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STATE-OF-THE-ART REVIEW

Ischemia With Nonobstructive Coronary Artery Disease

Concept, Assessment, and Management

Doyeon Hwang, MD, Sang-Hyeon Park, MD, Bon-Kwon Koo, MD, PhD

ABSTRACT

In daily clinical practice, physicians often encounter patients with angina or those with evidence of myocardial ischemia from noninvasive tests but not having obstructive coronary artery disease. This type of ischemic heart disease is referred to as ischemia with nonobstructive coronary arteries (INOCA). INOCA patients often suffer from recurrent chest pain without adequate management and are associated with poor clinical outcomes. There are several endotypes of INOCA, and each endotype should be treated based on its specific underlying mechanism. Therefore, identifying INOCA and discriminating its underlying mechanisms are important issues and of clinical interest. Invasive physiologic assessment is the first step in the diagnosis of INOCA and discriminating the underlying mechanism; additional provocation tests help physicians identify the vasospastic component in INOCA patients. Comprehensive information acquired from these invasive tests can provide a template for mechanism-specific management for patients with INOCA. (JACC: Asia 2023;3:169–184) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Patients suffering from exertional chest pain with or without signs of ischemic heart disease but without obstructive coronary artery disease are frequently encountered in daily practice (**Figure 1**).[1] Because the usual tests do not readily identify an atherosclerotic lesion on angiography, these patients are often dismissed as having noncardiac chest pain and may not receive sufficient explanation for their symptoms or receive adequate treatment for symptom relief. A common scenario may include continued recurrent angina, poor quality of life, repeated admission for un-necessary invasive tests or revascularization, and adverse clinical events.[2-6] Recently, clinical interest in these patients defined as having ischemia with nonobstructive coronary arteries (INOCA) has gained significant momentum, stimulating the quest to define, classify, and treat these patients according to the endotypes of INOCA. In addition, several studies have reported a higher prevalence of microvascular dysfunction and coronary artery spasm in Asian patients, emphasizing the clinical importance of INOCA in Asian patients.[7,8] The current review focuses on the clinical importance, mechanism, assessment, and management of INOCA according to its endotypes driven by the contribution of clinically relevant physiologic data acquired from specific invasive tests.

CLINICAL IMPORTANCE OF INOCA

Angina pectoris is the most common symptom of ischemic heart disease and is caused by the mismatch of demand and supply of coronary artery blood flow to the myocardium.[9] Although the prevalence of INOCA has not been well-documented, the American College of Cardiology National Cardiovascular Data Registry reported that only 37.6% of patients had obstructive coronary artery diseases, and 39.2% of

From the Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea.
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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

CCTA = coronary computed tomography angiography

CFR = coronary flow reserve

FFR = fractional flow reserve

HMR = hyperemic microvascular resistance

IMR = index of microcirculatory resistance

INOCA = ischemia with nonobstructive coronary arteries

NHPR = nonhyperemic pressure ratio

Tmn = mean transit time

patients were without evidence of coronary artery disease among about 400,000 patients with suspected ischemic heart disease.[1] More recently, a post hoc analysis of the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial reported that 13% of patients were without obstructive coronary artery disease even though these patients had evidence of moderate to severe ischemia according to noninvasive tests.[10] These patients often suffer from repeated chest pain that causes hospital readmission for invasive tests, leading to increased medical burden and cost. It is reported that about 50% of patients with nonobstructive coronary arteries experienced recurrent chest pain and impairment in functional capacity and quality of life.[11-13] A previous study reported that South Asians with heart failure were more frequently associated with impaired macrovascular and microvascular endothelial dysfunctions than others,[8] and other studies reported a higher prevalence of variant angina in Japanese cohorts than in White patients.[14,15] A retrospective cohort from Denmark with 11,223 patients showed that symptomatic patients with normal coronary arteries had a 3-fold higher risk for rehospitalization and a 2.3-fold higher risk of repeat angiography.[4] The WISE (Women's Ischemia Syndrome Evaluation) study also documented the increased medical costs of caring for patients with INOCA.[16] A recent meta-analysis reported that approximately half of the nonobstructive coronary artery disease patients were confirmed to have coronary microvascular disease and/or coronary artery spasm, indicating that a substantial number of INOCA patients are underdiagnosed in daily clinical practice.[17]

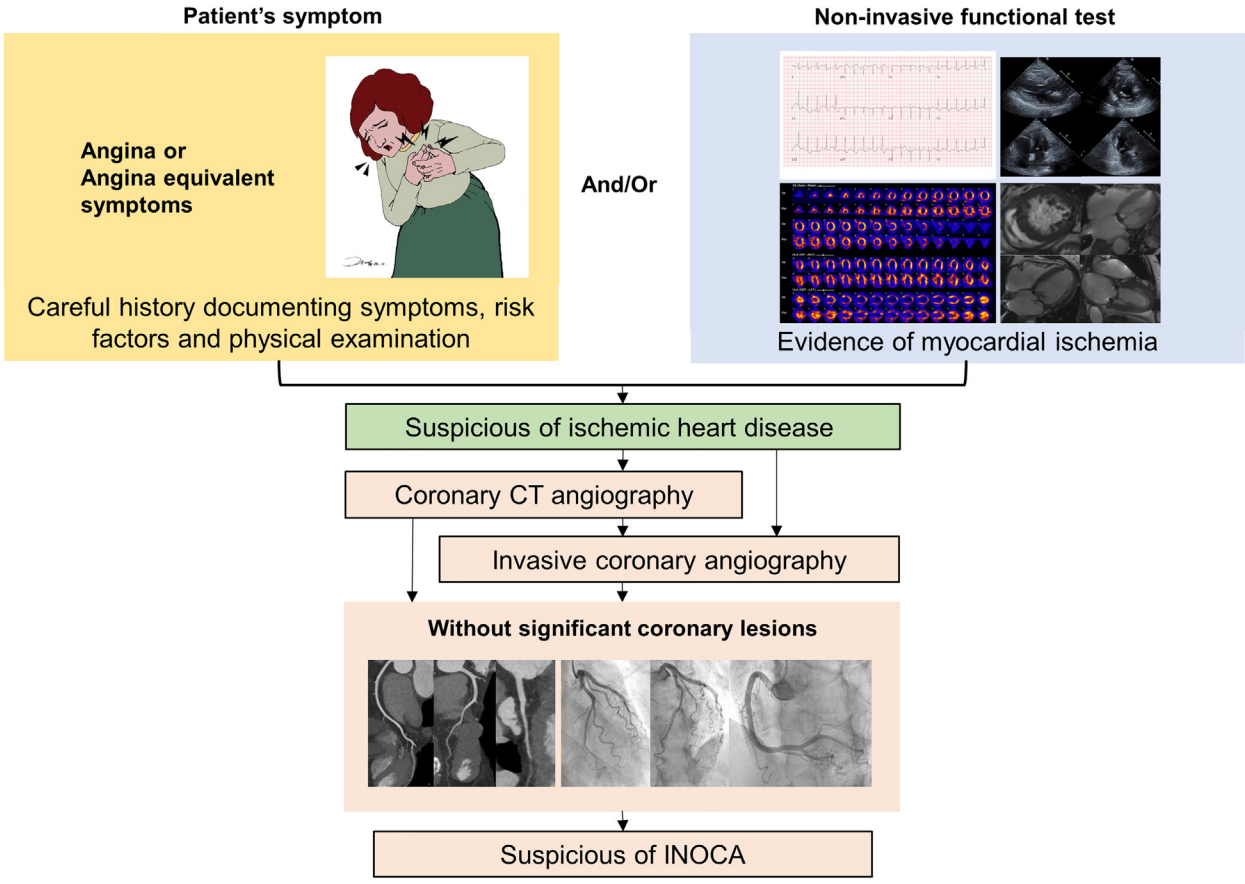
Even though previous studies have reported heterogeneous results on the prognosis of INOCA because of its various endotypes, it is evident that INOCA is not a benign disease. A recent meta-analysis of 54 studies with 35,039 INOCA patients reported a pooled incidence of all-cause death and nonfatal myocardial infarction of 0.98 per 100 person-years, which was higher than that of a similarly aged North American general population.[18] In a retrospective cohort study from eastern Denmark, INOCA was associated with a 1.3- to 1.8-fold higher risk of major adverse cardiovascular events, including cardiovascular death, myocardial infarction, stroke or heart failure, and all-cause death.[6] More specifically, microvascular angina with impaired coronary flow reserve (CFR) increased the risk of adverse cardiac events, including all-cause death, target vessel myocardial infarction, and clinically driven target vessel revascularization, about 4.0-fold.[19] A prospective registry from Japan also reported a 6% rate of major adverse cardiac events in patients with vasospastic angina during a median follow-up period of 32 months.[20]

