Unmet Needs of ANOCA/INOCA in Taiwan: From Vasospastic to Coronary Microvascular Dysfunction Endotypes

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Abstract

Purpose: Angina or ischemia with nonobstructive coronary arteries (ANOCA/INOCA) represents a heterogeneous syndrome caused by multiple coronary functional abnormalities, including coronary microvascular dysfunction (CMD), epicardial vasospasm, microvascular spasm, and endothelial dysfunction. This review aims to summarize current evidence regarding ANOCA/INOCA in east Asia and Taiwan, highlighting differences in endotype distribution compared with Western populations.

Methods: A narrative review of contemporary studies, meta-analyses, international guidelines, and Asian registry data was conducted. The epidemiology, pathophysiology, diagnostic approaches, and clinical implications of CMD and coronary vasomotor disorders were evaluated, with particular emphasis on Taiwanese and East Asian populations.

Results: Available evidence suggests that CMD is common among patients with ANOCA/INOCA worldwide, with a pooled prevalence of approximately 41%. However, Asian populations demonstrate a particularly high burden of vasospastic disorders, with reported vasospasm prevalence ranging from 26% to 79%. Taiwanese studies similarly indicate a substantial prevalence of epicardial coronary spasm, while comprehensive data on CMD remain limited. Conventional noninvasive stress testing shows poor diagnostic performance for coronary vasomotor dysfunction. Invasive coronary function testing incorporating coronary flow reserve (CFR), index of microcirculatory resistance (IMR), and pharmacological provocation testing provides a mechanism-based framework for endotype classification and targeted treatment.

Conclusions: The available Taiwanese data and East Asian evidence suggest that vasospastic and mixed vasomotor endotypes may be common among Taiwanese patients with ANOCA/INOCA; however, further prospective registry studies using standardized coronary function testing are needed to define the true endotype distribution. Establishment of standardized invasive coronary function testing and dedicated national registries is essential to define disease burden, improve diagnostic accuracy, and facilitate precision medicine for Taiwanese patients with ANOCA/INOCA.

Keywords: ANOCA, INOCA, coronary microvascular dysfunction, coronary vasospasm, coronary function testing, Taiwan

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Introduction

Ischemia with nonobstructive coronary arteries (INOCA) and angina with nonobstructive coronary arteries (ANOCA) are increasingly recognized as heterogeneous clinical syndromes rather than benign angiographic findings[1-4]. Although most contemporary diagnostic and therapeutic frameworks have been derived from Western cohorts, emerging evidence suggests that the distribution of underlying endotypes may differ across ethnic and geographic populations. Compared with Western studies[5-7], Asian populations appear to have a particularly high burden of coronary vasomotor disorders, especially epicardial coronary spasm[8], while the true prevalence of isolated CMD remains less well defined because of limited Asian registry data and heterogeneity in diagnostic protocols. A systematic review and meta-analysis[7] reported that, among patients with nonobstructive coronary artery disease, the pooled prevalence was 41% for CMD, 40% for epicardial vasospasm, and 24% for microvascular spasm, with combined CMD and vasospastic angina present in approximately 23% of patients. Importantly, another meta-analysis[9] focusing on provocation testing found a higher prevalence of epicardial spasm in Asian populations than in Western populations, suggesting that vasospastic and mixed vasomotor endotypes may be particularly relevant in East Asian clinical practice. In Taiwan, available studies[10] and clinical experience have similarly highlighted coronary artery spasm as an important and potentially under-recognized mechanism of ANOCA/INOCA; however, comprehensive endotype-specific data incorporating both adenosine-based assessment of CFR/IMR and acetylcholine or ergonovine provocation testing remain scarce. Therefore, a Taiwan-focused review is needed to contextualize ANOCA/INOCA within the Asian phenotype, clarify the relative contributions of CMD, epicardial spasm, microvascular spasm, and endothelial dysfunction, and promote standardized invasive coronary function testing to guide mechanism-based therapy.

Endotype classification of ANOCA/INOCA

Invasive coronary function testing has become the reference standard for defining the underlying mechanisms of ANOCA/INOCA and for moving beyond a purely anatomy-based interpretation of nonobstructive coronary arteries. A comprehensive invasive assessment should systematically evaluate both the microvascular and epicardial coronary compartments, because ischemia and angina may arise from multiple functional abnormalities despite the absence of flow-limiting stenosis[11].

Invasive coronary function testing provides a mechanism-based framework for classifying ANOCA/INOCA into distinct endotypes[12]. Broadly, these endotypes can be divided into two complementary domains: **endothelium-independent coronary microvascular dysfunction**, assessed by adenosine-mediated hyperemia, and **coronary vasomotor disorders**, assessed by acetylcholine or ergonovine provocation testing.

First, **endothelium-independent CMD** reflects abnormalities in coronary flow reserve[13] and microvascular resistance[13,14]. Adenosine-derived indices, including CFR and IMR, identify impaired vasodilatory capacity, increased microvascular resistance, or mixed flow-resistance abnormalities. These phenotypes are frequently emphasized in Western ANOCA/INOCA literature[15] and are closely associated with cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and subclinical atherosclerosis[14,16]. However, the ethnic difference in CMD remains uncertain, particularly in Asian populations, because comprehensive registry data incorporating standardized CFR/IMR assessment are still limited.

Second, **coronary vasomotor disorders** include epicardial coronary spasm, microvascular spasm, and endothelial dysfunction. These

endotypes are detected by acetylcholine or ergonovine provocation testing and are especially relevant in Asian clinical practice[17]. Taiwanese data[18] suggest that multiple-vessel spasm is present in 19.3% of INOCA patients. The frequency appears more frequent in Japanese (24.3%) and Taiwanese patients than in Caucasian (7.5%) cohorts[19]. This geographic and ethnic difference may be partly biological, reflecting greater coronary vasomotor hyper-reactivity, but may also be influenced by differences in diagnostic practice[20]. In Japan, provocation testing is routinely performed in many centers, whereas acetylcholine or ergonovine testing is much less frequently used in Europe and the United States. Therefore, the prevalence of coronary spasm in Western studies may be underestimated. In Taiwan, where provocation testing is not yet routinely used in INOCA/ANOCA diagnosis, vasospastic and mixed vasomotor endotypes may also be underdiagnosed despite their high clinical relevance.

Taken together, invasive coronary function testing should not be limited to adenosine-derived assessment of CMD alone. For Asian and Taiwanese ANOCA/INOCA patients, a comprehensive strategy incorporating provocation testing is particularly important, because epicardial spasm, microvascular spasm, endothelial dysfunction, and mixed CMD–spasm phenotypes may represent dominant mechanisms of symptoms and ischemia. This distinction provides the foundation for subsequent endotype-based classification and targeted therapy.

Prevalence of vasospastic angina in Asian populations

Among studies conducted in Asian populations, particularly those from Japan and Korea, the reported prevalence of coronary vasospasm ranged from 26% to 79% (Table 1), with most studies reporting prevalence rates exceeding 50%. Sun et al.[21] found a 79% prevalence rates in patients with microvascular angina or vasospastic angina, whereas lower rates were reported in selected populations undergoing evaluation for suspected vasomotor dysfunction. Overall, these findings suggest that coronary vasospasm represents a common pathophysiological mechanism among Asian patients with angina and nonobstructive coronary artery disease (ANOCA/INOCA).

In Taiwan, available population-based data suggest that angina symptoms are clinically relevant, with an estimated prevalence of approximately 3.5% in the general population and around 15% among individuals aged > 65 years[22,23]. A retrospective study from a single center in Taiwan found 59% of patients with INOCA had epicardial vasospasm[24]. However, Taiwan currently lacks population-based epidemiological data specifically addressing INOCA/ANOCA using standardized coronary angiography and coronary function testing. This represents a major knowledge gap, particularly because Asian populations may not share the same endotype distribution as Western populations. Whereas Western studies have often emphasized coronary microvascular dysfunction, Asian and Taiwanese data suggest a higher prevalence of vasospastic phenotypes, including epicardial coronary spasm and multiple-vessel spasm. Therefore, the prevalence and clinical implications of ANOCA/INOCA in Taiwan should be interpreted within an Asian vasomotor phenotype, and future studies should incorporate comprehensive invasive coronary function testing to define the relative burden of CMD, epicardial spasm, microvascular spasm, endothelial dysfunction, and mixed endotypes.

Prevalences of coronary microvascular dysfunction in Asian populations

The prevalence of coronary microvascular dysfunction in Asian patients with ANOCA/INOCA remains incompletely defined because available data are relatively limited, heterogeneous, and frequently derived from selected single-center cohorts rather than population-based registries (Table 2). In the meta-

Table 1. Prevalence of coronary vasospasm in Asian populations

Study	Country	Asian (%)	Indication / Population	Vasospasm prevalence	Definition	Diagnostic tool
Hoshino et al., 2016[71]	Japan	100%	292 consecutive patients undergoing acetylcholine provocation testing for suspected vasospastic angina	Severe spasm (≥75% constriction): 30.8% (90/292); Moderate spasm (50–74% constriction): 32.2% (94/292); Overall vasomotor dysfunction: 63.0%	Epicardial coronary artery diameter reduction ≥75% after acetylcholine relative to ISDN reference diameter. Moderate spasm defined as ≥50% diameter reduction.	Intracoronary acetylcholine provocation test with quantitative coronary angiography
Kim et al., 2018 (koROSE Registry)[72]	Korea	100%	328 patients with chest pain and no significant coronary stenosis undergoing provocation testing	39.0% (128/328)	Coronary vasospasm defined as >90% transient luminal narrowing accompanied by anginal symptoms after acetylcholine or ergonovine administration.	Intracoronary acetylcholine or ergonovine provocation test during coronary angiography
Mohri et al., 1998[73]	Japan	100%	117 consecutive patients with chest pain (rest, exertional, or both) and no flow-limiting (>50%) epicardial coronary stenosis	Large-vessel spasm: 63/117 (54%); Microvascular spasm: 29/117 (25%); Total vasospastic mechanism: 92/117 (79%)	Epicardial spasm: >75% diameter reduction after acetylcholine. Microvascular spasm: angina and/or ischemic ECG changes induced by acetylcholine without epicardial spasm.	Intracoronary acetylcholine provocation test with coronary angiography and ECG monitoring
Oh et al., 2019[74]	Korea	100%	158 patients undergoing ergonovine provocation testing for suspected variant angina	Positive vasospasm: 44/158 (27.8%)	Positive test defined as >90% transient diameter stenosis regardless of symptoms, or >70% stenosis with ischemic ECG changes and/or chest pain.	Selective intracoronary ergonovine provocation test during coronary angiography. Adenosine and nitroglycerin administered sequentially for vessel response assessment.
Ohba et al., 2012[75]	Japan	100%	370 stable patients with suspected angina and non-obstructive coronary arteries (<50% stenosis)	Microvascular CAS: 50/370 (13.5%)	Lactate production + decrease in coronary blood flow + chest pain/ischemic ECG changes without epicardial vasospasm during ACh test	ACh provocation + transcardiac lactate measurement + Doppler coronary blood flow assessment + ATP-CFR evaluation

(Continued)

Table 1. *(Continued)*

Study	Country	Asian (%)	Indication / Population	Vasospasm prevalence	Definition	Diagnostic tool
Suda et al., 2019[8]	Japan	100%	187 patients with angina and non-obstructive CAD undergoing comprehensive coronary function testing	Vasospastic angina: 128/187 (68%)	Epicardial spasm defined as >90% narrowing with chest pain and ischemic ECG changes (JCS criteria); MVS diagnosed according to COVADIS criteria	Acetylcholine provocation test + IMR + CFR + FFR assessment
Sun et al., 2002[76]	Japan	100%	55 patients with documented epicardial vasospastic angina induced by ACh	Microvascular spasm: 14/55 (25.5%)	ACh-induced chest pain and/or ischemic ECG changes with myocardial lactate production but without epicardial spasm	Intracoronary acetylcholine provocation + coronary angiography + coronary sinus lactate measurement
Sun et al., 2005[21]	Japan	100%	131 consecutive patients with chest pain and normal coronary angiography undergoing ACh provocation testing	MVS alone: 35/131 (26.7%); ES+MVS: 16/131 (12.2%); Total MVS: 51/131 (38.9%)	MVS defined as myocardial ischemia (≥2 of chest pain, ischemic ECG change, lactate production) induced by low-dose ACh without epicardial spasm	Intracoronary ACh provocation, coronary angiography, lactate production assessment, TIMI frame count analysis
Tsuchida et al., 2005[77]	Japan	100%	80 patients with coronary spastic angina diagnosed by ergonovine testing	CSA prevalence not evaluated (all patients had CSA)	Coronary spasm defined as occlusive/subocclusive epicardial constriction associated with chest pain or ischemic ECG changes	Intracoronary ergonovine provocation test + coronary angiography
Yamanaga et al., 2015[78]	Japan	100%	50 patients with angina-like symptoms and non-obstructive CAD (29 VSA, 21 non-VSA)	VSA prevalence 58% (29/50)	VSA defined as ≥90% transient stenosis with angina and ischemic ECG changes according to JCS criteria	Acetylcholine provocation test + Doppler/pressure dual-sensor guidewire + hMR/CFVR assessment

Ach = acetylcholine; ATP = adenosine; CAD = coronary artery disease; CAS = coronary artery spasm; CFR = coronary flow reserve; CFVR = coronary flow velocity reserve; CSA = coronary spastic angina; ECG = electrocardiography; ES = epicardial spasm; FFR = fractional flow reserve; hMR = hyperemic microvascular resistance; IMR = index of microvascular resistance; ISDN = isosorbide dinitrate; MVS = microvascular spasm; VSA = vasospastic angina.

