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JCS/CVIT/JCC 2023 Guideline Focused Update on Diagnosis and Treatment of Vasospastic Angina (Coronary Spastic Angina) and Coronary Microvascular Dysfunction

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on behalf of the Japanese Circulation Society and Japanese Association of Cardiovascular Intervention and Therapeutics and Japanese College of Cardiology Joint Working Group

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Refer to **Appendix 1** for the details of members.

JCS Joint Working Groups: The Japanese Circulation Society, Japanese College of Cardiology, Japanese Association of Cardiovascular Intervention and Therapeutics, Japanese Society of Pediatric Cardiology and Cardiac Surgery, Japanese Heart Rhythm Society, The Japanese Association of Cardiac Rehabilitation, The Japanese Coronary Association, Japanese Association of Cardioangioscopy

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Abbreviations

95% CI	95% confidence interval
ACE	angiotensin-converting enzyme
ACh	acetylcholine
ACS	acute coronary syndrome
AF	atrial fibrillation
ALDH2	aldehyde dehydrogenase 2
AMI	acute myocardial infarction
ARB	angiotensin-receptor blocker
ASCD	aborted sudden cardiac death
ATP	adenosine triphosphate
BMS	bare-metal stent
CAD	coronary artery disease
CAG	coronary angiography
CAS	coronary angioscopy
CCB	calcium-channel blocker
CCS	chronic coronary syndrome
CCTA	coronary computed tomography angiography
CFR	coronary flow reserve
CK	creatine kinase
CMD	coronary microvascular dysfunction
CMR	cardiovascular magnetic resonance
COR	Class of Recommendation
COVADIS	Coronary Vasomotion Disorders International Study
CSA	coronary spastic angina
CTP	CT perfusion
DES	drug-eluting stent
EES	everolimus-eluting stent
eNOS	endothelial nitric oxide synthase
EPS	electrophysiologic study
ER	early repolarization
ET-1	endothelin 1
FCA	invasive functional CAG
FFR	fractional flow reserve
FFRCT	computed tomography-derived fractional flow reserve
FMD	flow-mediated endothelium-dependent vasodilation
HF	heart failure
HFpEF	HF with preserved ejection fraction
HMR	hyperemic microvascular resistance
HR	hazard ratio
ICD	implantable cardioverter defibrillator
IDP	interventional diagnostic procedure
IHD	ischemic heart disease
IMR	index of microcirculatory resistance
INOCA	ischemia with non-obstructive coronary artery disease
IVUS	intravascular ultrasound
KD	kawasaki disease
LGE	late gadolinium enhancement
LOE	Level of Evidence
MACE	major adverse cardiac events
MBF	myocardial blood flow
MFR	myocardial blood flow reserve
MI-CAD	myocardial infarction with CAD
MINOCA	myocardial infarction with non-obstructive coronary arteries
MLC	myosin light chain
MLCK	myosin light chain kinase
MLCPh	myosin light chain phosphatase
MPRI	myocardial perfusion reserve index
MRI	magnetic resonance imaging
MVA	microvascular angina
MVS	microvascular spasm
NO	nitric oxide
OCT	optical coherence tomography
OR	odds ratio
PCI	percutaneous coronary intervention
PET	positron emission tomography
PVAT	perivascular adipose tissue
QOL	quality of life
RH-PAT	reactive hyperemia peripheral arterial tonometry
ROS	reactive oxygen species
SCAD	spontaneous coronary artery dissection
SCD	sudden cardiac death
SPECT	single-photon emission computed tomography
TIMI	Thrombolysis In Myocardial Infarction
TP-NOCA	troponin-positive non-obstructive coronary arteries
TWA	T wave alternans
VF	ventricular fibrillation
VSA	vasospastic angina
VSMC	vascular smooth muscle cell
VT	ventricular tachycardia
VV	vasa vasorum

Preface

In 2008, the Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina)[1] were developed by the Japanese Circulation Society, and the revised version was published in 2013.[2] Since then, new findings from various fields such as coronary microvascular dysfunction (CMD), biomarkers, imaging, physiological functions, and genes have accumulated. Furthermore, together with the spread of emergency coronary angiography (CAG) for acute coronary syndrome (ACS) and the development of diagnostic techniques using high-sensitive troponin, the new concepts of myocardial infarction with non-obstructive coronary arteries (MINOCA) and ischemia with non-obstructive coronary artery disease (INOCA) have been proposed.[3,4] The term "angina pectoris", named in the mid-18th century, was extended to include variant forms[5] in the 20th century, and as a result of advances in both invasive and noninvasive diagnostic techniques and pharmaco- or catheter therapy, the European Society of Cardiology (ESC) proposed the concept of chronic coronary syndrome (CCS), taking into account the need for ongoing risk management in the 21st century.[6]

Coronary spasm, for which regional and racial differences have been noted, is not rare in Europe and the USA.[7,8] The Coronary Vasomotion Disorders International Study

(COVADIS) group, an international research group on coronary artery dysfunction, published criteria on vasospastic angina (VSA) in 2017,[9] and microvascular angina (MVA) in 2018.[10] In the case of MINOCA or INOCA, the importance of recognizing and considering functional abnormalities in the absence of organic lesions and without seeking noncardiac causes of chest symptoms is challenged.[11–16]

This focused update is based on the Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (2013 revision),[2] JCS 2018 Guideline on diagnosis and treatment of acute coronary syndrome,[17] and JCS 2018 Guideline on diagnosis of chronic coronary heart diseases,[18] while considering the position of coronary spasm, CMD, coronary microvascular spasm (MVS), and non-obstructive coronary artery disease (CAD) in the field of ischemic heart disease (IHD). Updates on the following topics have been provided.

1. MINOCA and INOCA are described as new disease concepts related to coronary spasm.
2. New findings on the pathophysiology, diagnosis, and treatment of coronary spasm have been added since the 2013 revision.
   (1) For pathophysiology: aldehyde dehydrogenase 2 (*ALDH2*) gene polymorphism, coronary MVS, spasm after implantation of drug-eluting stents (DES), and pediatric diseases.
   (2) For diagnosis: a review of the criteria, intravascular imaging such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), and angioscopy, imaging such as computed tomography-derived fractional flow reserve (FFRCT) and magnetic resonance imaging (MRI), physiologic examinations such as coronary flow reserve (CFR), and index of microcirculatory resistance (IMR), and endothelial function tests.
   (3) For treatment: pharmacotherapy, nonpharmacotherapy, and cardiovascular rehabilitation.
3. The diagnostic criteria for diffuse coronary spasm as well as focal coronary spasm during coronary angiography (CAG) are added.
4. The diagrams are designed to help the reader understand the relationship among epicardial coronary spasm, coronary MVS and MVA related to CMD (**Figures 4**,**5**).

Table 1. Classes of Recommendation

Class I	There is evidence and/or general agreement that a given procedure or treatment is effective and/or useful
Class IIa	There is a high probability of efficacy/usefulness based on evidence and opinion
Class IIb	Effectiveness/usefulness is not well established based on evidence and opinion
Class III (No benefit)	There is evidence and/or general agreement that the procedure or treatment is not effective and/or useful
Class III (Harm)	There is evidence and/or general agreement that the procedure or treatment is harmful

Table 2. Levels of Evidence

Level A	Demonstrated by multiple randomized clinical trials and/or meta-analyses
Level B	Demonstrated by a single randomized clinical trial or large nonrandomized studies
Level C	Consensus from expert opinion and/or small clinical trials (including retrospective studies and case series)

Classes of Recommendation and Levels of Evidence

In this focused update, recommendations and levels of evidence are classified in accordance with the updated JCS statement, encompassing the estimated benefit in proportion to risk (**Tables 1**,**2**).

This focused update version was developed with the participation of 8 academic societies: The Japanese Circulation Society, Japanese College of Cardiology, Japanese Association of Cardiovascular Intervention and Therapeutics, Japanese Society of Pediatric Cardiology and Cardiac Surgery, Japanese Heart Rhythm Society, The Japanese Association of Cardiac Rehabilitation, The Japanese Coronary Association, and Japanese Association of Cardioangioscopy. Please note that the basic information is as in the 2013 revised edition, and that this is a focused update.

I. New Disease Concepts Related to Coronary Spasm

1. MINOCA

1.1 Pathophysiology of MINOCA

Cases of acute myocardial infarction (AMI) without acute coronary occlusion or obstructive CAD have been reported,[19,20] and in 2012, the term "MINOCA" was proposed to describe AMI without significant fixed stenosis (≥50%) in the epicardial coronary arteries on CAG.[4] It became widely accepted, together with the technical innovation of medical treatment for myocardial infarction (MI) with CAD (MI-CAD). The establishment of a measurement system for highly sensitive myocardial troponin, capable of detecting even minute myocardial injury, the proposal of a Universal Definition of AMI based on myocardial troponin variation,[21] the availability of routine emergency CAG for AMI and the widespread use of reperfusion therapy for ST-elevation MI have improved the prognosis of AMI patients. On the other hand, there are a certain number of cases of MI "without obstructive coronary arteries", and cardiologists have faced more than a few cases of difficulty in diagnosing and treating them, and the challenging problem has become apparent.

The Fourth Universal Definition of Myocardial Infarction clearly stated that MI, which is based on acute myocardial ischemia such as atherosclerosis, thrombosis, or imbalance between oxygen demand and supply, is distinguished from myocardial injury, although both present an elevation of myocardial troponin above the 99th percentile of healthy individuals.[21] Therefore, in diagnosing MINOCA, it is necessary to exclude myocardial injury of noncardiac

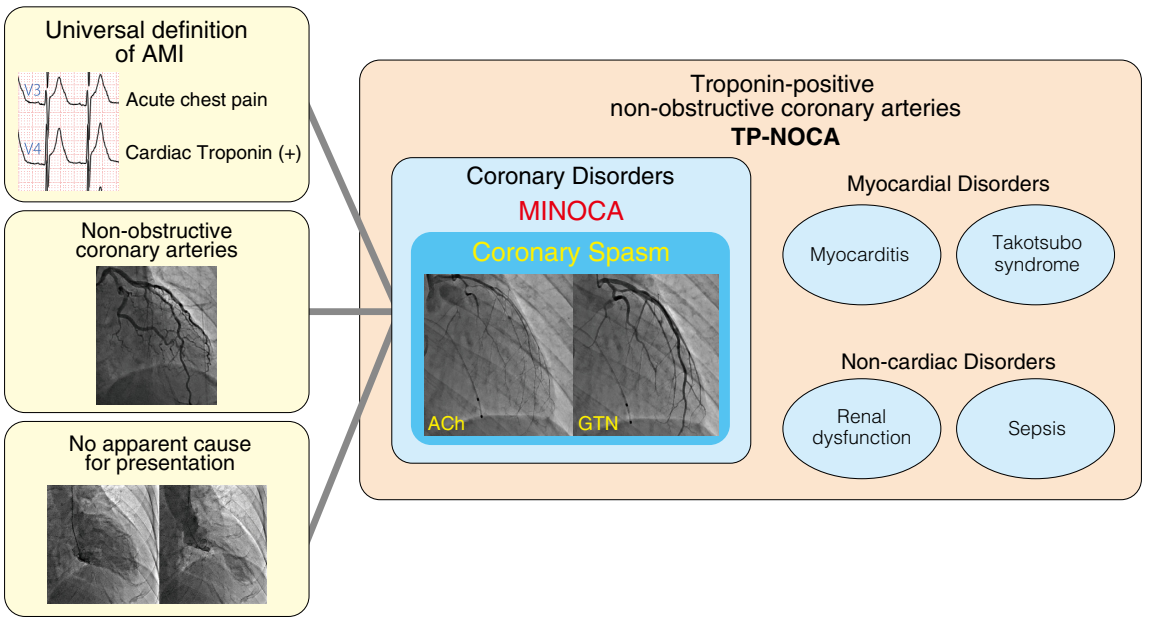


Figure 1. Relationship between TP-NOCA and MINOCA. ACh, acetylcholine; AMI, acute myocardial infarction; GTN, glyceryl trinitrate; MINOCA, myocardial infarction with non-obstructive coronary arteries; TP-NOCA, troponin-positive non-obstructive coronary arteries.

cause (e.g., sepsis or renal dysfunction) or myocardial injury from cardiac causes other than CAD (e.g., myocarditis or cardiomyopathy) that present similar symptoms to ACS. However, because MINOCA is a "working diagnosis", tentatively diagnosed by the absence of significant stenosis at the time of CAG,[22–24] it is not always practical to exclude all myocardial injury due to nonischemic causes at the time of performing CAG. Thus, attention should be paid to whether MINOCA is being used as a "working diagnosis" or a final diagnosis. To avoid confusion, the term "troponin-positive non-obstructive coronary arteries" (TP-NOCA) has been proposed as a term for conditions presenting with elevated myocardial troponin, including myocardial injury of cardiac or noncardiac cause[25] (**Figure 1**). Importantly, MINOCA is considered as a "working diagnosis" at the time of CAG, as in the differential diagnosis of the cause of heart failure (HF), and differential diagnosis of the causes should be performed by using various modalities, as described in **Chapter I.1.3**.

Potential causes of MINOCA are shown in **Figure 2**.[22,25] Main causes due to CAD include plaque rupture/erosion, coronary artery spasm, CMD, coronary MVS, coronary artery dissection, and coronary artery embolism.[22,24–26] Main causes due to non-CAD include myocarditis, takotsubo syndrome, cardiomyopathy, congenital coagulation abnormalities, pulmonary thromboembolism, and sepsis. Initially, MINOCA is a "working diagnosis", then non-coronary causes and differentiation of causes due to CAD, such as coronary spasm, are excluded. However, in daily practice, these might not be clearly distinguished and overlap with some other pathological conditions.[27] The etiology of coronary embolism, one of the causes of MINOCA, is mainly atrial fibrillation (AF), but septic emboli due to infective endocarditis or paradoxical embolism due to deep vein thrombosis may also occur.[26] The possibility of concurrent non-CAD should be considered. In addition, it has been reported that in some cases are coronary spasm induced by pharmacological provocation testing in patients presenting with transient left ventricular dysfunction such as takotsubo syndrome.[28,29] Therefore, in the clinical practice for MINOCA management, cardiologists and physicians should scrutinize for overlapping single or multiple etiologies and consider treatment according to the etiology.

1.1.1 Involvement of Coronary Spasm in MINOCA

Coronary spasm involves hypercontraction based on a hyperactivity of the Rho-kinase pathway in vascular smooth muscle cells (VSMCs),[30] endothelial dysfunction due to decreased production of nitric oxide (NO) by the vascular endothelium,[31] inflammation of the vascular adventitia and perivascular adipose tissue,[32] and increases in localized contraction of coronary arteries, resulting in decreased coronary blood flow and subsequent myocardial ischemia. Coronary spasm also leads to increases in coagulation,[33] decreases in fibrinolytic activity,[34] and promotion of platelet activation and release of adhesion molecules,[35] resulting in a thrombogenic state. A previous study using intravascular imaging investigated thrombus formation due to coronary spasm; the researchers observed the site of coronary spasm with OCT and found thrombus in 28% of coronary spasm sites or their proximal lesion, and plaque erosion with thrombus in 26%.[36] Another prospective observational study comparing OCT findings in vessels responsible for ACS due to coronary spasm and coronary spastic angina (CSA) reported that coronary spasm-induced ACS had more frequency of plaque erosion (69% vs. 27%),

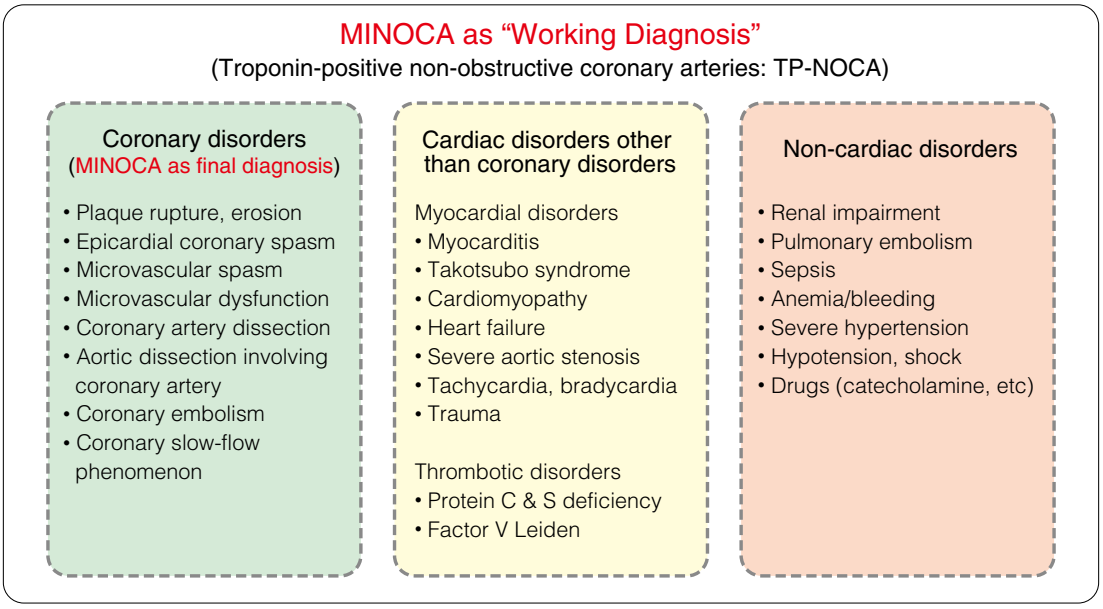


Figure 2. Plausible causes of MINOCA. MINOCA, myocardial infarction with non-obstructive coronary arteries; TP-NOCA, troponin-positive non-obstructive coronary arteries. (Adapted from Pasupathy S, et al. 2016,[22] 2017.[25])

intimal tears (46% vs. 7%), and thrombus formation (28% vs. 5%) than CSA.[37] Based on these OCT studies and autopsy studies,[38] it is assumed that one of the mechanisms of vulnerable plaque rupture in ACS might be rupture of the fibrous capsule at the plaque surface and the protrusion of plaque contents into the vessel due to mechanical stress caused by coronary spasm, resulting in thrombus formation. In spontaneous coronary artery dissection (SCAD), another cause of MINOCA, the involvement of coronary spasm in the pathogenesis of coronary artery dissection has been reported.[39,40] On the other hand, a retrospective study comparing 10 patients with SCAD with a control group after performing an acetylcholine (ACh) provocation testing and measurement of CFR showed no involvement of coronary spasm or CMD in coronary artery dissection.[41] The association between coronary artery dissection and coronary spasm in MINOCA should be investigated in future large, prospective studies. Another single-center prospective observational study investigating the association between myocardial bridging, coronary spasm, and MINOCA reported that ACh-induced coronary spasm was a high risk for MINOCA in patients with myocardial bridge,[42] but not in patients without it, suggesting that myocardial bridge may be a cause of MINOCA and that coronary spasm may be involved in the pathogenesis of MINOCA due to myocardial bridge.

1.2 Epidemiology of MINOCA

We summarized previous reports from Japan and abroad regarding the epidemiology of coronary spasm and MINOCA[43–53] (**Table 3**). The frequency of MINOCA in AMI ranged from approximately 3.5% to 11.1%, with no significant differences between reports, and the frequency of coronary spasm in MINOCA ranged from 3.7% to 72.6%, with a wide variation between reports. Because the frequency of provoked coronary spasm after AMI has been reported to be higher in Asians, including Japanese, than in Caucasians,[8,54] racial differences may be a factor in the difference in the frequency of coronary spasm. On the other hand, the ACOVA study[55] and an international study of Japanese and German patients reported that the frequency of ACh-induced coronary spasm was also high in Westerners.[56] Thus, there is a common understanding that there are no racial differences in the frequency of coronary spasm. The ESC and the American Heart Association have issued recommendations regarding the diagnostic protocol for MINOCA.[23,24] The COVADIS group in which Japan participates, has proposed standardization of diagnostic criteria for CSA.[9] To clarify the epidemiology of coronary spasm and MINOCA, universal diagnostic criteria and protocols should be established not only in Japan but also worldwide.

Previous reports show that MINOCA patients are younger, female, and have fewer coronary risk factors such as dyslipidemia, diabetes, hypertension, and a history of smoking, and more frequency of Killip class I/II compared withMI-CAD.[43,44,48–52] In addition, they report that MINOCA has more frequency of a history of HF, AF and systemic comorbidity such as chronic lung disease, cerebrovascular disease, peripheral arterial disease, chronic liver disease, renal disease, and hemodialysis.[44,48,49,51] Two reports investigating racial differences found that black patients were observed more frequently in MINOCA cases compared with MI-CAD.[44,50] Although, as environmental factors, air pollutants such as fine particulate matter PM2.5 and Asian dust are known to be a risk factor for MI-CAD or death due to ischemic heart disease (IHD),[57–59] short-term exposure to air pollutants has also been reported to be a risk factor in MINOCA.[60,61] In addition, smoking

Table 3. Frequency and Prognosis of Coronary Spasm in MINOCA

Authors	Year of publication	Study design	Frequency of MINOCA	Frequency of coronary spasm	Comparison of in-hospital mortality rate between MINOCA and MI-CAD	Comparison of long-term mortality rate between MINOCA and MI-CAD
Pasupathy S et al[43]	2015	Systematic review Meta-analysis	6% (95% CI: 5–7%)	28%	MINOCA: 1.1% (95% CI: −0.1–2.2%) MI-CAD: 3.2% (95% CI: 1.8–4.6%)	All-cause mortality at 12 months MINOCA: 3.5% (95% CI: 2.2–4.7%) MI-CAD: 6.7% (95% CI: 4.3–9.0%)
Smilowitz NR et al[44]	2017	Multicenter Observational Study: ACTION Registry-GWTG	5.9%	–	MINOCA: 1.1% MI-CAD: 2.9%	–
Lindahl B et al[45]	2017	Multicenter observational study: SWEDEHEART Registry	8.0%	–	–	–
Montone RA et al[46]	2018	Single-center observational study	–	30%	–	–
Safdar B et al[47]	2018	Multicenter observational study: VIRGO Study	11.1%	3.7%	–	–
Choo EH et al[48]	2019	Multicenter observational study: KAMIR-NIH Registry	3.5%	24%	MINOCA: 2.8% MI-CAD: 3.5%	All-cause mortality at 24 months MINOCA: 9.1% MI-CAD: 8.8%
Eggers KM et al[49]	2019	Multicenter observational study: TOTAL-AMI Study	9.5%	–	–	All-cause mortality (median follow-up 3.8 years) MINOCA: 12.1% MI-CAD: 14.9%
Dreyer RP et al[50]	2020	Multicenter observational study: National Cardiovascular Data Registry CathPCI Registry	5.9%	–	MINOCA: 2.1% MI-CAD: 4.1%	All-cause mortality at 12 months MINOCA: 12.3% MI-CAD: 16.7%
Ishii M et al[51]	2020	Multicenter observational study: JROAD-DPC database	9.5% (10.2% for working diagnosis)	11.7%	MINOCA: 6.4% MI-CAD: 6.2%	–
Pasupathy S et al[52]	2021	Systematic review Meta-analysis	8.1% (95% CI: 6.3–9.9 %)	–	MINOCA: 0.7% (95% CI: 0.3–1.2%) MI-CAD: 2.2% (95% CI: 1.3–3.1%)	All-cause mortality at 12 months MINOCA: 3.3% (95% CI: 2.5–4.1%) MI-CAD: 5.6% (95% CI: 4.1–7.0%)
Sueda S et al[53]	2021	Single-center observational study	6.3%	72.6%	–	–

MI-CAD, myocardial infarction with coronary artery disease; MINOCA, myocardial infarction with non-obstructive coronary arteries.

is a coronary risk factor and widely recognized as a risk factor for coronary spasm.[62,63] A single-center, retrospective observational study in Japan reported that patients with MINOCA due to coronary spasm had 91% prevalence of smoking history.[53] As for genetic factors, a significant association between Glu298Asp mutation, one of the polymorphisms of the endothelial nitric oxide synthase (eNOS) gene, and CSA[64] has been reported, and an association between this gene polymorphism and AMI has been also reported.[65,66] In addition, an association between genetic polymorphisms of ALDH2, a member of the ALDH superfamily, and coronary angina[67] and high creatinine kinase levels in patients with ST-elevation MI[68] has been reported. Based on these findings, gene polymorphisms may be involved in pathogenesis of MINOCA due to coronary spasm. Further studies are needed to confirm the mechanistic role of gene polymorphism in MINOCA.

The short- and long-term prognoses for MINOCA compared with MI-CAD are summarized in **Table 3**. In a meta-analysis reported in 2015,[43] the in-hospital mortality rate for MINOCA was 1.1% and 3.2% for MI-CAD, indicating a better in-hospital outcome for MINOCA (odds ratio [OR]: 0.37, 95% confidence interval [CI]: 0.2–0.67). At 12 months, the mortality rate for MINOCA was 3.5% and 6.7% for MI-CAD and MINOCA was also significantly associated with a lower risk for all-cause death at 12 months, compared with MI-CAD (OR: 0.59, 95% CI: 0.41–0.83). In a meta-analysis reported in 2021,[52] the in-hospital mortality rate for MINOCA was 0.7% and 2.2% for MI-CAD, indicating that MINOCA had a favorable in-hospital prognosis. At 12 months, the mortality rate for MINOCA was 3.3% and 5.6% for MI-CAD, with a significantly lower OR for in-hospital death of MINOCA (OR: 0.60, 95% CI: 0.5–0.7). The OR for cardiovascular death and re-infarction at 12 months was also significantly lower for MINOCA than for MI-CAD (OR: 0.40, 95% CI: 0.2–0.7; OR: 0.48, 95% CI: 0.3–0.9), but not for worsening HF (OR: 0.71, 95% CI: 0.4–1.4).

Although there are many reports showing better prognosis of MINOCA,[44,49,50,69] there are also reports showing

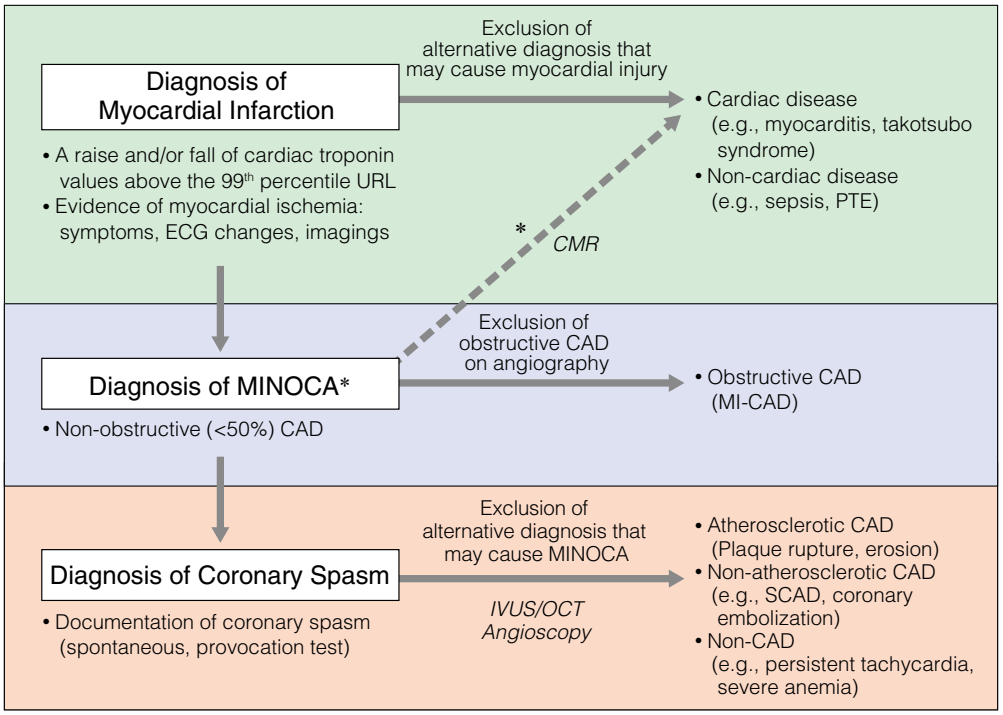


Figure 3. Flow chart for diagnosis of coronary spasm in patients with MINOCA. *, If final diagnosis of MI has not been obtained yet, alternative disorders that may cause myocardial injury should be excluded under working diagnosis (TP-NOCA). Italics indicates diagnostic modalities that are useful for differential diagnosis. CMR, cardiovascular magnetic resonance; IVUS, intravascular ultrasound; CAD, coronary artery disease; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; OCT, optical coherence tomography; PTE, pulmonary thromboembolism; SCAD, spontaneous coronary artery dissection; TP-NOCA, troponin-positive non-obstructive coronary arteries; URL, upper reference limit.

almost no difference in prognosis[48] or poor prognosis of MINOCA.[51] Further epidemiological studies are needed to clarify the prognosis of MINOCA. In addition, although predictors of in-hospital death for MINOCA are common to those for MI-CAD, cardiogenic shock and ST-segment elevation on ECG were more strongly associated with in-hospital death in MINOCA than in MI-CAD.[44] On the other hand, coronary spasm is not a significant predictor of in-hospital death,[48] but rather a lower risk.[51] It has been reported that poor long-term prognostic factors in MINOCA are age, male sex, atypical chest symptoms, smoking history, cardiogenic shock, diabetes, HF, prior stroke, peripheral artery disease, cancer, chronic lung disease, AF, and chronic kidney disease.[48,49] Angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs) and statins have been reported to reduce the risk of all-cause death and major cardiovascular events,[45,48] and subgroup analyses showed an interaction between age and ACE inhibitors/ARBs, with a decreased risk of major cardiovascular events in MINOCA patients aged 70 years and older (<70 years: hazard ratio [HR]: 0.96, 95% CI: 0.80–1.15, ≥70 years: HR: 0.74, 95% CI: 0.63-0.87).[45]

1.3 Diagnosis

The diagnosis of coronary spasm in MINOCA consists of (1) the diagnosis of MINOCA and (2) of coronary spasm as the cause of MINOCA (**Figure 3**).

1.3.1 Diagnosis of MINOCA

MINOCA is MI without evidence of occlusive coronary artery lesions, and its diagnosis consists of a diagnosis of MI and evidence of non-obstructive coronary arteries.

The universal definition of MI was proposed by a joint task force of European and USA societies and the current 4th edition was published in 2018.[21] The universal definition defines MI as the presence of acute myocardial injury detected by myocardial biomarkers on the basis of acute myocardial ischemia. Myocardial troponin is a myofibrillar protein that is expressed almost exclusively in the myocardium and is released into the blood upon myocardial injury. Myocardial troponin includes myocardial troponin T and myocardial troponin I, both of which have extremely high sensitivity and specificity compared with conventional myocardial biomarkers such as creatine kinase (CK) and CK-MB, and elevated myocardial troponin levels indicate the presence of myocardial injury. Myocardial troponin can be analyzed by multiple methods, and myocardial injury is defined as an increase in myocardial troponin levels above the 99th percentile of the upper reference limit in each assay. Acute myocardial injury is judged as a raise and a subsequent fall, or either of them. An elevated myocardial troponin level suggests myocardial injury, but does not reflect the cause of myocardial injury. The diagnosis of MI therefore requires evidence of myocardial

Table 4. Recommendations and Levels of Evidence for Coronary Spasm Provocation Test During Acute Coronary Angiography in MINOCA

	COR	LOE
Coronary spasm provocation test may be considered in the acute setting for patients in whom alternative conditions, such as plaque disruption and SCAD, have been definitely ruled out, under conditions in which adequate safety considerations have been taken into account[46,71,72]	IIb	C
Coronary spasm provocation test is not recommended in patients with documented attacks, such as spontaneous or nitroglycerin-induced remission of ST-segment elevation on ECG or occlusive or severely stenotic lesions on coronary angiography	III (No benefit)	C
Coronary spasm provocation test should not be performed in the acute phase in patients in whom drug-induced coronary spasm is expected to cause severe complications (e.g., patients with severely depressed cardiac function, congestive heart failure, etc.)	III (Harm)	C

COR, Class of Recommendation; LOE, Level of Evidence; MINOCA, myocardial infarction with non-obstructive coronary arteries; SCAD, spontaneous coronary artery dissection.

ischemia as indicated by symptoms suggestive of ischemia, ECG changes, loss of new viable myocardium, or abnormal wall motion, in addition to a rise and/or fall in myocardial troponin. The diagnosis of MINOCA requires careful evaluation of the CAG findings by reviewing the images to ensure that side-branch occlusions are not overlooked.[23,24]

If the cause of elevated troponin cannot be identified as MINOCA at the time of emergency CAG, other causative diseases should be excluded under the working diagnosis of TP-NOCA.[25] Diseases to be differentiated include those of cardiac origin, such as acute myocarditis and takotsubo syndrome, and those of noncardiac origin, such as sepsis and acute pulmonary thromboembolism. The distinction between acute myocardial injury from CAD and that of nonischemic origin is determined by comprehensive evaluation of medical history and imaging, among which cardiovascular magnetic resonance (CMR) images are particularly useful.[70] In patients with MI, late gadolinium enhancement (LGE) is present in the subendocardial or transmural area that corresponds to the coronary artery territory, whereas the CMR patterns observed in myocardial injury due to nonischemic causes such as myocarditis, often include intramyocardial or subepicardial LGE. T2-weighted images show a similar distribution pattern of the high signals suggestive of myocardial edema, even in the absence of LGE.

1.3.2 Diagnosis of Coronary Spasm as the Cause of MINOCA

MINOCA is classified according to its underlying pathophysiological mechanisms into type 1 MI caused by atherosclerotic plaque disruption, or type 2 MI caused by a mismatch between oxygen supply and demand.[21] The oxygen demand/supply mismatch can be divided into increased demand, such as sustained tachycardia or severely elevated blood pressure, and decreased supply. Decreased oxygen supply can be caused by coronary artery abnormalities such as coronary spasm, SCAD and coronary artery embolism, or non-CAD such as persistent bradycardia and high levels of anemia. The diagnosis of coronary spasm requires first ruling out other conditions that may cause MINOCA.

Plaque disruption may be seen on CAG as wall irregularities or haziness, but often requires evaluation with intravascular imaging modalities such as OCT. For patients with the findings of plaque disruption or intracoronary thrombus, antiplatelet therapy should be prescribed. However, the presence of these findings alone does not rule out the involvement of coronary spasm as the cause of MINOCA, because such findings are often seen in patients with VSA. SCAD is more common in women younger than 50 years of age. Intravascular imaging is also useful in the diagnosis of SCAD as the presence of a false lumen within the coronary artery wall. Coronary artery embolism is seen as an abrupt interruption of the coronary artery on CAG. It often occurs as systemic embolism based on AF, cardiomyopathy, or valvular disease, but may be a distal embolization of a mural thrombus in the coronary artery as it dissolves.

Although some patients with MINOCA caused by coronary spasm may already have a previous diagnosis of VSA, or a history of symptoms suggestive of VSA, MINOCA is often the first presentation. Diagnosis of coronary spasm is made according to the diagnostic criteria of this guideline (see **Chapter III.1**, **III.2**), but spontaneous attacks are rarely captured, requiring a coronary spasm provocation test in most cases. Regarding the timing of the coronary spasm provocation test, performing it during emergency CAG for ACS has been considered dangerous and was classified as Class III in the 2013 revised JCS guidelines, which recommended coronary spasm provocation test after stabilization.[2] The COVADIS group, published their international standardization of the diagnosis of VSA in 2017, which similarly contraindicated coronary spasm provocation test in emergency situations.[9] On the other hand, as the importance of MINOCA in ACS became increasingly recognized, studies of the safety and utility of coronary spasm provocation test during acute CAG began to be reported. In a study of 80 patients diagnosed with MINOCA who underwent immediate CAG followed by coronary spasm provocation test with ACh or ergonovine, 37 patients were diagnosed as having coronary spasm with no complications from the emergency coronary spasm provocation test.[46] Patients with a positive coronary spasm provocation test are more likely to die or be rehospitalized for ACS after hospital discharge, suggesting the coronary spasm provocation test is useful for identifying high-risk patients. In a study comparing 84 patients who underwent coronary spasm provocation test with ACh at the time of emergency CAG with 445 patients who underwent the provocation test at the time of non-emergency CAG, the rate of serious complications was similar in both groups (1.2% vs. 1.3%, P=1.00), with no deaths.[71] In a study comparing 80 patients who underwent coronary spasm provocation test with ACh following diagnostic CAG for MINOCA and 100 patients with INOCA, there were no irreversible complications, suggesting that the coronary spasm provocation test in the

acute phase of MINOCA can be performed as safely as with INOCA.[72] In light of these results, the coronary spasm provocation test may be considered for patients with MINOCA even during acute CAG under conditions in which other diseases such as plaque disruption and SCAD have been definitely excluded and adequate safety precautions are taken (**Table 4**). On the other hand, for patients in whom the diagnosis of coronary spasm has already been made with documentation of spontaneous attacks, such as spontaneous or nitroglycerin-induced remission of ST-segment elevation on ECG or remission of occlusion or severe stenosis on CAG, performing the coronary spasm provocation test during acute CAG has no benefit. In addition, the coronary spasm provocation test should not be performed during acute CAG for patients in whom drug-induced coronary spasm may cause severe complications, such as severely depressed cardiac function or congestive HF.

Coronary MVS can also produce MINOCA, but caution should be paid in assessing CMD in MINOCA because it can also occur as a result of myocardial ischemia/infarction.[73]

2. INOCA

2.1 Emerging Concept and Universal Definition of INOCA

Approximately half of patients undergoing CAG for suspected angina pectoris due to typical anginal pain, angina-equivalent symptoms, or noninvasive stress test results suggestive of myocardial ischemia do not have significant (≥50%) organic stenosis in the epicardial coronary arteries.[74–83] Coronary vasomotion abnormalities such as coronary vasospasm and CMD have been shown to be more prevalent than previously thought in these patients of both sexes, with a predominance of women, associated with worse clinical outcomes,[79,84–95] decreased quality of life (QOL),[96] and increased medical cost due to hospitalization for unstable angina pectoris and repeat CAG.[97–100] In 2017, the concept of ischemia with non-obstructive CAD (i.e., INOCA) was proposed as a chronic syndrome with symptoms, signs, and objective findings suggestive of myocardial ischemia but without significant organic stenosis in the epicardial coronary arteries.[3] Subsequently in 2020, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) published the first expert consensus document on INOCA, which proposed the universal definition, diagnosis, and management of INOCA and recommends performing interventional diagnostic procedure (IDP) or invasive functional CAG (FCA) including coronary vasospasm provocation testing in order to identify the endotype of INOCA.[101] The consensus document published in the UK in 2022 also recommends endotyping of INOCA by IDP or FCA and providing individualized treatment based on the cause of INOCA.[102]

2.2 Definition of INOCA

INOCA is defined as (1) stable, chronic (> several weeks) chest symptoms (typical angina) or atypical symptoms (angina equivalent), (2) objective findings of myocardial ischemia detected by ECG, echocardiography, CMR imaging, or nuclear medicine imaging, and increased myocardial lactate production during coronary vasospasm provocation testing,[103–110] and (3) no flow-limiting stenosis as defined by ≥50% organic stenosis (obstructive CAD) or a fractional flow reserve (FFR) ≤0.80 on CAG or CCTA.[3,101] Although INOCA is by definition assumed to be symptomatic as mentioned above, the initial evaluation

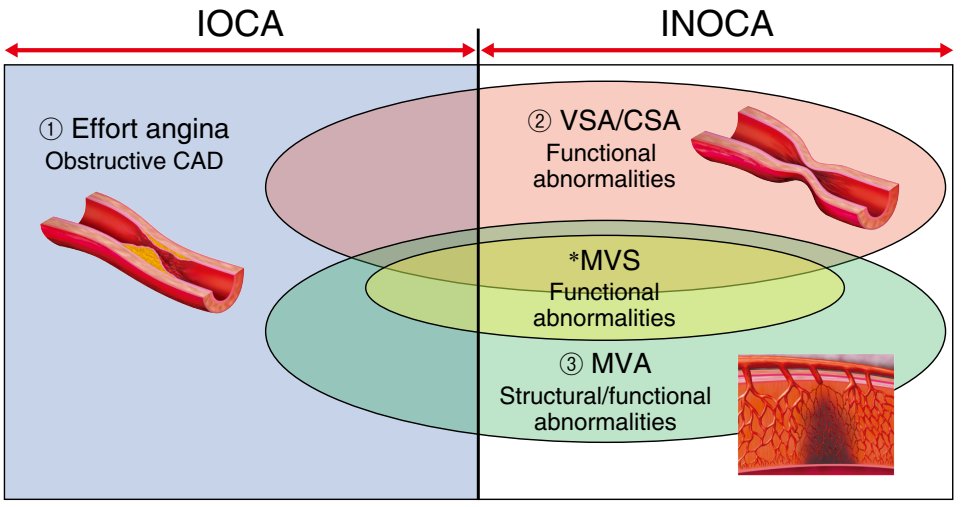


Figure 4. Major mechanisms of myocardial ischemia in chronic coronary syndromes. The major culprit of myocardial ischemia in the absence of obstructive coronary artery disease (CAD) in INOCA includes epicardial coronary vasospasm and coronary microvascular dysfunction, which are manifested as vasospastic angina and microvascular angina (MVA), respectively. Although the mechanisms (①, ②, ③, and *) often overlap and coexist in various combinations even in a subclinical manner, INOCA is assumed to be symptomatic and excludes obstructive CAD by definition. CSA, coronary spastic angina; INOCA, ischemia with non-obstructive CAD; IOCA, ischemia with obstructive CAD; MVS, microvascular spasm; VSA, vasospastic angina.

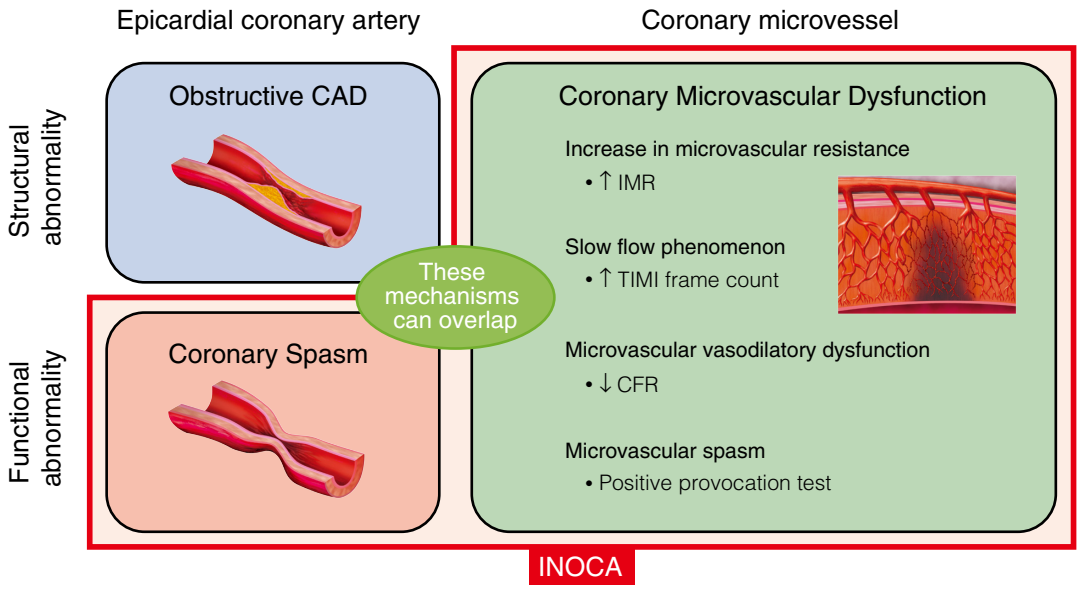


Figure 5. Ischemic mechanisms. Ischemic mechanisms can be divided into functional or structural abnormalities of epicardial coronary arteries or coronary microvessels. CAD, coronary artery disease; CFR, coronary flow reserve; IMR, Index of microcirculatory resistance.

should rule out noncardiogenic and nonischemic conditions that may produce angina-like symptoms.[101]

2.3 Pathogenesis and Epidemiology of INOCA

2.3.1 Mechanisms of Myocardial Ischemia

The 2 major mechanisms of myocardial ischemia in INOCA are coronary vasospasm and CMD, both of which can cause myocardial ischemia due to an imbalance between myocardial oxygen demand and supply, either alone or in combination with varying degrees of CAD (**Figure 4**). The ESC guidelines for chronic coronary syndrome[s] (CCS) published in 2019 classify patients with angina pectoris associated with coronary vasospasm or CMD, which corresponds to INOCA, as CCS V, one of the most frequently encountered 6 clinical scenarios of CCS.[6] As shown in **Figure 5**, ischemic mechanisms can be divided into functional or structural abnormalities of epicardial coronary arteries or coronary microvessels. Coronary vasospasm can cause myocardial ischemia by transient hypercontraction of the epicardial coronary arteries or coronary microvessels (i.e., supply ischemia/primary angina) (**Figure 5**).[111] On the other hand, impaired metabolic vasodilatation of coronary microvessels due to functional or structural abnormalities as represented by decreased CFR or by increased IMR can cause myocardial ischemia when myocardial oxygen consumption is increased (i.e., demand ischemia/secondary angina), similar to effort angina pectoris in the presence of obstructive CAD (**Figure 5**). Although these mechanisms can contribute to myocardial ischemia in combination with obstructive CAD, it should be noted that patients with obstructive CAD are not included in the definition of INOCA (**Figure 4**).[101]

2.3.2 Coronary Vasospasm in INOCA

A growing body of evidence has shown the importance of endotyping/phenotyping of coronary vasospasm.[42,106,112–116] A large retrospective study from Japan (n=1,877) showed that focal coronary vasospasm was associated with more major cardiovascular events than diffuse coronary vasospasm during a mean follow-up period of 49 months.[106] A report from a large multicenter prospective Korean registry (n=2,960) also showed that focal coronary vasospasm was associated with worse clinical outcomes than diffuse coronary vasospasm during a median follow-up period of 30 months.[116] Furthermore, a study from Japan enrolling patients with INOCA who underwent coronary vasospasm provocation testing and optical frequency domain imaging (n=329) showed that focal coronary vasospasm was associated with the highest incidence of major cardiovascular events during a median follow-up period of 3 years in association with intraplaque neovascularization.[112] Patients with diffuse coronary vasospasm showed an intermediate prognosis, associated with increased vasa vasorum.[112] These findings suggest that the combined assessment of function and morphology may be useful for prognostic stratification of patients with INOCA.[112]

2.3.3 CMD in INOCA

CMD has been attracting much attention in recent years because of its association with various cardiovascular diseases as well as its important role in the mechanisms of myocardial ischemia in INOCA.[80,84,88,93,117–130] The mechanisms of CMD are multifactorial and result from functional or structural abnormalities of the coronary microvessels, including (1) increased vasoconstriction (e.g., coronary MVS), (2) impaired endothelium-dependent or -independent coronary vasodilator capacities (e.g., endothelial or vascular smooth muscle dysfunction), (3) structural

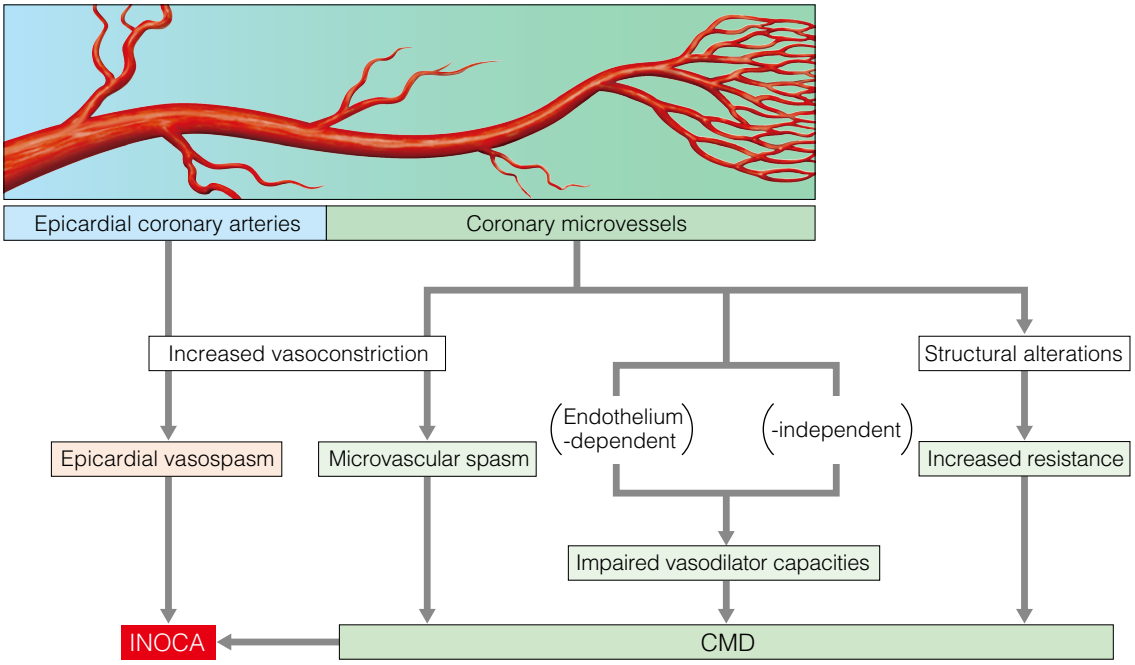


Figure 6. Coronary functional and structural abnormalities in ischemia with non-obstructive coronary artery disease (INOCA) and mechanisms of coronary microvascular dysfunction (CMD). (Adapted from Godo S, et al. 2021.[134])

alterations leading to increased coronary microvascular resistance (e.g., luminal narrowing, vascular remodeling, vascular rarefaction, and extramural compression), which may occur alone or in combination (**Figure 6**).[131–136] Angina pectoris caused by CMD is referred to as MVA, and the international diagnostic criteria of MVA were proposed in 2018.[10] The guidelines in Japan, the USA, and Europe recommend performing IDP or FCA for the diagnosis of CMD,[2,6,24] which is based on the following criteria: decreased CFR, MVS, increased IMR, and decreased coronary blood flow velocity (e.g., increased contrast delay and Thrombolysis In Myocardial Infarction [TIMI] frame counts).[2,10,137,138]

2.3.4 Overlap and Coexistence of Mechanisms in INOCA

In a recent systematic review and meta-analysis of the prevalence of coronary vasomotion abnormalities in patients with INOCA (56 studies, 14,427 patients), coronary vasospasm was present in 40%, CMD in 41%, combination of both in 23%, and MVA in 24% of the patients.[139] Women had 1.45-fold more CMD than men.[139] It is important to note that these mechanisms of INOCA and organic coronary stenosis often overlap and coexist in varying degrees in individual patients and may affect prognosis and the treatment strategy (**Figure 4**).[14,80,104,113,140–145] The EAPCI expert consensus document published in 2020 proposed classifying INOCA into 5 endotypes based on the results of coronary reactivity testing by IDP or FCA (**Table 5**).[101]

2.4 Knowledge Gaps and Perspectives

Many knowledge gaps still exist for INOCA.

Table 5. Endotypes and Ischemic Mechanisms of INOCA

Endotype	Ischemic mechanism
MVA	CMD
VSA	Epicardial coronary vasospasm
MVA + VSA	CMD + epicardial coronary vasospasm
Chest pain syndrome of non-cardiac origin	None
No flow-limiting stenosis	Diffuse, non-obstructive CAD

CAD, coronary artery disease; CMD, coronary microvascular dysfunction; INOCA, ischemia with non-obstructive CAD; MVA, microvascular angina; VSA, vasospastic angina. (Adapted from Kunadian V, et al. 2020.[101])

2.4.1 INOCA and Obstructive CAD

Although INOCA by definition does not include patients with obstructive CAD (i.e., ≥50% organic stenosis), the ESC guidelines on CCS published in 2019 state that if a coronary stenosis is not physiologically significant, as defined by FFR >0.80, it is considered as non-obstructive CAD and may warrant close examination for coronary vasomotion abnormalities.[6] Although patients with obstructive CAD are excluded from the definition of INOCA, those with INOCA may have varying degrees of coronary atherosclerosis.[112,140,146–151] Indeed, VSA and CMD combined with organic stenosis can lead to increased myocardial ischemia and worse prognosis.[14,79,91,142,146,148,149,152–154]

Table 6. Recommendations and Levels of Evidence for Various Tests in Diagnosing INOCA

	COR	LOE
In patients with angina pectoris and demonstrated myocardial ischemia but no significant stenosis of the epicardial coronary arteries, a pharmacological coronary spasm provocation test should be considered to confirm the presence of coronary microvascular spasm during coronary angiography[10]	IIa	C
In patients with angina pectoris and demonstrated myocardial ischemia but no significant stenosis in the epicardial coronary arteries, coronary flow reserve and index of microcirculatory resistance evaluation using a guide wire should be considered[3,11,90,169,170]	IIa	B
In patients with angina pectoris and demonstrated myocardial ischemia but no significant stenosis of the epicardial coronary arteries, Doppler blood flow in the left anterior descending branch by transthoracic echocardiography may be considered for coronary flow reserve assessment[183,184]	IIb	B

COR, Class of Recommendation; INOCA, ischemia with non-obstructive coronary artery disease; LOE, Level of Evidence.

2.4.2 Diagnostics of INOCA

For the diagnosis of coronary vasospasm and CMD, comprehensive evaluation of coronary artery function by invasive cardiac catheterization is recommended by the guidelines[2,6,24] and consensus documents[101,102] in Japan, the USA, and Europe, because it has been shown to be a safe[46,114,155–160] and cost-effective strategy.[161] However, there is no uniformity in the method used to evaluate coronary reactivity.[162] Specifically, it remains to be elucidated which should be evaluated first, coronary vasospasm or CMD, in a single cardiac catheterization.

2.4.3 Treatment and Management of INOCA

The Coronary MICrovascular Angina (CorMicA) trial is the only randomized controlled trial addressing the treatment and management of INOCA, using therapeutic interventions stratified by the endotype of INOCA based on the results of IDP or FCA.[11,81] Patients with VSA were treated with calcium-channel blockers (CCBs), nitrates, and nicorandil, and those with CMD with β-blockers, CCBs, and nicorandil. Although the CorMicA study showed a 27% improvement in anginal symptom scores as assessed by the Seattle Angina Questionnaire compared with controls, the study was limited to a comprehensive evaluation of coronary artery function in only 1 coronary artery, mainly the left anterior descending coronary artery, and thus further studies are needed. The efficacy of CCBs for the treatment of coronary vasospasm is well established.[2,6,24] Several randomized controlled trials addressing the treatment and management of INOCA are currently underway, including the Precision Medicine with Zibotentan in Microvascular Angina (PRIZE) study to evaluate the efficacy of an endothelin A receptor antagonist zibotentan in the treatment of MVA,[163] Coronary Microvascular Function and CT Coronary Angiogram (CorCTCA) study to evaluate endotype-specific management of INOCA based on IDP results,[164] and Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR) trial to evaluate the effect of high-intensity statins and ACE inhibitors/angiotensin II receptor blockers in women with INOCA.[165]

2.5 Diagnosis of INOCA

The endotypes of INOCA are broadly divided into VSA and MVA. Although these causes can coexist, it is important to identify the endotype in order to provide appropriate treatment.[101]

2.5.1 Diagnosis of VSA

Coronary spasms can be divided into those occurring in the epicardial coronary artery and those occurring in the coronary microvasculature, and examination methods for spasm in the epicardial coronary artery have been established as described in **Chapter III.1**. The details of coronary MVS are given in **Chapter II.3**,[10] but during pharmacological provocation test not only chest symptoms and ECG changes but also biochemical ischemia evaluation based on blood lactate levels from the coronary sinus are recorded.[166] However, the test sensitivity and specificity of ACh-induced testing for spasm in epicardial coronary arteries (VSA) have proven to be high,[167] but those for spasm in coronary microvessels are still unclear.

2.5.2 Diagnosis of MVA (Table 6)

The diagnostic criteria of MVA are (1) symptoms due to myocardial ischemia, (2) absence of significant stenotic lesions in the epicardial coronary arteries, (3) proven myocardial ischemia on other examinations, and (4) presence of CMD.[10,101] In addition to invasive evaluation of coronary microvascular function using guidewires in catheterization, noninvasive methods such as cardiac MRI, PET, and transthoracic Doppler echocardiography are also used to evaluate coronary microvascular function.

As an invasive evaluation method using a guidewire, it is currently possible in Japan to diagnose CMD by measuring the CFR and IMR using a pressure wire with a temperature sensor. Although details are given in **Chapter III.7**, optimal cutoff values for CMD diagnosis have been reported from Europe and the USA,[6,101,168] and it has been suggested that the diagnosis of CMD using an invasive evaluation method with a guidewire during catheterization may lead to improved QOL through risk stratification of cardiovascular events and therapeutic intervention.[3,11,90,169,170]

As a noninvasive assessment method, CFR can be measured by cardiac MRI[171,172] or PET.[173] In recent years, assessment of myocardial perfusion reserve by CMR[173–175] and PET[176–182] has been shown to be associated with prediction of cardiovascular events. For details on noninvasive methods of evaluating coronary microvasculature by cardiac MRI and PET, please refer to **Chapter III.5**.

The association between CFR and the risk of cardiovascular events in the left anterior descending coronary branch on transthoracic Doppler echocardiography has also been reported. Because of the limited number of reports compared with CMR and PET[183,184] and the limited measurement sites in the left anterior descending coronary

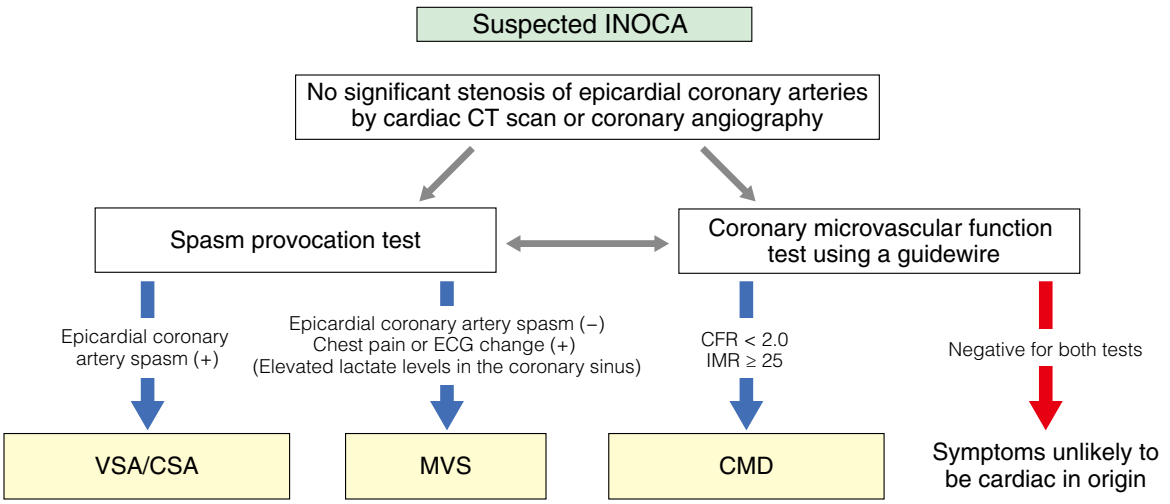


Figure 7. Procedure to reveal the endotype of INOCA by invasive assessment methods. CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CSA, coronary spastic angina; CT, computed tomography; IMR, index of microcirculatory resistance; INOCA, ischemia with non-obstructive coronary artery disease; MVS, microvascular spasm; VSA, vasospastic angina.

artery, we recommend Class IIb in this focused update in consideration of consistency with the European and USA guidelines.[6,168]

2.5.3 Revealing the INOCA Endotype by Invasive Assessment (Figure 7)

INOCA is suspected in patients with angina pectoris and documented myocardial ischemia on other examinations without significant stenotic lesions in the epicardial coronary arteries on cardiac CT scan or CAG. If CAG is performed, the endotype is subsequently clarified by pharmacological coronary spasm provocation test and evaluation of coronary microvascular function using a guidewire.

Regarding which should be performed first, the coronary spasm induction test or coronary microvascular function evaluation, it is recommended in Europe and the USA that CFR and IMR measurements be performed first, followed by ACh-induced testing as a diagnostic procedure for INOCA.[101,102] However, as described in **Chaper II.4**, the drugs used to maximally dilate resistance vessels when assessing coronary microvascular function may affect the subsequent induction of coronary spasm, so in Japan, the coronary spasm induction test is generally performed first.[142] Continued research is needed to establish more optimal diagnostic methods and procedures (**Table 6**).

3. Oncocardiology

3.1 Cancer Therapy-Induced Vascular Toxicity and VSA

Survival rates and longevity of cancer patients have improved significantly due to advances in therapy, including new molecular targeted drugs and immune checkpoint inhibitors, in addition to conventional cytotoxic anticancer drugs. However, most anticancer drugs are toxic and may cause cardiovascular diseases; various cardiovascular complications have been reported, such as hypertension, arrhythmia, HF, valvular heart disease, IHD, and vein thrombosis. Cancer therapy-induced vascular toxicity can lead to various pathological conditions in IHD: VSA as a functional abnormality; atherosclerosis as a structural abnormality; and AMI due to coronary embolism. Anticancer drug-induced cardiotoxicity can be classified into 2 types: structural and functional impairment. Vascular toxicity can also be classified into 2 types: type 1 (e.g., nilotinib, ponatinib), which causes long-term structural impairment; and type 2 (e.g., 5-fluorouracil), which is transient and often results in functional impairment.[185,186] The most common drugs that can cause VSA are 5-fluorouracil, an anticancer drug classified as an antimetabolite, and its oral prodrug, capecitabine. These drugs induce myocardial ischemia, and the frequency is 4.0–8.5% according to recent major prospective studies.[187–189] 5-Fluorouracil and capecitabine cause VSA by inducing hyperreactivity in vascular smooth muscle,[190] and direct toxicity to vascular endothelial cells.[191,192] Other anticancer drugs, such as molecular targeted drugs and immune checkpoint inhibitors, have also been reported to induce VSA.[193,194]

3.2 Evaluation and Management of Anticancer Drug-Induced VSA

The goals of treatment of VSA in cancer patients are to prevent adverse cardiac events and to continue cancer treatment. However, guidelines do not provide recommendations for the methods because there is currently a lack of evidence regarding the evaluation and treatment of chest pain in cancer patients. Previous studies have reported that 5-fluorouracil-induced VSA can be effectively controlled by discontinuing 5-fluorouracil or avoiding high doses. It has also been reported that re-administration of 5-fluorouracil is effective with pretreatment with CCBs or nitrates when treatment is once discontinued due to VSA.[195–197] Anticancer

drug-induced VSA often occurs during drug administration. Therefore, when these drugs are administered to patients with a history of anticancer drug-induced cardiovascular toxicity, it may be effective to detect myocardial ischemia and arrhythmias by 12-lead ECG before and after administration and ECG monitoring during and after administration. Further evidence is needed for screening, risk assessment, and treatment of cancer therapy-induced VSA.

II. New Insights Into Pathogenesis

1. Genetic Factors Pathogenesis

Because coronary artery disease often appears in families and some cases occur even in patients with no lifestyle-related problems, the involvement of "genetic factors" has been suggested. In recent years, many genes involved in the pathogenesis of coronary spasm have been cloned, and the 2013 Guidelines for the diagnosis and treatment of patients with VSA[2] describe the relationship between coronary spasm and genetic polymorphisms. More recently, mutation in the -786T/C eNOS gene, female sex, and diabetes mellitus have been shown to correlate with ACh-provoked myocardial ischemia in patients with coronary spasm.[107]

The elucidation of genetic factors of diseases may contribute to primary prevention through tailor-made medicine based on individual genetic information.

2. ALDH2 Polymorphism and Alcohol Metabolism

Coronary spasm attacks are more common during the post-drinking sobering-up period, depending on the individual. Drinking alcohol is a risk factor for coronary spasms, and one of the mechanisms of alcohol's toxic effects is that it increases urinary excretion of Mg, resulting in Mg deficiency in tissues.[198,199]

Acetaldehyde, which is synthesized during the metabolism of ethanol, has been associated with cancers of the oral cavity, pharynx, and esophagus, as well as colon, liver, and breast cancer,[200] and in the cardiovascular system, it is particularly associated with coronary spasm.[67,201]

ALDH2 protein contributes to the oxidation and detoxification of acetaldehyde, a metabolite of ethanol, in various tissues and cells, but mainly in the human liver.[202–205] Furthermore, *ALDH2* gene polymorphism causes individual differences in the time course of acetaldehyde levels during alcohol metabolism.

In a genome-wide association study of Japanese cardiovascular disease cases, a locus (rs671) exhibiting a defective *ALDH2* genotype (*ALDH2*2*) was identified as a strong predictor.[206] An association between *ALDH2*2* and CAD and MI has also been reported in an East Asian meta-analysis.[207] *ALDH2*2* is common in East Asians (30–50%) and rare in other populations, and is associated with alcohol flushing syndrome, which is characterized by facial flushing, nausea, palpitations, sleepiness, and headache after drinking alcohol.[205] On the other hand, because CSA is associated with alcohol flushing syndrome and positive ethanol patch test responses,[208] a case–control study was conducted and revealed a significant relationship between *ALDH2*2* and CSA. Together with other genetic factors, *ALDH2*2* is also an important factor in coronary spasm.[67] If CSA is suspected, the presence or absence of alcohol flushing or the results of an ethanol patch test can be helpful during the medical history interview, even if genetic testing is not available.

Furthermore, when *ALDH2*2* is combined with smoking, the risk of coronary spasm is synergistically amplified.[209] In addition, *ALDH2*2* is common found in MI cases in Japan, and the involvement of coronary spasm is a factor.[68]

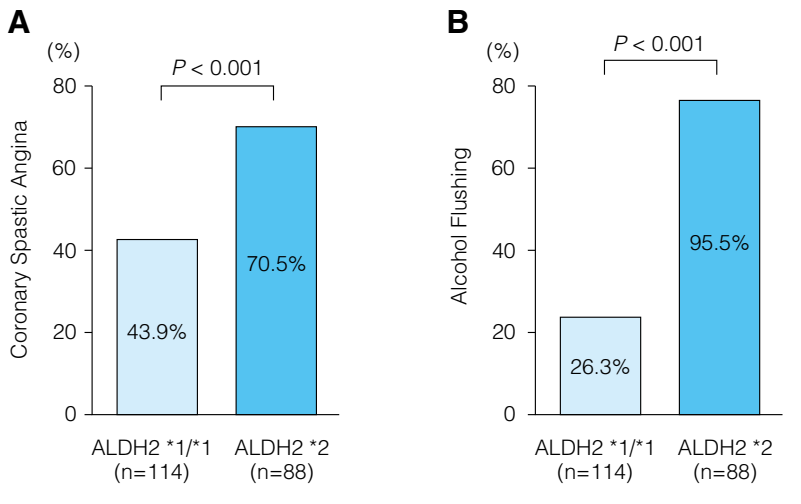


Figure 8. Frequency of coronary spastic angina and alcohol flushing syndrome according to ALDH2 genotype. Both coronary spastic angina (**A**) and alcohol flushing (**B**) are significantly more frequent in the mutant genotype ALDH2 *2 group than in the wild-type genotype ALDH2 *1 / *1 group. ALDH2, aldehyde dehydrogenase 2. (Adapted from Mizuno Y, et al. 2015.[67]) https://www.ahajournals.org/journal/circ © 2015 American Heart Association Inc.

Table 7. Clinical Classification of CMD Based on Clinical Scenarios

Group	Clinical presentation	Syndrome	Major pathogenic mechanisms
Type 1 CMD without obstructive coronary artery disease or myocardial disease	Angina pectoris equivalent	INOCA MINOCA Takotsubo syndrome Post-PCI/CABG	Vascular smooth muscle dysfunction Vascular remodeling Vascular endothelial dysfunction
Type 2 CMD in patients with cardiomyopathy or valvular disease	Dyspnea Exercise intolerance	Diabetic cardiomyopathy Aortic stenosis Cardiac amyloidosis Fabry's disease Myocarditis Hypertensive heart disease Dilated cardiomyopathy	Vascular smooth muscle dysfunction Vascular remodeling Microvascular rarefaction Extramural compression
Type 3 CMD in patients with obstructive coronary artery disease	Angina pectoris equivalent	Chronic coronary syndrome Acute coronary syndrome	Vascular smooth muscle dysfunction Vascular remodeling Vascular endothelial dysfunction
Type 4 Iatrogenic CMD	Often asymptomatic	Post-elective PCI Post-elective CABG Cardiac allograft vasculopathy	Lumen narrowing/obstruction Autonomic dysfunction Systemic inflammatory reactions

CABG, coronary artery bypass grafting; CMD, coronary microvascular dysfunction; INOCA, ischemia with non-obstructive coronary artery disease; MINOCA, myocardial infarction with non-obstructive coronary arteries; PCI, percutaneous coronary intervention. (Adapted from Crea F, et al. 2014,[132] 2022.[16])

ALDH2 also affects the bioactivation of nitroglycerin.[210] Continuous administration of nitroglycerin leads to its tolerance and even cardiac events through inactivation of ALDH2 and elevated reactive oxygen species (ROS) levels.[205,211] Thus, carriers of *ALDH2*2* are less responsive to nitroglycerin, more prone to nitroglycerin tolerance, and more susceptible to increased ROS.[212,213]

Although racial differences in the incidence of CSA have not yet been fully investigated, it is generally believed that it is more common in East Asians than in Westerners.[8,201] The reason for this is unclear, but may be explained by the high prevalence of *ALDH2*2* and high smoking rates among East Asians.

In general, alcohol abstinence should be advised in the presence of alcohol flushing, and even more so if CSA is suspected. On the other hand, even in the absence of alcohol flushing, moderation is necessary in patients with CSA, because heavy drinking increases the amount of acetaldehyde in the body and increases the likelihood of its effects (**Figure 8**).

3. Coronary Microvascular Spasm

3.1 Disease Concept of CMD and Coronary MVS

The coronary vascular bed consists of epicardial coronary arteries and coronary microvessels (pre-arterioles [500–100 μm], arterioles [<100 μm], pre-capillary arterioles [<20 μm], capillaries).[133,214,215] The epicardial coronary arteries are responsible for only about 5% of the total coronary vascular resistance in the absence of significant stenotic lesions, which means that coronary microvessels play a central role in regulating myocardial blood flow (MBF), and failure of the regulatory mechanism can induce ischemia with or without abnormalities (stenosis or spasm) in the epicardial coronary arteries. CMD is a syndrome that includes a wide range of conditions in which structural and functional changes in coronary microvessels and extravascular factors cause impaired coronary blood flow, ultimately leading to myocardial ischemia and infarction.[131,216]

In the clinical classification of CMD based on clinical scenarios, there are 4 types: CMD in the absence of obstructive CAD or myocardial diseases (Type 1), CMD in cardiomyopathy or valvular disease (Type 2), CMD in obstructive CAD (Type 3), and iatrogenic CMD (Type 4) (**Table 7**).[10,14,16,131,132] CMD is thought to play an important role not only as INOCA/MINOCA, but also as epicardial CAD, primary cardiomyopathy, takotsubo syndrome, HF (especially HF with preserved ejection fraction: HFpEF).

It is known that among patients who complain of angina-like symptoms during exertion or at rest and undergo CAG, there are cases in which neither severe stenotic lesions that obstruct blood flow nor coronary spasm is found in the epicardial coronary arteries, and such cases are diagnosed as MVA, which is considered Type 1 CMD in the CMD clinical classification.

The COVADIS group has proposed diagnostic criteria for MVA (Type 1 CMD) (**Table 8**).[10,16] The diagnostic criteria for MVA include anginal symptoms on exertion or at rest, absence of significant organic stenosis of the epicardial coronary arteries, evidence of ischemia, and of CMD, including (1) impaired coronary microvascular dilation as represented by an increased coronary perfusion response to adenosine, (2) coronary MVS, (3) increased IMR, and (4) decreased coronary blood flow velocity (slow-flow phenomenon)[217] (**Table 8**).

In individual cases, both structural abnormalities (organic stenosis) and functional abnormalities in both the epicardial coronary arteries and coronary microvasculature can overlap causing myocardial ischemia (**Figure 5**, **Chapter I.2.3**). The condition that excludes stenosis of the epicardial coronary arteries constitutes INOCA.

Although the pathophysiology of CMD has not been fully elucidated, oxidative stress due to overproduction of

Table 8. Diagnostic Criteria for Microvascular Angina
1. Symptoms of myocardial ischemia
• Exertional and/or resting angina pectoris
• Angina-like symptoms (e.g., shortness of breath)
2. Non-obstructive coronary artery disease
• Evaluation by coronary CT
• Evaluation by invasive CAG
*No significant stenotic lesions in epicardial coronary arteries on the above examinations
3. Proof of myocardial ischemia
• Ischemic ECG changes during chest pain attacks
• Chest pain and/or ischemic ECG changes associated with loading
4. Coronary microvascular dysfunction
• