct quantification of absolute coronary blood flow and resistance under steady-state hyperemia, which is best achieved using an intravenous hyperemic agent such as adenosine. In contrast to bolus thermodilution, the continuous technique avoids the inherent variability of discrete transit-time sampling and is less influenced by blood pressure, loading conditions, or operator technique. As a result, MMR is more reproducible and is regarded as the most specific invasive marker of structural microvascular disease. Reference values from cohorts with angiographically normal coronary arteries define MMR <2.5 mmHg·(mL^{-1}·s) as normal, 2.5-3.0 mmHg·(mL^{-1}·s) as an intermediate range, and ≥3.0 mmHg·(mL^{-1}·s) as abnormal. Importantly, MMR can detect structural microvascular dysfunction even when IMR remains normal, refining CMD classification and enhancing diagnostic accuracy in INOCA populations [35].

Integrated CMD Phenotyping (CFR + IMR + MMR)

A comprehensive invasive evaluation combining CFR, IMR, and MMR allows precise phenotyping of coronary microvascular dysfunction. Each index contributes complementary physiological information-CFR reflecting global vasodilatory capacity, IMR quantifying hyperemic resistance via bolus thermodilution, and MMR providing a load-independent measure of minimal structural resistance. Their integrated interpretation distinguishes the following clinically relevant phenotypes [12,35]:

- **Structural CMD:** Characterized by low CFR together with elevated IMR and/or elevated MMR (≥3.0 mmHg·[mL^{-1}·s]). This pattern indicates fixed microvascular remodeling, increased minimal resistance, and impaired hyperemic vasodilation.
- **Functional CMD:** Defined by low CFR with normal IMR and normal MMR (<2.5). This profile suggests preserved structural resistance but abnormal resting tone-often related to autonomic imbalance, metabolic dysregulation, or heightened sympathetic activity-leading to elevated resting flow and reduced CFR.
- **Mixed CMD:** Occurs when CFR or IMR provides equivocal results while MMR is abnormal, revealing structural microvascular dysfunction not detected by bolus-based indices. This discordant pattern underscores the diagnostic value of continuous thermodilution in refining CMD classification.
- **Normal Microvascular Function:** Normal CFR, IMR, and MMR reliably exclude structural CMD. However, vasospastic or endothelial dysfunction cannot be ruled out solely by these indices and still requires acetylcholine testing.

3.3. Vasospasm provocation testing,

Acetylcholine (ACh) provocation testing is an essential component of invasive coronary function evaluation and represents the definitive modality for diagnosing both epicardial and microvascular vasospasm.

According to the contemporary ESC/EAPCI ICFT framework, ACh is administered after excluding significant epicardial obstruction to permit safe interpretation of vasomotor responses. As an endothelium-dependent vasodilator, ACh causes vasodilation in healthy endothelium but induces paradoxical vasoconstriction when endothelial dysfunction or smooth muscle hyperreactivity is present, thereby triggering angina, ischemia, or both [38].

ACh uniquely enables differentiation between **epicardial vasospasm**, which manifests as angiographically visible constriction, and **microvascular vasospasm**, which produces ischemia and symptoms without significant epicardial narrowing. These abnormalities cannot be detected by angiography or adenosine-based microvascular indices, underscoring the need for ACh to complete ANOCA/INOCA phenotyping.

ACh is administered intracoronarily in escalating doses, typically 10-200 µg in the right coronary artery and 10-100 µg in the left coronary artery, while continuously monitoring symptoms, ECG changes, and angiographic lumen caliber. Epicardial vasospasm is defined as a ≥90% reduction in epicardial vessel diameter accompanied by reproduction of the patient's typical angina and/or ischemic ST-segment deviations. In contrast, microvascular vasospasm is diagnosed when angina and ischemic ECG changes occur **without** ≥90% epicardial constriction, reflecting vasoconstriction confined to intramyocardial resistance vessels. At the conclusion of the testing sequence, or as soon as diagnostic criteria are fulfilled, intracoronary nitrates are administered to promptly reverse vasoconstriction and restore basal coronary tone [11,26,38].

The ACh test has a strong safety profile in experienced centers, with serious complications occurring in fewer than 0.5% of cases. Potential risks include prolonged vasospasm or transient arrhythmias, underscoring the need for trained personnel and immediate availability of vasodilators[27,36]. Given the elevated prevalence of vasospastic angina in Asian populations, ACh testing remains especially relevant in this clinical context [27,40].