CORONARY CIRCULATION AND ENDOTYPES OF INOCA

The coronary arterial system consists of epicardial coronary arteries, prearterioles, and arterioles with different sizes, distinct functions, and uninterrupted borders (Figure 2).[21] Myocardial ischemia from the mismatch of demand and supply of coronary artery blood flow to the myocardium can originate from any part of this coronary arterial system (Table 1).[9] The epicardial coronary artery is the most proximal compartment of the system with a diameter >500 μm and acts as a conduit for coronary blood flow with little resistance. The intermediate compartment is composed of prearteriolar vessels; they have a diameter of 500 to 100 μm and are characterized by measurable pressure drops along their path. This compartment maintains the coronary pressure at the proximal end of arterioles within a narrow range in the variations in flow and pressure. The distal compartment is represented by intramural arterioles with a diameter <100 μm and also generates a considerable pressure drop. This part plays a key role in matching the demand and supply of coronary artery blood flow to the myocardium. Prearteriolar vessels and arterioles compose the coronary microcirculation.

CORONARY MICROVASCULAR DISEASE. Although obstructive epicardial coronary artery disease is the most common cause of myocardial ischemia, not all visually obstructive lesions cause flow limitation to the myocardium. Therefore, in patients with non-flow-limiting coronary lesions, myocardial ischemia or angina can be caused by abnormalities in coronary microvasculature. The abnormalities in the microvascular system can be explained by 2 mechanisms: structural and functional abnormalities, which can occur independently or concomitantly. The possible causes of structural microvascular disease are luminal narrowing of microvessels by medial wall or intimal thickening, luminal obstruction caused by thromboembolism, capillary rarefaction, extrinsic vascular

FIGURE 1 Clinical Diagnostic Flow of INOCA



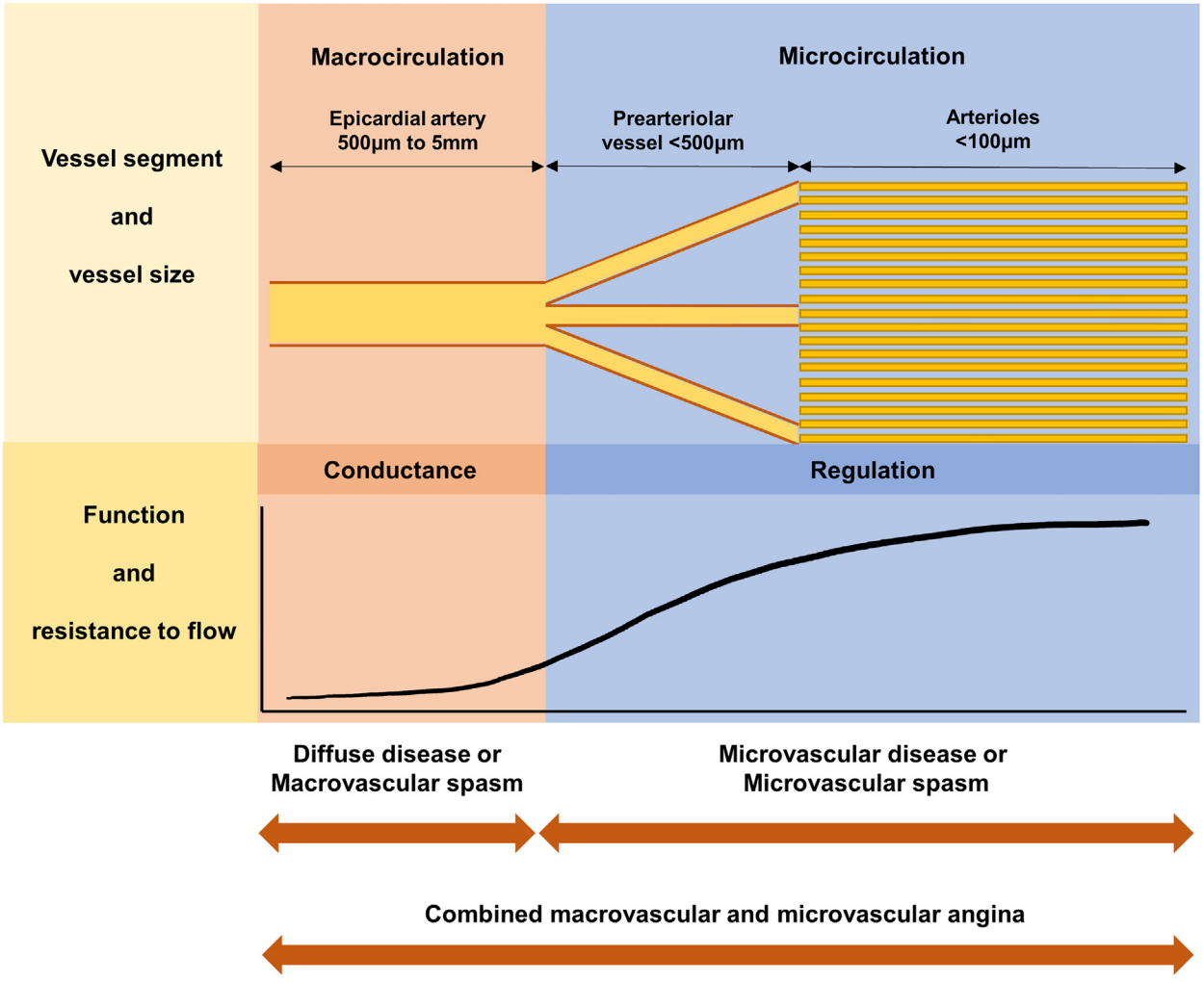
Ischemic heart disease is suspected when patients have symptoms and/or signs of ischemic heart disease. When there is no flow-limiting obstructive coronary artery disease, ischemia with nonobstructive coronary arteries (INOCA) should be suspected. CT = computed tomography.

compression, and vascular wall infiltration.[21,22] These microvasculature abnormalities, which are associated with the risk factors of cardiovascular disease, underlying ventricular hypertrophy, or underlying cardiomyopathies, can cause a limitation in the vasodilatory ability and absolute conductance ability of the microvascular system, thereby reducing blood and oxygen supply to the myocardium.[21-23] Impaired vasodilatory ability is known to be associated with endothelium-dependent and/or endothelium-independent mechanisms.[21,23,24]

VASOSPASTIC ANGINA. Epicardial coronary artery spasm, also known as variant angina or vasospastic angina, is characterized by resting chest pain not associated with increased myocardial oxygen demand, chest pain with diurnal variation frequently at night or early morning, and a prompt response to nitroglycerin.[7,25] Compared with Western countries, the incidence of epicardial coronary artery spasm is reported to be higher in Asian countries.[25-28] Epicardial coronary artery spasm is associated with a hyper-reactive response of the epicardial coronary artery segment to vasoconstrictive stimuli.[29] Non-endothelial-dependent contraction of vascular smooth muscle cells has been consistently demonstrated in patients with epicardial coronary artery spasm, but endothelial dysfunction is also associated with epicardial coronary artery spasm.[7]

Vasospastic angina can also be caused by coronary microvascular spasm, which is associated with the spasm of vascular smooth muscle cells in prearteriolar vessels and arterioles.[30] The potential mechanisms of microvascular spasm are an increased release of vasoconstrictive substances, increased susceptibility of vascular smooth muscle cells, or an

FIGURE 2 Coronary Anatomy and Possible Causes of INOCA



The coronary arterial system is composed of 3 compartments: epicardial coronary arteries, prearterioles, and arterioles. Each compartment has different sizes and functions with uninterrupted borders. Myocardial ischemia can originate from any part of this coronary arterial system. INOCA = ischemia with non-obstructive coronary arteries.

abnormal increase of sympathetic tone.[22] Both epicardial and microvascular spasms can occur simultaneously.[31]

MASKED DIFFUSE DISEASE. Even in INOCA patients, the presence of coronary atherosclerosis is common in intravascular imaging studies.[32,33] An intravascular ultrasound substudy of the WISE study reported that 79% of patients had coronary atherosclerosis with a percent atheroma volume of 27%, whereas coronary angiography demonstrated only 30% of patients had minimal coronary artery disease among 100 women with nonobstructive coronary artery disease.[33] Because most of these lesions showed positive remodeling and a preserved lumen size, diffuse coronary atherosclerosis can be unrevealed or underestimated by coronary angiography. When clinically suspected, the use of intracoronary imaging or invasive physiologic studies can be helpful in assessing the presence and functional significance of these masked diffuse diseases.[32]

DIAGNOSIS OF INOCA

Identifying patients with INOCA is not simple because there are multiple causes of chest pain and myocardial ischemia. Therefore, careful and detailed history

TABLE 1 Endotypes of INOCA

Endotypes	Features	Diagnosis
Coronary microvascular disease	Structural and/or functional abnormalities in the microvascular system A limitation in the vasodilatory ability and absolute conductance ability of the microvascular system Associated with risk factors of cardiovascular disease, ventricular hypertrophy, or cardiomyopathies	Based on invasive physiologic assessment • FFR >0.80 or NHPR >0.89 • CFR <2.0-2.5 • IMR >25 U or HMR >2.5 mm Hg/cm/s
Epicardial vasospastic angina	Hyper-reactive response of the epicardial coronary artery segment to vasoconstrictive stimuli	Based on provocation test using ergonovine or acetylcholine • Ischemic symptom during provocation test • A transient total or subtotal coronary artery occlusion • Ischemic ECG changes (ST-segment depression or elevation ≥0.1 mV) in at least 2 contiguous leads
Microvascular vasospastic angina	Spasm of vascular smooth muscle cells in prearteriolar vessels and arterioles	Based on the provocation test using acetylcholine • Ischemic symptom during provocation test • Without significant epicardial artery constriction during provocation test • Ischemic ECG changes (ST-segment depression or elevation ≥0.1 mV) in at least 2 contiguous leads
Masked diffuse disease	Coronary angiography can underestimate diffuse coronary atherosclerosis. Invasive physiologic assessment and/or intravascular coronary imaging can reveal hidden coronary atherosclerosis.	Based on invasive physiologic assessment • FFR ≤0.80 or NHPR ≤0.89 with gradual step-up during pull back tracing Based on intravascular imaging studies

CFR = coronary flow reserve; ECG = electrocardiogram; FFR = fractional flow reserve; HMR = hyperemic microvascular resistance; IMR = index of microcirculatory resistance; INOCA = ischemia with nonobstructive coronary artery disease; NHPR = nonhyperemic pressure ratio.

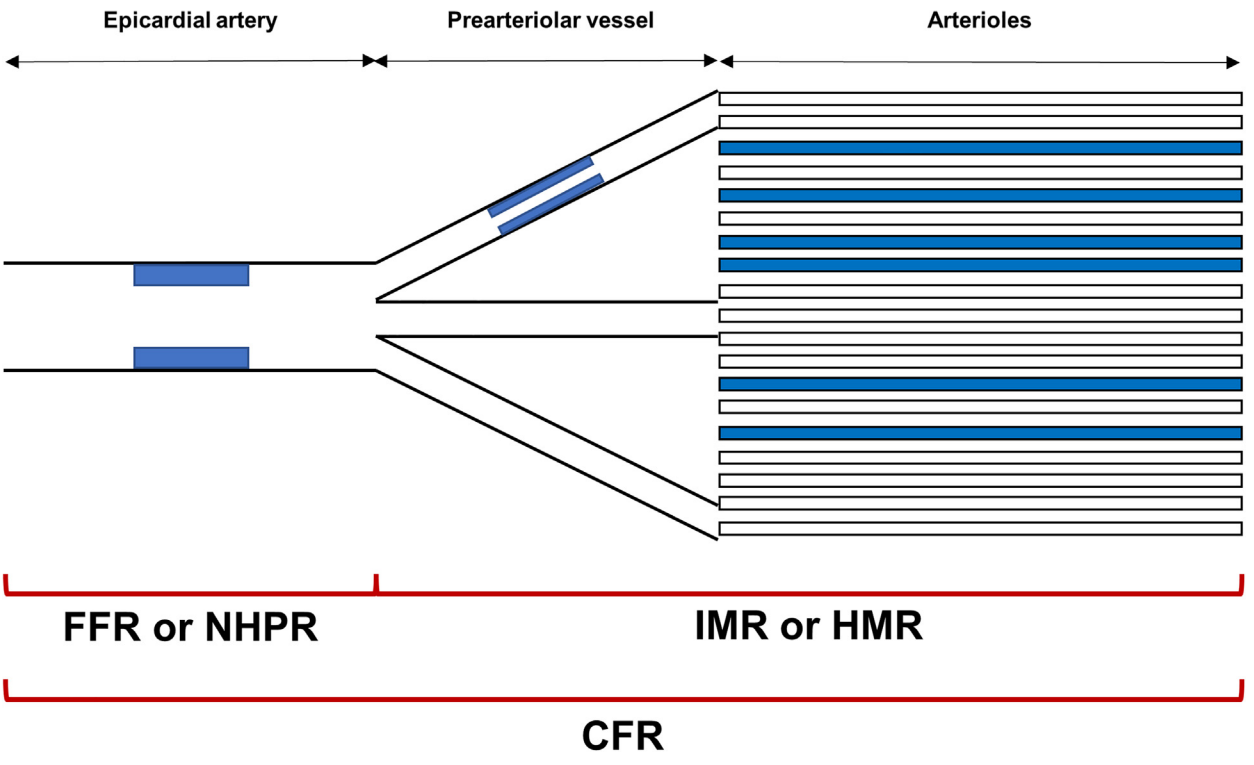
taking, the evaluation of risk factors, and physical examination are prerequisites for discriminating the noncardiac origin of chest pain. If a noncardiac origin of chest pain is suspected, proper further evaluation is needed to exclude the diagnosis of ischemic heart disease. When the noncardiac cause of chest pain is excluded, the evidence of myocardial ischemia should be evaluated. Typical symptoms, ischemic electrocardiograms, impaired perfusion identified by myocardial perfusion imaging, and stress-induced regional wall motion abnormality are clinical surrogate markers for myocardial ischemia. Because the diagnosis of INOCA requires both myocardial ischemia and no obstruction in epicardial coronary arteries, defining myocardial ischemia represents the first step in the diagnosis of INOCA (Figure 1).

NONINVASIVE TESTS FOR EVALUATING INOCA. Various modalities to evaluate the presence of myocardial ischemia include an exercise electrocardiogram, resting or stress echocardiography, stress nuclear myocardial perfusion imaging, and cardiac magnetic resonance.[34] Because current noninvasive functional tests rely on detecting large regional differences in myocardial perfusion or regional wall motion abnormalities in the left ventricle, these tests are hampered in their ability to diagnose coronary microvascular disease that can affect the whole myocardium or vasospastic angina that occurs in a given specific situation.[25,35,36] In addition, most of the noninvasive functional tests cannot provide anatomical information, and anatomical assessment to exclude obstructive coronary artery diseases is needed to diagnose INOCA.

Coronary computed tomography angiography (CCTA) is a representative noninvasive diagnostic tool that can detect significant coronary artery stenoses and coronary atherosclerotic plaque.[37-39] Its negative predictive value for excluding significant plaque or coronary stenosis is very high.[40] However, the presence of significant stenosis in CCTA does not always mean the presence of ischemia-causing stenosis.[41,42] Therefore, it is important to recognize that the presence of epicardial stenosis or atherosclerotic plaque on CCTA does not exclude the possibility of INOCA.

INVASIVE CORONARY ANGIOGRAPHY AND PHYSIOLOGIC TESTS TO DIAGNOSE CORONARY MICROVASCULAR DISEASE. Invasive coronary angiography is the current gold standard method for evaluation and treatment planning for obstructive coronary artery disease.[34,43] Invasive coronary angiography can intuitively provide information on microvascular dysfunction by showing slow coronary flow.[44] However, invasive coronary angiography alone cannot provide adequate information regarding whether coronary artery stenoses cause flow limitation or

FIGURE 3 Schematic Concept of Invasive Physiologic Indexes



Invasive physiologic indexes are helpful in identifying the presence of myocardial ischemia and discriminating the mechanisms of myocardial ischemia. Fractional flow reserve (FFR) or nonhyperemic pressure ratio (NHPR) reflects the degree of flow limitation caused by epicardial coronary artery lesions, and the index of microcirculatory resistance (IMR) or hyperemic microvascular resistance (HMR) represents the status of the microcirculatory system. Coronary flow reserve (CFR) is influenced by both macrovascular and microvascular disease status.

objective evidence of microvascular dysfunction. Furthermore, the diagnosis of coronary vasospasm generally requires provocation testing.

Comprehensive physiologic assessment using a pressure sensor guidewire is needed to discriminate myocardial ischemia caused by epicardial coronary artery lesions and coronary microvascular disease (Figure 3, Table 2). Fractional flow reserve (FFR) or nonhyperemic pressure ratio (NHPR) is a standard invasive method to define ischemia-causing

TABLE 2 Invasive Physiologic Indexes for Evaluating INOCA

Physiologic Index	Definition	Cutoff Value	Features
FFR	Ratio of distal coronary pressure to aortic pressure during hyperemia	≤0.80	Reflecting disease burden of epicardial coronary artery
NHPR	Ratio of distal coronary pressure to aortic pressure during the resting state	≤0.89	Reflecting disease burden of epicardial coronary artery Several NHPRs: instantaneous wave-free ratio, resting full cycle ratio, and diastolic pressure ratio.
CFR	Ratio of hyperemic coronary flow and resting coronary flow	<2.0-2.5	Reflecting both epicardial coronary artery disease and microvascular dysfunction
IMR	Distal coronary artery pressure multiplied by hyperemic mean transit time	>25 U	Microvascular-specific index
HMR	Ratio of maximal coronary flow velocity to distal coronary artery pressure during hyperemia	>2.5 mm Hg/cm/s	Microvascular-specific index

INOCA = ischemia with nonobstructive coronary arteries.

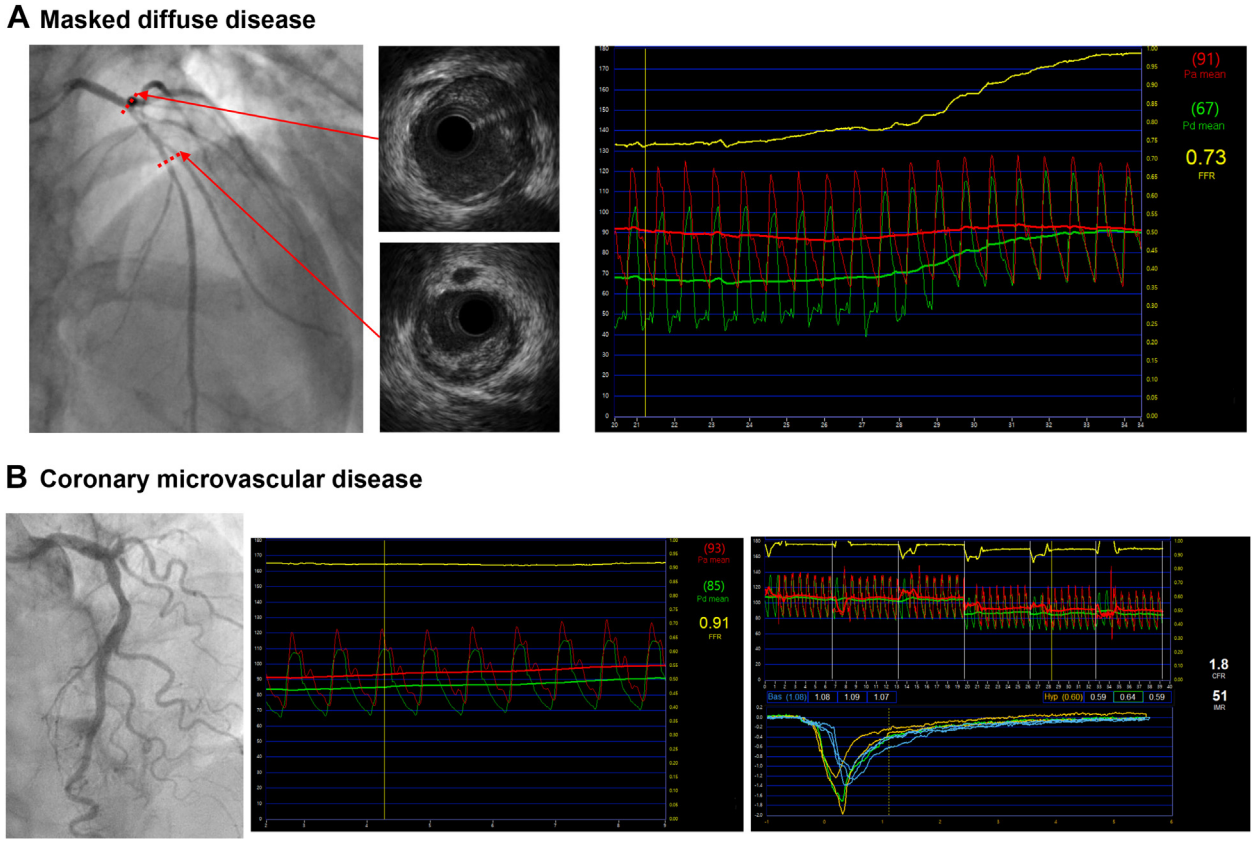
epicardial coronary artery lesions.[34,43,45,46] These indexes estimate flow reduction caused by the epicardial coronary artery lesions, and FFR ≤0.80 and NHPR ≤0.89 indicate flow-limiting or ischemia-causing epicardial coronary artery stenosis. If there is evidence of flow-limiting epicardial coronary artery stenosis, careful pull back tracings help physicians in their judgment of plaque distribution, along with the coronary artery, whether it is focal or diffuse. Therefore, the first step in evaluating INOCA during invasive coronary angiography is detecting the flow-limiting epicardial coronary artery stenosis and assessing its disease pattern using FFR or NHPR. Intracoronary imaging studies can also reveal hidden diffuse coronary atherosclerosis (**Figure 4A**). Recently, quantitative flow ratio, a 3-dimensional quantitative coronary angiography-based computation of FFR, has been proposed, which also can help to define the degree and disease pattern of flow-limiting epicardial coronary artery disease.[47,48]

After excluding the presence of flow-limiting obstructive coronary artery disease, the assessment of microvascular function is needed to define coronary microvascular disease (**Figures 3 and 4B, Tables 1 and 2**). CFR is an index of how coronary blood flow can be increased during a hyperemic state compared with a resting state, and it is affected by both epicardial coronary artery stenosis and microvascular function.[46,49-51] CFR can be measured in a cardiac catheterization laboratory using a Doppler wire or a pressure-temperature sensor-equipped guidewire.[46,52-55] Using the Doppler wire, CFR can be obtained as the ratio of hyperemic average peak coronary flow velocity to resting average peak coronary flow velocity.[51,55] The thermodilution technique is used to calculate CFR via the saline bolus transit time (Tmn), which is a surrogate marker of coronary blood flow. Thermodilution curves are obtained by 3 injections of 3 to 4 mL room temperature saline during the resting state and hyperemic state to derive the mean Tmn. CFR is a ratio of the resting Tmn and the hyperemic Tmn.[49,50] CFR ≤2.0 or 2.5 indicates the presence of flow-limiting stenosis, microvascular dysfunction, or both.[52-55] Therefore, CFR represents the presence of microvascular dysfunction in the absence of flow-limiting epicardial disease.

The thermodilution technique can derive a more microvascular-specific index, the index of microcirculatory resistance (IMR) (**Figure 3, Table 2**). The uncorrected IMR is defined as distal coronary artery pressure multiplied by hyperemic Tmn. In the presence of significant epicardial stenosis, collateral flow is substantial, and this leads to a decrease in coronary flow and an increase in distal coronary pressure; therefore, uncorrected IMR can overestimate the microvascular resistance.[56] To correct this phenomenon, Yong's formula is often used; the corrected IMR with this formula is calculated as: proximal aortic pressure × Tmn × ([1.35 × distal coronary artery pressure/proximal aortic pressure] − 0.32).[56] An IMR value >25 is considered to indicate the presence of microvascular dysfunction.[57] In the international registry study, patients with low CFR and high IMR showed an increased risk of all-cause death, any myocardial infarction, and any revascularization (HR: 2.873; 95% CI: 1.476-5.594; $P = 0.002$) compared with those with high CFR and low IMR among high FFR patients.[58] Another microvascular-specific index is hyperemic microvascular resistance (HMR).[59-61] HMR is defined as the ratio between the distal coronary artery pressure and maximal coronary flow velocity during hyperemia (**Figure 3, Table 2**). Previous studies reported that HMR >2.5 mm Hg/cm/s has a good predictive value for microvascular disease.[61,62]

PROVOCATION TEST TO DIAGNOSE VASOSPASTIC ANGINA. Even though invasive coronary angiography with comprehensive physiologic assessment may help physicians to diagnose coronary microvascular disease, it cannot provide information on vasospastic angina, another endotype of INOCA (**Table 1**). If physicians cannot find the specific mechanism of INOCA based on a comprehensive invasive physiologic assessment or if there are specific features of vasospastic angina, such as resting chest pain, diurnal variation, or a prompt response to nitroglycerin, a provocation test is needed to diagnose vasospastic angina.[25] The acetylcholine provocation test and the ergonovine provocation test during coronary angiography are the most widely used methods to confirm the presence of coronary artery spasm (**Figure 4C, Table 1**).[63,64] Acetylcholine acts on the muscarinic cholinergic receptors in vascular smooth muscle cells[25,63,65] and ergonovine on the serotonin receptors in vascular smooth muscle cells.[25,63] Both have high sensitivity and specificity to confirm the presence of epicardial vasospasm.[25,28,63,65] Because these 2 drugs use different mediators, there is a possibility of different coronary responses to the drugs. Previous studies reported that spasms caused by acetylcholine are distal and diffuse, whereas those caused by ergonovine are proximal and focal.[65] In addition to these different patterns of spasms according to the drugs, different test results

FIGURE 4 Representative Cases for INOCA



(A) Masked diffuse disease. Invasive coronary angiography showed an insignificant coronary lesion at the proximal left anterior descending (LAD) artery. However, FFR was 0.73 with a gradual step-up at pressure pull back tracing. Intracoronary ultrasound showed diffuse atherosclerotic plaque at the proximal LAD. **(B)** Coronary microvascular disease. Invasive coronary angiography showed insignificant epicardial coronary stenosis. FFR was 0.91 at the distal LAD artery, but CFR was 1.8 and IMR was 51 U. **(C)** Epicardial vasospastic angina. Baseline angiography showed spastic coronary arteries. After intravenous ergonovine infusion, the patient complained of severe chest pain, and significant coronary spasms (>90% constriction) occurred in the LAD and right coronary arteries, whereas the electrocardiogram showed significant ST-segment elevation. **(D)** Microvascular vasospastic angina. The ergonovine provocation test showed diffuse insignificant epicardial artery constriction (<90%). However, the patient complained of severe chest pain, and the electrocardiogram showed significant ST-segment elevation at inferior leads. Abbreviations as in Figures 2 and 3.

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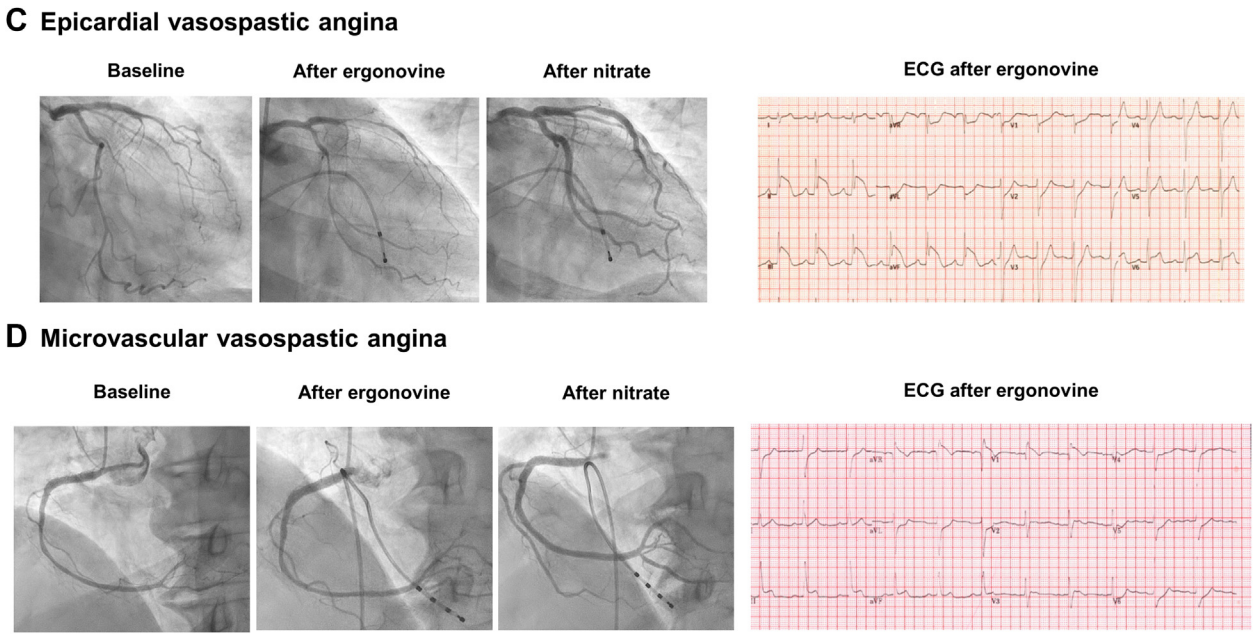
between acetylcholine and ergonovine were also reported.[65] Because of this, the supplementary use of both drugs can be useful when vasospastic angina is strongly suspected, but the provocation test is negative with 1 drug.

Microvascular vasospastic angina can be diagnosed with acetylcholine infusion during coronary angiography, and it occurs with a lower dose of acetylcholine compared with that of epicardial coronary spasm.[30] When angina and ischemic electrocardiographic changes (ST-segment depression or elevation ≥0.1 mV) in at least 2 contiguous leads occur after acetylcholine infusion without significant epicardial coronary artery constriction (<90%), the presence of microvascular spasm can be diagnosed (Table 1).[44,64] Epicardial vasospastic angina and microvascular vasospastic angina can occur concomitantly,[31] and their coexistence can be confirmed in cases with microvascular vasospasm occurring with a lower dose of acetylcholine than epicardial artery spasm. Recently, the acetylcholine rechallenge test was introduced as a novel method to define

FIGURE 4 Continued



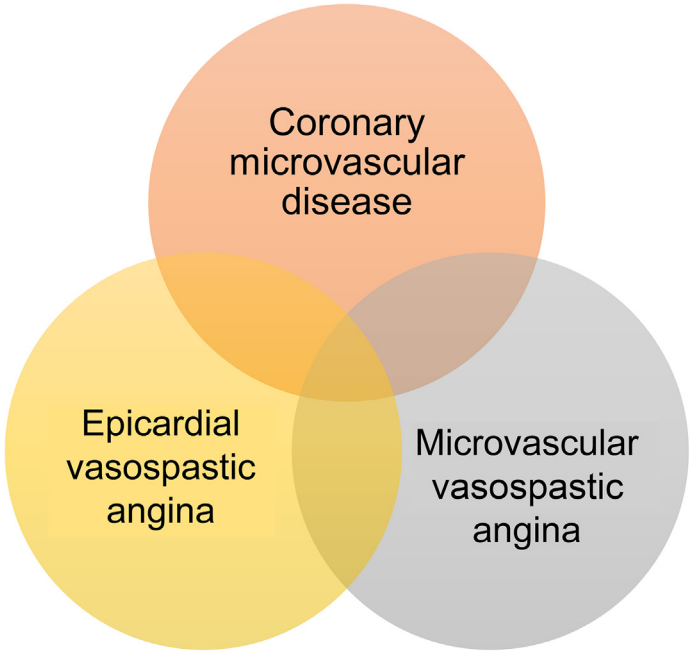
coexisting epicardial and microvascular vasospasm.[66] When there is transient total or subtotal coronary artery occlusion (>90% constriction) after intracoronary acetylcholine infusion, intracoronary nitroglycerin is injected, and intracoronary acetylcholine is reinfused after 3 minutes to confirm the microvascular vasospasm. Recently, the application of an intracoronary ergonovine test to diagnose microvascular spasms was also reported (**Figure 4D**).[67] Sueda and Sakaue[67] defined microvascular vasospasm as <75% stenosis, usual chest symptoms, and ischemic electrocardiographic changes during the ergonovine provocation test; they found 12 patients (2%) among 505 patients with suspected vasospastic angina. Even though there can be complications with provocation tests, such as refractory spasm by provocation test or fatal arrhythmia,[65] a recent meta-analysis reported its safety during daily practice.[68] Takahashi et al[68] reported that major complications, including death, ventricular fibrillation or ventricular tachycardia, myocardial infarction, and shock requiring resuscitation, occurred in 0.5% of the pooled 12,585 patients without any reports of deaths.

DIAGNOSTIC FLOW OF INOCA. Recent studies reported that multiple mechanisms could coexist in patients with INOCA (**Figure 5**). Feenstra et al[69] reported that endothelial dysfunction was prevalent in patients with vasospastic angina and dilatory microvascular dysfunction. Seitz et al[66] reported that concomitant epicardial artery vasospasm and microvascular vasospasm are more common than previously reported. Furthermore, previous studies reported that comprehensive physiologic assessment is helpful not only in the diagnosis of INOCA but also in risk stratification.[19,52] Therefore, when INOCA is suspected based on symptoms and/or noninvasive tests, a systematic approach to diagnose INOCA and define underlying mechanisms is needed. After the careful assessment of the presence of obstructive coronary artery disease based on coronary angiography with or without intracoronary imaging or physiologic studies, comprehensive physiologic tests are needed to define the coronary microvascular disease. After these tests, provocation tests are helpful in finding the concomitant vasospastic angina (**Central Illustration**).

MANAGEMENT OF INOCA

To date, there is no standard evidence-based treatment of INOCA because of its heterogeneous mechanisms and the lack of well-designed clinical trials.

FIGURE 5 Occurrence and Overlap of INOCA Endotypes



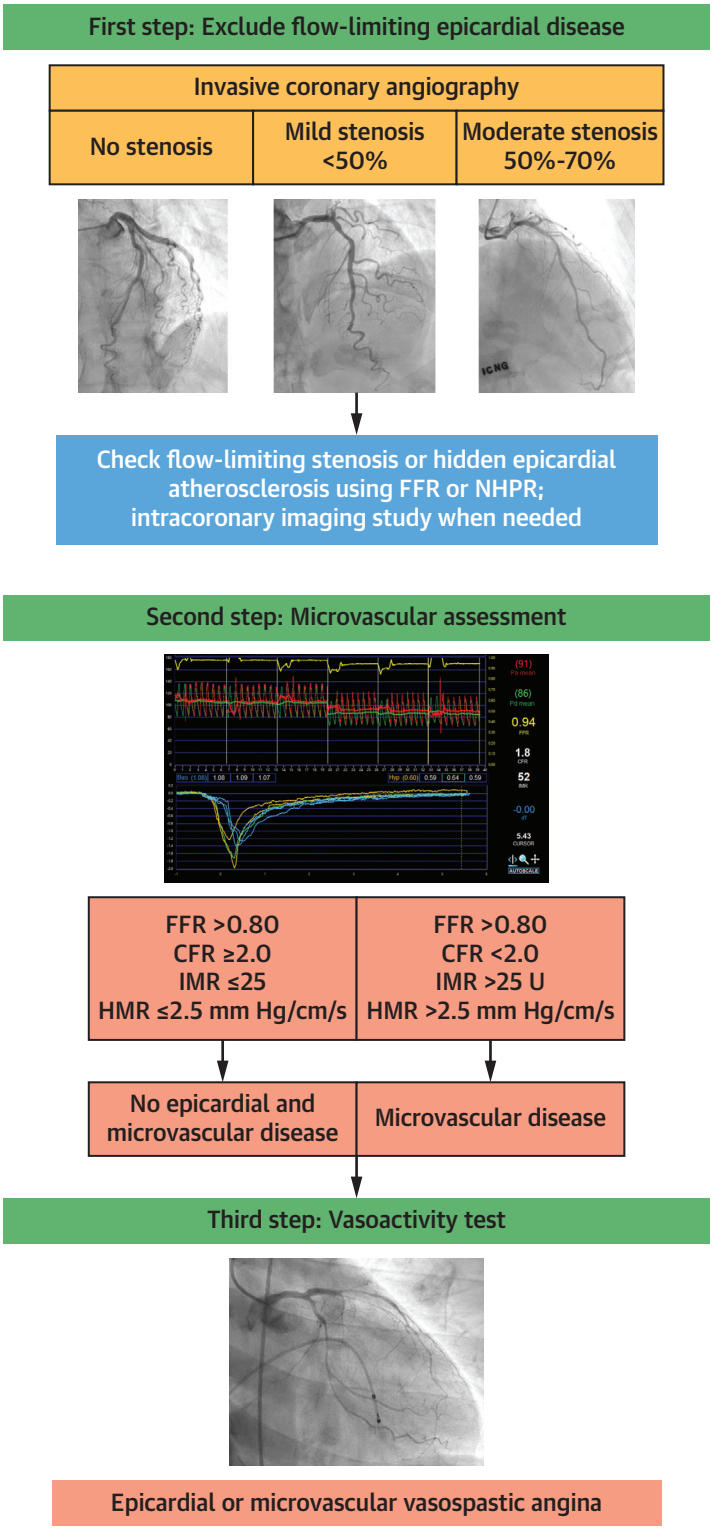
There are several endotypes of ischemia with nonobstructive coronary arteries (INOCA), and multiple mechanisms can coexist in patients with INOCA.

Because the underlying mechanisms in each endotype of INOCA are different, a patient-centered treatment strategy based on the mechanism of INOCA should be recommended. The CorMicA (Coronary Microvascular Angina) study evaluated the benefits of invasive coronary functional tests in INOCA patients.[70] The investigator performed invasive diagnostic tests to discriminate the underlying mechanisms of angina in INOCA patients and applied specific treatment strategies according to the test results. Briefly, if there was evidence of coronary microvascular disease, aspirin, statin, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) were considered as a baseline therapy, and a beta-blocker was considered as first-line therapy and a calcium-channel blocker as second-line therapy for antianginal effects. In the case of vasospastic angina, a calcium-channel blocker was considered as first-line therapy and nitrates as second-line therapy. They reported that stratified management in INOCA patients leads to significant and sustained angina improvement and quality of life at 1 year compared with standard care of patients with guideline-directed medical therapy and antianginal treatment depending on the physician's discretion.[70]

CORONARY MICROVASCULAR DISEASE. Coronary microvascular disease is characterized by the impaired vasodilatory function of the microvascular system, and its causes are heterogeneous.[21] Conventional cardiovascular risk factors, including hypertension, diabetes, hypercholesterolemia, obesity, and smoking, are associated with coronary anatomical and functional microvascular disease.[23] Optimal management of these cardiovascular risk factors may prevent the progression of microvascular disease with or without improving microvascular vasodilatory function. The proper management of hypertension is known to improve CFR, and insulin sensitizer metformin has been shown to improve endothelial function.[71,72] Statins may be beneficial because of their pleiotropic effects improving endothelial function.[73,74] Weight reduction with exercise and smoking cessation also have consistent benefits in improving CFR and clinical outcomes.[75-78] Therefore, the management of INOCA should start with the proper assessment and management of cardiovascular risk factors.

There are several medical treatment options for coronary microvascular disease (**Table 3**). An ACE inhibitor or ARB has demonstrated the improvement of microvascular vasodilatory function, exercise tolerance, and angina symptoms.[79-81] In some studies, an ACE inhibitor or ARB also demonstrated reverse microvascular remodeling and regression of periarteriolar fibrosis on biopsy.[81,82] Beta-blockers reduce myocardial oxygen consumption by reducing heart rate and myocardial contractility and increase the diastolic filling time. These effects reduce the number of ischemic episodes and increase the threshold of ischemic symptoms.[83-86] In a previous report, beta-blockers were also associated with an improvement of endothelial functions.[87] Calcium-channel blockers can also be used because of their vasodilatory effects. Despite limited data regarding the effects of calcium-channel blockers on endothelial and microvascular function, their use is associated with improved exercise tolerance and symptoms.[88] Nitrates can also be used to relieve angina, but their effects on microvascular disease are inconclusive and are often reported as ineffective and poorly tolerated because of their stealing effect.[89] Ranolazine inhibits the late sodium current and reduces intracellular calcium levels, leading to the

CENTRAL ILLUSTRATION **Identifying Mechanisms of Ischemia With Nonobstructive Coronary Arteries With Invasive Coronary Angiography**



Hwang D, et al. JACC: Asia. 2023;3(2):169-184.

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TABLE 3 Currently Available Medical Treatment Options for INOCA

Treatment Agents	Clinical Effects	Applicable Endotypes of INOCA		
		Coronary Microvascular Disease	Epicardial Vasospastic Angina	Microvascular Vasospastic Angina
ACE inhibitor/ARB	• Improve endothelial function • Improve small vessel remodeling • Regress periarteriolar fibrosis	+	–	–
Beta-blocker	• Reduce myocardial oxygen demand and increase diastolic perfusion time by reducing heart rate and contractility • Increase the threshold of ischemic symptom • Improve endothelial function	+	–	–
Nitrates	• Dilate vascular smooth muscle • Reduce preload via systemic vasodilation	–	+	±
CCB	• Dilate vascular smooth muscle • Increase the threshold of ischemic symptom • Reduce myocardial oxygen demand • Improve symptom and exercise tolerance	±	+	+
Statin	• Anti-inflammatory and antioxidant properties • Improve coronary endothelial function	+	–	–
Nicorandil	• Coronary microvascular dilatory effect • Balanced vasodilator in veins and arteries	±	+	+
Ranolazine	• Reduce myocardial oxygen demand and improve microvascular perfusion via improvement of ventricular relaxation	+	–	–
Trimetazidine	• Increase cell tolerance to ischemia via cellular homeostasis	+	-	-

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; INOCA = ischemia with nonobstructive coronary arteries.

improvement of ventricular relaxation.[90] A previous study reported symptom improvement in women with INOCA and CFR improvement with ranolazine.[91] Nicorandil is a vasodilating agent via nitrate and potassium channel activation with minimal side effects.[92] Other drugs, such as ivabradine, a specific Rho-kinase inhibitor, or an endothelin receptor antagonist, are also suggested as potential treatment options for treating microvascular disease.[93-95] Even though there are various options for treating coronary microvascular disease, they have not been evaluated in well-designed clinical trials, and further study is warranted.

VASOSPASTIC ANGINA. Vasospastic angina is characterized by the spasm of vascular smooth muscle cells in the epicardial coronary artery or microvasculature, including the prearteriolar vessels and arterioles. Therefore, vasodilating drugs, such as calcium-channel blockers and nitrates, are the most important treatment options for vasospastic angina (Table 3).[25] Nondihydropyridine calcium-channel blockers are preferred in vasospastic angina, but dihydropyridine calcium-channel blockers also can be used in vasospastic angina.[25,96,97] Long-acting nitrates are beneficial in patients with persistent symptoms with calcium-channel blockers, and short-acting nitrates are useful to relieve acute episodes of vasospasm.[25,96,97] Considering the diurnal variation of vasospastic attack, prescription time can be an important issue. To prevent angina in the early morning or at midnight, medication before sleep, not after dinner, can be useful to prevent the symptom.[25]

CENTRAL ILLUSTRATION Continued

A systematic approach to diagnose ischemia with nonobstructive coronary arteries (INOCA) and define the underlying mechanisms is presented. The first step is excluding flow-limiting epicardial coronary artery disease using invasive coronary angiography. Invasive physiologic assessment using fractional flow reserve (FFR) or nonhyperemic pressure ratio (NHPR) and/or invasive coronary imaging is helpful. After excluding the presence of ischemia-causing epicardial lesions, comprehensive physiologic assessments should be performed to identify the microvascular dysfunction. Finally, provocation tests are helpful in the diagnosis of vasospastic angina. HMR = hyperemic microvascular resistance; IMR = index of microvascular resistance.

TABLE 4 Ongoing Studies for Evaluating the Prevalence, Prognosis, and Management of INOCA

Diagnosis	Diagnosis	Diagnosis
INOCAIT (NCT05164640)	Prospective registry	Prevalence, proportion of endotypes, and prognosis of INOCA
DISCOVER INOCA (NCT05288361)	Prospective registry	Prevalence, proportion of endotypes, and prognosis of INOCA
CorCTCA (NCT03477890)	Randomized controlled trial	Impact of invasive diagnostic tests for INOCA in classifying and managing INOCA patients
iCorMicA (NCT04674449)	Randomized controlled trial	Benefit of stratified management of INOCA based on invasive tests
WARRIOR (NCT03417388)	Randomized controlled trial	Prognostic impact of intensive statin/ACE inhibitor/ARB treatment in INOCA patients
PRIZE (NCT04097314)	Randomized controlled trial	Antianginal effect of zibotentan in patients with coronary slow flow phenomenon

CorCTCA = Coronary Microvascular Function and CT Coronary Angiography; DISCOVER INOCA = Determining the Cause of Coronary Vasomotor Disorders in Patients With Ischemia and No Obstructive Coronary Artery Disease; iCorMicA = International Study of Coronary Microvascular Angina; INOCAIT = Ischemia in Patients With Non-obstructive Disease [INOCA] in Italy INOCA IT Multicenter Registry; PRIZE = Precision Medicine With Zibotentan in Microvascular Angina; WARRIOR = Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD; other abbreviations as in Table 3.

In patients with refractory symptoms during treatment with calcium-channel blockers and nitrates, nicorandil, alpha-1 receptor blockers, or Rho-kinase inhibitors can be additional options for vasospastic angina.[25,92,96,97] For patients with vasospastic angina, the use of beta-blockers, both selective or nonselective, should be avoided because of the possible effects on smooth muscle vasospasm with blocking beta-2 receptors.[25,96,97]

Most medical options for vasospastic angina have focused on epicardial coronary vasospasm, and the evidence for microvascular spasms is limited.[98,99] Because the coronary vessel tone regulation by endothelium-derived relaxing factors varies according to vessel size, the effects of vasodilatory drugs on the coronary microvasculature can be diminished.[99] Seitz et al[99] reported that nitrates could prevent microvascular vasospasm only in 20% of patients and attenuate microvascular vasospasm in 49% of patients. Even though calcium-channel blockers and nitrates are the recommended treatment options for microvascular vasospastic angina, like epicardial vasospastic angina, different treatment strategies may be needed, considering the different underlying pathophysiologic mechanisms. However, a trial-and-error principle is still needed to find optimal, tailored medical treatment for microvascular vasospastic angina.

FUTURE PERSPECTIVES

It is evident that the diagnosis of INOCA is often dismissed, leading to inadequate management of patients with possible INOCA. The prevalence of INOCA according to its endotypes, the proportion of concomitant mechanisms, and clinical relevance according to its mechanisms are limited. The ongoing INOCAIT (Ischemia in Patients With Non-obstructive Disease [INOCA] in Italy INOCA IT Multicenter Registry; NCT05164640), DISCOVER INOCA (Determining the Cause of Coronary Vasomotor Disorders in Patients With Ischemia and No Obstructive Coronary Artery Disease; NCT05288361), and CorCTCA (Coronary Microvascular Function and CT Coronary Angiography; NCT03477890) trials will reveal the prevalence and patterns of overlapping mechanisms and their prognosis (Table 4). However, a standard definition of INOCA and systematic diagnostic flow are still lacking, and these are needed to uniformly define the disease and classify its endotypes while considering their concomitant occurrence. Recently, there have been several efforts to establish the methods and criteria for diagnosing INOCA. The COVADIS (Coronary Vasomotor Disorders International Study) group and the Japanese Circulation Society proposed standardized diagnostic criteria for microvascular angina and vasospastic angina.[44,64,100,101] However, because several different mechanisms can be concurrently present in INOCA patients, a systematic diagnostic flow to define INOCA is needed. Using future well-designed, adequately powered, population-based prospective registry data may help physicians understand INOCA regarding its prevalence according to its endotypes, distribution of overlapping mechanisms, and prognosis according to its endotypes. For adequate management of INOCA, targeting the underlying mechanisms of INOCA is needed, but a stratified management strategy and its efficacy for INOCA still remain controversial. Even though the recent CorMicA trial demonstrated the benefits of invasive diagnostic tests for discriminating the underlying mechanisms of INOCA patients in their treatments, further studies are needed to verify the underlying mechanism-guided treatment strategy. The ongoing iCorMicA (International Study of

Coronary Microvascular Angina; NCT04674449) will provide an answer to this issue. Furthermore, to date, there is no disease-modifying management of INOCA (**Table 4**). The randomized WARRIOR (Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD; NCT03417388) trial is investigating the impact of statin and ACE inhibitor/ARB therapy on major adverse cardiovascular events in women INOCA patients (**Table 4**). Other potential drugs for treating INOCA, such as endothelin receptor antagonists (PRIZE [Precision Medicine With Zibotentan in Microvascular Angina; NCT04097314), are also under investigation (**Table 4**).

CONCLUSIONS

Patients whose symptoms are suspicious of INOCA are often dismissed and underdiagnosed in clinical practice. Considering the clinical importance of INOCA and its prognosis, this should be diagnosed adequately, and invasive physiologic assessment is mandatory to define the presence of INOCA and discriminate its underlying mechanisms. Mechanism-specific management of INOCA might be more beneficial, and ongoing studies will shed light on this issue. Further treatment options with disease-modifying drugs are under investigation; these might further enhance INOCA patients' outcomes.

HIGHLIGHTS

- Patients with INOCA are underdiagnosed in daily practice.
- Because the presence of INOCA is associated with poor clinical outcomes, identifying INOCA and discriminating the underlying mechanisms are clinically important.
- Invasive coronary evaluation with physiologic assessment and provocation tests is needed to diagnose INOCA.
- Mechanism-specific management can improve the prognosis of INOCA patients.

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ADDRESS FOR CORRESPONDENCE: Dr Bon-Kwon Koo, Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 101 Daehang-ro, Chongno-gu, Seoul 110-744, Korea. E-mail: bkkoo@snu.ac.kr.

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