Table 2. Prevalence of coronary microvascular dysfunction in Asian populations

Study	Country	Asian (%)	Indication / Population	CMD prevalence	CMD definition	Diagnostic tool
Godo et al., 2020[79]	United States	Mixed ethnicity	Chest pain with angiographically normal or non-obstructive CAD (n=148)	59% (87/148)	Coronary microvascular endothelial dysfunction: ≤50% increase in coronary blood flow after acetylcholine	Doppler guidewire assessment of coronary blood flow response to intracoronary acetylcholine
Kim et al., 2013[26]	Korea	100%	Chest pain with normal coronary angiography (n=77)	52% (40/77, microvascular angina group)	Microvascular angina identified by ischemic treadmill test and abnormal coronary flow characteristics	TIMI frame count and nitroprusside-induced hyperemia
Lee et al., 2015[80]	United States/ Korea	Partial Asian	Angina without obstructive CAD (n=139)	21%	Coronary microvascular dysfunction defined by IMR ≥25	Invasive assessment including IMR, CFR, FFR, acetylcholine testing, and IVUS
Sakamoto et al., 2012[25]	Japan	100%	Patients without obstructive CAD and vasospasm (n=73)	16% (12/73)	Reduced coronary flow reserve (CFR ≤2.8)	Doppler flow-wire derived CFR measurement in LAD
Suda et al., 2019[8]	Japan	100%	Angina with non-obstructive CAD (n=187)	40.1% (75 / 187)	Increased coronary microvascular resistance (IMR ≥18)	Acetylcholine provocation testing, IMR, CFR, and FFR measurements
Ishimori et al., 2011[81]	United States	Mixed ethnicity (Asian subgroup included)	Women with SLE and anginal chest pain without obstructive CAD (n=18)	44% (8/18)	Abnormal stress myocardial perfusion suggestive of CMD	Adenosine stress cardiac magnetic resonance with myocardial perfusion reserve index
Kobayashi et al., 2015[82]	United States	Mixed ethnicity (Asian subgroup included)	Angina without obstructive CAD (n=157)	25%	Coronary microvascular dysfunction assessed by invasive physiology	Thermodilution-derived CFR and IMR measurements

CAD = coronary artery disease; CFR = coronary flow reserve; CMD = coronary microvascular disease; FFR = fractional flow reserve; IMR = index of microvascular resistance; IVUS = intravascular ultrasound; SLE = systemic lupus erythematosus.

analysis by Mileva et al.[7], the overall pooled prevalence of CMD in patients with nonobstructive coronary artery disease was 41%; however, a dedicated ethnicity-stratified pooled estimate for Asian populations was not provided. Among Asian studies (Table 2) included in the analysis, reported CMD prevalence varied substantially according to diagnostic methods, thresholds, and patient selection. For example, Japanese studies[8,25] using coronary flow reserve reported CMD rates ranging from approximately 16% to 40% in selected patients without obstructive coronary artery disease and vasospasm, whereas a Korean study[26] using angiographic hyperemic TIMI frame count suggested microvascular dysfunction-related findings in patients with microvascular angina. In the Japanese cohort of 187 patients with angina and nonobstructive coronary artery disease undergoing comprehensive coronary function testing, 35.3% had low CFR and 40.1% had high IMR, while 68.4% had vasospastic angina, indicating that CMD frequently coexists with vasospastic phenotypes rather than occurring as an isolated abnormality in Asian ANOCA/INOCA cohorts[8]. Therefore, current evidence supports that CMD is present and clinically relevant in Asian patients, but its true prevalence remains uncertain and should be interpreted in the context of high vasospasm burden and variable diagnostic protocols.

It should be noted that the prevalence estimates summarized in Tables 1 and 2 are descriptive because of the substantial heterogeneity among the included studies with respect to patient populations, diagnostic criteria, provocation agents, and coronary function testing protocols. Therefore, direct comparisons across studies should be interpreted with caution.

Limitation of traditional noninvasive testing

In Taiwan, treadmill exercise testing and thallium myocardial perfusion imaging remain commonly used for the evaluation of suspected ischemic heart disease. However, these conventional stress tests are primarily designed to detect obstructive epicardial coronary artery disease and have limited ability to identify the functional mechanisms underlying ANOCA/INOCA, including epicardial coronary spasm, microvascular spasm, endothelial dysfunction, and CMD. In patients with nonobstructive coronary artery disease who underwent invasive coronary function testing, conventional noninvasive stress modalities showed poor diagnostic performance for coronary vasomotor dysfunction, with a sensitivity of approximately 41% and specificity of 58%[27]. Thus, negative treadmill or thallium scan results cannot reliably exclude spasm- or CMD-related ischemia.

Because coronary spasm is dynamic and often requires acetylcholine or ergonovine provocation for diagnosis, and because CMD may present as diffuse perfusion impairment without a focal ischemic pattern, reliance on conventional noninvasive testing alone is insufficient. Comprehensive invasive coronary physiology testing, including CFR, IMR, and vasoreactivity assessment, is therefore crucial for accurate endotype classification and mechanism-based treatment of ANOCA/INOCA.

Noninvasive Techniques for Diagnosing Coronary Microvascular Dysfunction

The evaluation of coronary microvascular dysfunction has evolved significantly with the development of noninvasive imaging modalities capable of assessing coronary flow and myocardial perfusion beyond the limitations of traditional stress testing. Unlike conventional diagnostic approaches that primarily detect obstructive epicardial coronary artery disease, contemporary noninvasive techniques aim to quantify coronary flow reserve (CFR) and myocardial blood flow (MBF), thereby enabling indirect assessment of microvascular function.