***Table 2**. Acetylcholine Provocation Testing After Microvascular Assessment*

Step	Dose	Description	Evaluation Criterion
1	ACh 2 µg i.c. over 60 s	Repeat angiogram after infusion (Step 1-4)	Evaluates endothelial dysfunction (not an endotype diagnostic criterion)
2	ACh 20 µg i.c. over 60 s		Initial doses for microvascular spasm
3	ACh 100 µg i.c. over 60 s		Microvascular and/or epicardial spasm (intermediate doses)
4	ACh 200 µg i.c. over 60 s		Maximum doses for epicardial spasm, risk of complications.
5	NTG 200 µg i.c.	Final angiogram after nitrate	Complete spasm reversal

4. ENDOTYPE-STRATIFIED THERAPEUTIC IMPLICATIONS

The value of invasive functional testing lies in its ability to move from empiric, "one-size-fits-all" therapy to endotype-specific management. This precision-based approach was validated in the randomized **CorMicA trial**, in which physiology-guided diagnosis and tailored treatment significantly improved angina burden and quality of life compared with standard care [9,39].

4.1. Therapy for Vasospastic Angina (VSA)

Management of VSA is usually highly effective when the diagnosis is accurate. Treatment targets vascular smooth muscle hyperreactivity and endothelial dysfunction[38].

First-Line Therapy: Calcium Channel Blockers (CCBs)

CCBs are the cornerstone of VSA therapy by directly relaxing vascular smooth muscle and attenuating hyperreactive constriction.

- **Dihydropyridines:** amlodipine, nifedipine
- **Non-dihydropyridines:** diltiazem, verapamil

Titration to the maximally tolerated dose is often necessary, and **dual-CCB therapy** is appropriate in persistent VSA.

Adjunctive Therapy: Long-Acting Nitrates

Helpful for nocturnal or recurrent spasm but should not replace high-dose CCBs as foundation therapy.

Avoidance of Harm

- **Non-selective β-blockers** (e.g., propranolol) are contraindicated, as blockade of β-mediated vasodilation leaves α-mediated vasoconstriction unopposed, potentially worsening spasm (40).
- **Selective β-blockers** (e.g., metoprolol) may be used only if another indication exists, but they are not preferred for VSA [38].

Prognosis

Although generally favorable with optimal therapy, prognosis correlates with:

- severity of ACh-induced spasm,
- presence of multivessel spasm,
- adherence to CCBs/nitrates.

Poorly controlled VSA carries a persistent risk of recurrent angina, ventricular arrhythmias, and adverse events [20,22].

4.2. Therapy for Coronary Microvascular Dysfunction (CMD)

CMD management is more complex because it encompasses **structural** and **functional** abnormalities. Treatment is therefore divided into two domains (13, 16):

1- **Disease-modifying therapy** (risk factor and endothelial modulation)

2- **Symptom-directed antianginal therapy**

A. Cardiovascular Risk Modification (Foundation Therapy)

CMD is strongly associated with systemic cardiometabolic risk; aggressive management is central to improving outcomes.

- **Statins:** Improve endothelial function and reduce oxidative stress in addition to lowering LDL-C.
- **ACE Inhibitors/ARBs:** Enhance microvascular function via RAAS modulation and reduction of vascular stiffness; recommended in patients with CMD,

hypertension, or diabetes[19].

• **Blood Pressure and Glycemic Control:** Hypertension and diabetes drive **structural CMD**, increasing resting microvascular resistance and impairing vasodilatory capacity[24, 27].

B. Endotype-Specific Antianginal Therapy

β-Blockers: First-line agents for CMD with increased resting heart rate or demand-induced ischemia. They reduce myocardial oxygen consumption and prolong diastolic perfusion time; specifically supported for functional/early CMD (27).

CCBs: Useful, though their effect is generally smaller than in VSA; helpful when microvascular tone is elevated.

Second-Line Agents for Refractory Symptoms:

Ranolazine: improves diastolic relaxation and reduces ischemia via late-Na^+ current modulation.

Trimetazidine: metabolic modulator improving efficiency of myocardial oxygen utilization.

Evidence is modest but favorable in small trials and observational studies[39].

Justification for Physiology-Guided Care

The **CorMicA trial** demonstrated that assigning therapy based on invasive endotype-VSA, microvascular spasm, functional CMD, or structural CMD-was superior to undirected standard care for improving angina, symptoms, and quality of life[39]. This finding represents the most substantial evidence supporting routine invasive functional assessment in ANOCA/INOCA.

Implementing invasive coronary functional testing in resource-limited health systems such as Vietnam poses substantial practical barriers.

5.1. Healthcare System Barriers

Invasive physiology requires adequate infrastructure-including pressure-temperature consoles, single-use sensor wires, and reliable access to adenosine and acetylcholine-which may be inconsistently available in developing settings [27,36]. The accurate and safe performance of CFR/IMR and ACh testing demands dedicated operator training and familiarity with vasodilators, vasoconstrictors, and management of coronary spasm complications [36,40]. Cost and reimbursement remain limiting factors, as the prices of equipment and disposables are substantial and are often not recognized by payers [11,27]. Workflow integration represents an additional challenge: a full ICFT protocol typically adds 30-45 minutes to a catheterization procedure and requires adequate scheduling, staffing, and quality oversight [35].

5.2. Suggested Roadmap for Implementation in Vietnam

A phased strategy can support safe and sustainable adoption [27]. High-volume referral centers should initiate **pilot programs** in partnership with regional or international training sites, leveraging strong Asia-Pacific expertise in VSA (Japan, Korea) [27,40]. **Protocol standardization**, following COVADIS or EAPCI recommendations, is essential to ensure procedural quality and data comparability[26, 35,41]. Establishing a **national ANOCA/INOCA registry** will generate local evidence on the prevalence, endotypes, and outcomes of stratified therapy, supporting the adaptation

of guidelines and reimbursement policies [22, 27]. Finally, **interdisciplinary education**-training both interventional and clinical cardiologists in the interpretation of physiology and long-term management-will be critical for embedding precision-based care into routine practice [13].

A measured, quality-focused implementation pathway can help Vietnam achieve the benefits of physiology-guided diagnosis, reduce rehospitalizations, and improve cardiovascular outcomes across a growing ANOCA/INOCA population [11]

6. RESEARCH PRIORITIES AND FUTURE DIRECTIONS

Despite significant progress, major gaps remain in understanding and managing CMD and VSA.

6.1. Open Questions in Invasive Physiology

Significant uncertainties persist regarding invasive microvascular assessment. The reproducibility and device-dependence of IMR remain under debate, particularly around the widely used threshold of >25 [37]. More data are needed on the **prognostic interaction** between CFR, IMR, and ACh phenotypes, including whether specific abnormalities (e.g., high IMR vs. low CFR) confer differential risk [17]. Although CorMicA demonstrated the benefit of physiology-guided therapy, larger randomized trials are required to define optimal, endotype-specific antianginal and risk-modifying regimens [39,14].

6.2. The Growing Role of Non-Invasive Imaging

Non-invasive modalities increasingly complement invasive investigation [3].

- **Stress CMR** detects subendocardial ischemia and can quantify diffuse fibrosis using T1 mapping and ECV, supporting identification of structural CMD [25].
- **PET-MBF** provides the most accurate non-invasive measurement of CFR and offers substantial prognostic value, helpful in selecting patients for invasive confirmation[25].
- **CT-based metrics**, including FFR-CT and CT perfusion, are evolving toward non-invasive estimates of microvascular resistance but require further validation before routine use[35].

6.3. Technological Innovation and Automation

Technological progress aims to streamline and standardize invasive physiology. Developments include **accelerated thermodilution protocols**, AI-assisted software to automate resistance and flow calculations, and predictive AI tools to identify ANOCA patients at the highest likelihood of CMD or VSA based on multimodal clinical and imaging data [36, 41].

7. CONCLUSION

A transition from anatomy-centered evaluation to integrated coronary physiology is essential for patients with angina and non-obstructive coronary arteries. Invasive endotyping with CFR, IMR, and acetylcholine provocation clarifies mechanisms of ischemia, enables targeted therapy, and strengthens shared clinical decision-making. Health systems-including Vietnam's-can progressively adopt these protocols by prioritizing training,

infrastructure, and standardized workflows, while generating local data to refine global knowledge. Such implementation reduces missed diagnoses, improves symptom control, and enhances cardiovascular outcomes in a historically underserved population.

Ultimately, incorporating coronary physiology into routine practice represents more than a diagnostic enhancement-it signifies a paradigm shift toward mechanism-guided management of ischemic heart disease. As growing evidence continues to validate the efficacy of physiology-based care, broader adoption will bridge the gap between anatomical imaging and functional impairment, improving patient outcomes and advancing scientific understanding worldwide.

REFERENCES:

1. Beltrame JF, Crea F, Kaski JC, et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J. 2017;38(33):2565-2568. doi:10.1093/eurheartj/ehv351
2. Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J. 2012;33(6):734-744. doi:10.1093/eurheartj/ehr331
3. Kunadian V, Chieffo A, Camici PG, et al. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. EuroIntervention. 021;16(13):1049-1069. doi.org/10.1093/eurheartj/ehaa503
4. Taqueti VR, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(21):2625-2641. doi:10.1016/j.jacc.2018.09.042
5. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-3537. doi.org/10.1093/eurheartj/ehae177
6. Murthy VL, Naya M, Foster CR, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation. 2012;126(15):1858-1868. doi:10.1161/CIRCULATIONAHA.112.120402
7. Konst RE, Damman P, Pellegrini D, et al. Vasomotor dysfunction in patients with angina and nonobstructive coronary artery disease is dominated by vasospasm. Int J Cardiol . 2021; 333:14-20. doi:10.1016/j.ijcard.2021.02.079
8. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia, as reported in the National Heart, Lung, and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol. 2010;55(25):2825-2832. doi:10.1016/j.jacc.2010.01.054.
9. Ford TJ, Berry C. How to Diagnose and Manage

Angina Without Obstructive Coronary Artery Disease: Lessons from the British Heart Foundation CorMicA Trial. *Interv Cardiol*. 2019;14(2):76-82. doi:10.15420/icr.2019.04.R1.

10. Johnson NP, Kirkeeide RL, Gould KL. Coronary anatomy to predict physiology: fundamental limits. Circ Cardiovasc Imaging. 2013;6(5):817-832. doi:10.1161/CIRCIMAGING.113.000373.
11. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J. 2014;35(17):1101-1111. doi:10.1093/eurheartj/eht513
12. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. Circulation. 2017;135(11):1075-1092. doi:10.1161/CIRCULATIONAHA.116.024534.
13. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med. 2007;356(8):830-840. doi:10.1056/NEJMra061889.
14. Savulescu-Fiedler I, Baz RO, Baz RA, Scheau C, Gegiu A. Coronary Artery Spasm: From Physiopathology to Diagnosis. *Life.* 2025;15(4):597. doi.org/10.3390/life15040597
15. Steinberg RR, Dragan A, Mehta PK, Toleva O. Coronary microvascular disease in women: epidemiology, mechanisms, evaluation, and treatment. Can J Physiol Pharmacol. 2024;102(10):594-606. doi:10.1139/cjpp-2023-0414.
16. Ciaramella L, Di Serafino L, Mitrano L, et al. Invasive Assessment of Coronary Microcirculation: A State-of-the-Art Review. Diagnostics (Basel). 2023;14(1):86. doi:10.3390/diagnostics14010086.
17. Rahman H, Ryan M, Lumley M, et al. Coronary Microvascular Dysfunction Is Associated With Myocardial Ischemia and Abnormal Coronary Perfusion During Exercise. Circulation. 2019;140(22):1805-1816. doi:10.1161/CIRCULATIONAHA.119.041595.
18. Shimokawa H, Suda A, Takahashi J, et al. Clinical characteristics and prognosis of patients with microvascular angina: an international and prospective cohort study by the Coronary Vasomotor Disorders International Study (COVADIS) Group. Eur Heart J. 2021;42(44):4592-4600. doi:10.1093/eurheartj/ehab282.
19. Gori T, Münzel T. Oxidative stress and endothelial dysfunction: therapeutic implications. Ann Med. 2011;43(4):259-272. doi:10.3109/07853890.2010.54392020.
20. Mehta PK, Wei J, Wenger NK. Ischemia in women: evolving knowledge. J Am Coll Cardiol. 2018;71(11):1231-40. doi:10.1016/j.jacc.2009.04.098
21. Crea F, Montone RA, Rinaldi R. Pathophysiology of Coronary Microvascular Dysfunction. Circ J. 2022;86(9):1319-1328. doi:10.1253/circj.CJ-21-084822.
22. Bilak JM, Alam U, Miller CA, McCann GP, Arnold JR, Kanagala P. Microvascular Dysfunction in Heart Failure with Preserved Ejection Fraction: Pathophysiology, Assessment, Prevalence and Prognosis. Card Fail Rev. 2022;8:e24. doi:10.15420/cfr. 2022.1223.
23. Bairey Merz CN, Handberg EM, Shufelt CL, et al. The WISE studies: design and key insights. J Am Coll Cardiol. 2015;66(15):190-202.

24. Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. Int J Cardiol. 2018; 250:16-20. doi:10.1016/j.ijcard.2017.08.068.
25. Green, R., Cantoni, V., Acampa, W. *et al.* Prognostic value of coronary flow reserve in patients with suspected or known coronary artery disease referred to PET myocardial perfusion imaging: A meta-analysis. J. Nucl. Cardiol. 28, 904-918 (2021). doi.org/10.1007/s12350-019-02000-7
26. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal Coronary Vasomotion in patients with stable angina and unobstructed coronary arteries). J Am Coll Cardiol. 2012;59(7):655-662. doi:10.1016/j.jacc.2011.11.015
27. Gould KL, Johnson NP. Coronary Physiology Beyond Coronary Flow Reserve in Microvascular Angina: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(21):2642-2662. doi:10.1016/j.jacc.2018.07.106
28. Mangiacapra F, Viscusi MM, Verolino G, et al. Invasive Assessment of Coronary Microvascular Function. J Clin Med. 2021;11(1):228. doi:10.3390/jcm11010228
29. Aziz A, Hansen HS, Sechtem U, Prescott E, Ong P. Sex-Related Differences in Vasomotor Function in Patients with Angina and Unobstructed Coronary Arteries. J Am Coll Cardiol. 2017;70(19):2349-2358. doi:10.1016/j.jacc.2017.09.016
30. Hao K, Takahashi J, Kikuchi Y, et al. Prognostic Impacts of Comorbid Significant Coronary Stenosis and Coronary Artery Spasm in Patients With Stable Coronary Artery Disease. *J Am Heart Assoc*. doi:10.1161/JAHA.120.017831
31. Hoshino M, Jukema RA, Pijls N, et al. Microvascular resistance reserve before and after PCI: A serial FFR and [15O] H2O PET study. Atherosclerosis. 2024; 395:117555. doi:10.1016/j.atherosclerosis.2024.117555
32. Kothawade K, Bairey Merz CN. Microvascular coronary dysfunction in women: pathophysiology, diagnosis, and management. Curr Probl Cardiol. 2011;36(8):291-318. doi:10.1016/j.cpcardiol.2011.05.002.
33. Modi BN, Rahman H, Ryan M, et al. Comparison of fractional flow reserve, instantaneous wave-free ratio, and a novel technique for assessing coronary arteries with serial lesions. EuroIntervention. 2020;16(7):577-583. doi:10.4244/EIJ-D-19-0063533.
34. Lee JM, Lee SH, Hwang D, et al. Long-Term Clinical Outcomes of Nonhyperemic Pressure Ratios: Resting Full-Cycle Ratio, Diastolic Pressure Ratio, and Instantaneous Wave-Free Ratio. J Am Heart Assoc. 2020;9(18):e016818. doi:10.1161/JAHA.120.016818
35. Namba HF, Boerhout CKM, Damman P, et al. Invasive coronary function testing in clinical practice: Implementing the 2024 ESC guidelines on chronic coronary syndromes. Int J Cardiol. 2025; 430:133176. doi:10.1016/j.ijcard.2025.133176

36. Rahman H, Demir OM, Ryan M, et al. Optimal Use of Vasodilators for Diagnosis of Microvascular Angina in the Cardiac Catheterization Laboratory. Circ Cardiovasc Interv. 2020;13(6): e009019. doi:10.1161/CIRCINTERVENTIONS.120.009019
37. Fearon, W, Dash, R. Index of Microcirculatory Resistance and Infarct Size. J Am Coll Cardiol Img. 2019 May, 12 (5) 849-851. doi.org/10.1016/j.jcmg.2018.04.004
38. Ong P, Athanasiadis A, Borgulya G, Voehringer M, Sechtem U. 3-year follow-up of patients with coronary artery spasm as cause of acute coronary syndrome: the CASPAR (coronary artery spasm in patients with acute coronary syndrome) study follow-up. J Am Coll Cardiol. 2011;57(2):147-152. doi:10.1016/j.jacc.2010.08.626
39. Ford TJ, Stanley B, Good R, et al. Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. J Am Coll Cardiol. 2018;72(23 Pt A):2841-2855. doi:10.1016/j.jacc.2018.09.006
40. Sueda S, Kohno H, Ochi T, Uraoka T. Overview of the Acetylcholine Spasm Provocation Test. Clin Cardiol. 2015;38(7):430-438. doi:10.1002/clc. 22403
41. Fearon WF, Kobayashi Y. Invasive Assessment of the Coronary Microvasculature: The Index of Microcirculatory Resistance. Circ Cardiovasc Interv. 2017;10(12): e005361. doi:10.1161/CIRCINTERVENTIONS.117.005361