Positron Emission Tomography (PET)

Positron emission tomography (PET) is currently regarded as the reference standard noninvasive technique for the assessment of CMD. PET allows for absolute quantification of myocardial blood flow at rest and during hyperemia, enabling calculation of myocardial flow reserve (MFR), which is analogous to CFR. Reduced MFR reflects impaired vasodilatory capacity of the coronary microcirculation and has been consistently associated with adverse cardiovascular outcomes, including heart failure and mortality. In a study of chest pain patients without CAD history[28], PET-assessed rest and post hyperemic flow, i.e. coronary flow reserve, was a powerful incremental predictor of major adverse cardiac events (hazard ratio: 0.80 per 10% increase in coronary flow reserve, $P < 0.0001$). Importantly, PET can detect diffuse microvascular dysfunction, which may not produce regional perfusion defects detectable by conventional imaging[29]. Furthermore, PET imaging provides high spatial and temporal resolution, as well as reproducibility, making it a robust tool for both diagnosis and risk stratification. However, its use is limited by availability, cost, and exposure to ionizing radiation.

Cardiac Magnetic Resonance Imaging (CMR)

Cardiac magnetic resonance (CMR) imaging has emerged as a powerful modality for the noninvasive assessment of myocardial perfusion and microvascular function[16]. Stress perfusion CMR enables both qualitative and quantitative evaluation of myocardial blood flow, with newer techniques allowing pixel-wise quantification of perfusion and estimation of myocardial perfusion reserve[30].

CMR offers several advantages, including high spatial resolution, lack of ionizing radiation, and the ability to provide comprehensive cardiac assessment, including ventricular function, tissue characterization, and detection of fibrosis through late gadolinium enhancement[16]. These features are particularly relevant in patients with CMD, in whom microvascular dysfunction may coexist with myocardial remodeling or fibrosis.

Despite these advantages, quantitative CMR remains technically demanding and less widely available than PET, with some variation in acquisition and analysis methods.

Transthoracic Doppler Echocardiography (TDE)

TDE provides a noninvasive means of assessing coronary flow reserve, most commonly in the distal portion of the left anterior descending coronary artery. By measuring coronary flow velocity at rest and during pharmacologically induced hyperemia, this technique allows estimation of coronary flow velocity reserve as a surrogate of microvascular function[31,32].

This modality is widely available, cost-effective, and free of radiation exposure[16]. TDE-coronary flow velocity reserve is known to provide an independent prognostic value for the prediction of cardiovascular events[33]. However, it is highly operator-dependent and limited by acoustic window quality, which may reduce feasibility in certain patient populations. It requires a well-trained operator. Additionally, assessment is typically restricted to a single coronary territory, limiting its ability to evaluate global microvascular function.

Limitations of Noninvasive Techniques

While noninvasive imaging can suggest the presence of CMD, it often lacks the ability to differentiate between specific endotypes, such as between structural microvascular disease and vasomotor dysfunction. As a result, a practical diagnosis algorism (Figure 1) for invasive coronary function testing remains indispensable

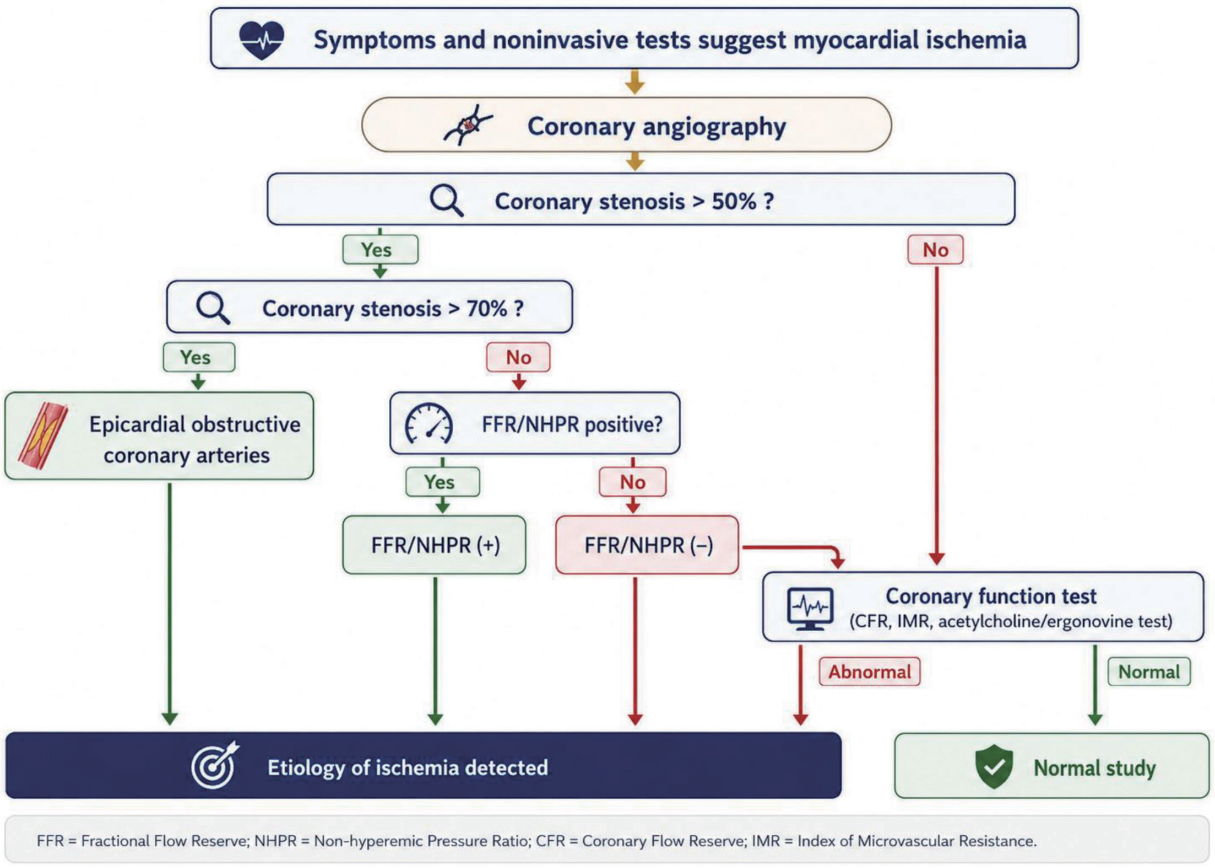

Figure 1. A practical diagnostic algorithm for CCS patients in Taiwan.

for definitive mechanistic classification and targeted therapy.

Invasive techniques for diagnosing coronary microvascular dysfunction

Endothelium-independent coronary microvascular dysfunction is primarily assessed using adenosine-mediated hyperemia, which evaluates the ability of the coronary microcirculation to appropriately augment myocardial blood flow. Because one of the principal functions of the coronary microvasculature is to regulate blood supply according to myocardial demand, impaired hyperemic flow response reflects clinically relevant abnormalities in microvascular function. These abnormalities may result from functional dysregulation, structural microvascular remodeling, increased arteriolar resistance, or capillary rarefaction. Therefore, adenosine-based testing plays a central role in identifying CMD and provides prognostically meaningful information in patients with ANOCA/INOCA.

Two key physiological indices are commonly used: coronary flow reserve and the index of microcirculatory resistance. Coronary flow reserve is defined as the ratio of hyperemic to resting coronary blood flow and reflects the integrated vasodilatory capacity of the coronary circulation[34]. CFR is a sensitive but less specific marker of coronary circulatory dysfunction. Index of Microcirculatory Resistance (IMR) provides a more specific and quantitative assessment of microvascular resistance during hyperemia[35]. Because IMR is less affected by resting hemodynamics and epicardial disease than CFR, an elevated IMR more directly suggests

structural microvascular abnormalities, including microvascular remodeling, luminal narrowing of intramural arterioles, capillary rarefaction, and increased arteriolar resistance.

From a practical standpoint, CMD can be assessed using wire-based techniques, including Doppler flow velocity systems[36] or pressure-temperature sensor guidewires[37]. Doppler-based systems estimate coronary flow velocity, whereas thermodilution-based systems calculate mean transit time, which is inversely related to coronary flow. Measurement of microvascular resistance requires simultaneous assessment of distal coronary pressure and flow during hyperemia. In Taiwan, the most clinically accessible platform for invasive CMD assessment is the thermodilution-based systems using pressure-temperature sensor guidewires, which enables thermodilution-derived CFR and IMR measurements during adenosine-induced hyperemia. With standardized acquisition and interpretation, this platform provides a feasible method for incorporating CMD testing into routine invasive evaluation of patients with suspected ANOCA/INOCA.

Invasive techniques for diagnosing vasomotor disorders

Endothelium-dependent coronary function and vasomotor disorders are assessed by intracoronary pharmacological provocation testing, which is essential for identifying epicardial vasospasm (EVS), microvascular spasm (MVS), and endothelial dysfunction in patients with ANOCA/INOCA.

Epicardial vasospasm is characterized by severe and transient vasoconstriction of the epicardial coronary arteries. Current Japanese[38], European[39], and American[40] guidelines define a positive spasm provocation test for EVS as > 90% luminal narrowing accompanied by anginal symptoms and ischemic electrocardiographic changes. In contrast, previous Taiwanese studies[24,41] adopted a threshold of > 70% epicardial coronary artery constriction during provocation testing in the presence of angina and/or ST-segment changes. The optimal angiographic cutoff for defining epicardial spasm remains debated, but the reproduction of anginal symptoms and ischemic electrocardiographic changes during provocation testing represents the essential feature of a positive test. Recent evidence has emphasized the importance of invasive coronary function testing for identifying treatable endotypes in ANOCA/INOCA, and complete provocation testing of both the right and left coronary arteries is recommended when contraindications are absent[18].

MVS is defined as reproduced angina, ischemic electrocardiographic ST-T changes and no epicardial coronary artery vasoconstriction[38]. MVS can coexist with EVS or CMD and is associated with significant symptom burden. Andreas Seitz, et al.[42] found that patients with MVS had higher rates of recurrent angina (HR: 1.311; 95% CI: 1.013-1.697) and psychological disorders that cause higher healthcare expenditure burden.

Acetylcholine is the most physiologically comprehensive agent for evaluating endothelium-dependent coronary function. In normal coronary arteries, acetylcholine stimulates muscarinic receptors and promotes nitric oxide-mediated vasodilation; in the presence of endothelial dysfunction, this response is impaired or paradoxically converted into vasoconstriction[43,44]. Therefore, acetylcholine testing can simultaneously assess endothelial integrity, epicardial vasospasm, and microvascular spasm. This feature cannot be fully replaced by ergonovine, because these agents predominantly provoke vasoconstriction through direct smooth muscle hyperreactivity rather than bidirectional endothelium-dependent vasomotor responses. Methylergonovine causes similar effects on the vascular smooth muscle, but contractions are inhibited by the release of NO from the endothelium[45]. Endothelial dysfunction may coexist with epicardial coronary artery spasm and may also be present even when adenosine-

mediated vasodilation and spasm provocation are normal, thereby increasing the diagnostic yield of coronary function testing. McChord J, et al.[46] reported that endothelial dysfunction was present in 84% ANOCA patients, while coronary spasm and CMD were detected in 80% and 45%, respectively.

However, in Taiwan, intracoronary acetylcholine is currently unavailable, which represents a limitation for comprehensive endothelial function assessment. Consequently, local provocation testing is performed using methylergonovine, and Taiwan has developed its own standardized methylergonovine-based protocol. In a Taiwan prior review article[18], calcium-channel blockers and nitrates, except sublingual nitrates, are suggested to be withheld for at least 24 hours; nitroglycerin is prepared before testing; 12-lead ECG, symptoms, and angiographic responses are continuously monitored; and methylergonovine is administered intracoronary in stepwise doses of 5, 10, and 30 μg at 3-minute intervals. Intracoronary nitroglycerin is then administered after completion of provocation testing, regardless of the test result.

Although methylergonovine cannot fully replace acetylcholine for the diagnosis of endothelial dysfunction, its diagnostic ability for epicardial and microvascular spasm is clinically acceptable and supported by safety data. Previous studies in Asian and white patients have demonstrated that the test is reasonably safe. Bertrand et al.[19] using intravenous ergonovine, had no serious irreversible complications among their 1088 patients, and Harding et al.[47] reporting 3447 intracoronary ergonovine tests in American patients, only had a single patient with serious complications such as myocardial infarction or ventricular tachycardia/fibrillation, corresponding to a complication rate of 0.03%. Japanese Cardiac Society provides standardized protocols in its guidelines for using either ACh or ER[48]. Large prior experiences with ergonovine-based testing reported very low serious complication rates, and Taiwanese and Japanese data have also shown acceptable safety profiles for intracoronary ergonovine or methylergonovine provocation testing.

Given the high prevalence of vasospastic endotypes and the current absence of intracoronary acetylcholine, methylergonovine-based provocation testing should be incorporated into invasive evaluation of suspected ANOCA/INOCA.

Pharmacological management for ANOCA/INOCA

There are no definitive guidelines for the treatment of ANOCA, but management should be tailored to the results of CFT[11,49,50] (Figure 2). The pharmacological management of ANOCA/INOCA in Asian populations differs from that in Western populations because coronary artery spasm, particularly epicardial vasospasm, appears to be substantially more prevalent among East Asians. Previous studies (Table 1.) have demonstrated a higher prevalence of vasospastic angina in Asian compared with Western populations, with EVS representing one of the most common endotypes identified during coronary function testing[11]. Consequently, vasodilator-based therapy plays a more central role in Asian patients with ANOCA/INOCA. Calcium channel blockers (CCBs) can be the empirical treatment. Anti-anginal dose of CCBs is often prescribed at higher doses (eg. Diltiazem 30-60 mg three times a day or diltiazem SR 120-360 mg) than those used for hypertension. In patients with persistent symptoms, combination therapy using both dihydropyridine and non-dihydropyridine CCBs may be required[51]. Although nitrates provide effective acute symptom relief, long-term use should be individualized because of concerns regarding inconsistent prognostic benefits observed in Asian vasospastic angina registries[52,53].

In addition to vasospastic disorders, coronary microvascular dysfunction is increasingly recognized in Asian patients with ANOCA/INOCA. Recent studies suggest

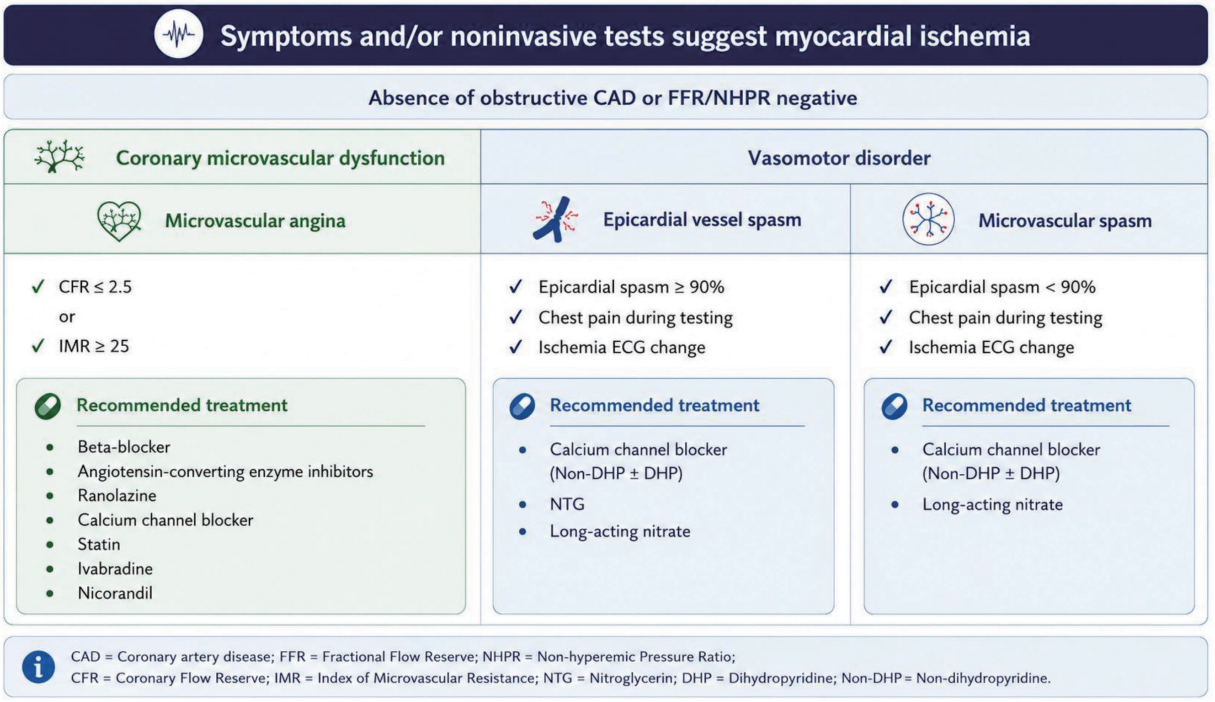

Figure 2. Endotype-specific pharmacological management for ANOCA/INOCA.

that CMD frequently coexists with epicardial or microvascular spasm[54], highlighting the importance of comprehensive coronary function testing for endotype-specific treatment[55]. For patients with structural CMD characterized by impaired coronary flow reserve and/or increased microvascular resistance, therapies aimed at reducing myocardial oxygen demand and improving microvascular perfusion should be considered, including β-blockers[12,56-59], ACE inhibitors[60-62], ranolazine[63-65], ivabradine[66], Nicorandil[67,68] and statins[69]. By contrast, functional CMD, characterized by elevated resting coronary blood flow and reduced CFR despite preserved hyperemic vasodilatory capacity, appears to result primarily from increased resting flow rather than insufficient hyperemic flow augmentation[14]. In this setting, conventional vasodilator therapy may provide limited benefit. Instead, treatment strategies that reduce myocardial oxygen demand and resting coronary blood flow, such as β-blockers, or agents that improve myocardial metabolic efficiency, such as ranolazine, may be more appropriate. The management of Asian ANOCA/INOCA patients should extend beyond symptom control and incorporate a mechanism-based approach that addresses both vasomotor abnormalities and microvascular dysfunction[70].

Future directions for ANOCA/INOCA research and care in Taiwan

Future efforts in Taiwan should prioritize the establishment of a dedicated ANOCA/INOCA research framework that defines the local epidemiology of coronary artery spasm, coronary microvascular dysfunction, endothelial dysfunction, and mixed vasomotor endotypes. At present, Asian data suggest a high burden of vasospastic disease, but the Taiwanese prevalence of epicardial spasm, microvascular spasm, isolated endothelium-independent CMD, endothelial dysfunction, and overlapping CMD-spasm phenotypes remains incompletely characterized. Population-based studies and prospective catheterization laboratory registries using

standardized invasive coronary function testing are therefore needed to determine the actual disease burden and to clarify whether Taiwanese patients demonstrate a distinct Asian vasomotor phenotype compared with Western cohorts.

The future direction of ANOCA/INOCA care in Taiwan should move from empirical diagnosis and treatment toward a standardized, physiology-based, and endotype-specific model. Defining the prevalence and prognostic relevance of coronary spasm and CMD in Taiwan will be essential for understanding local disease epidemiology, optimizing diagnostic algorithms, guiding access to pharmacological provocation agents, and developing precision treatment strategies tailored to Taiwanese patients.

Conclusion

Available evidence suggests that CMD is a common mechanism in patients with nonobstructive coronary arteries across populations, but Asian-specific CMD prevalence remains less precisely defined than Western estimates. Available Taiwanese data, together with evidence from East Asian populations, suggest that vasospastic and mixed vasomotor endotypes may be relatively common among Taiwanese patients with ANOCA/INOCA. Nevertheless, further prospective registry studies using standardized coronary function testing are required to better define the true distribution of endotypes in Taiwan. Therefore, in Taiwan, ANOCA/INOCA endotypes, including CMD and vasospasm should be evaluated systematically.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Reference

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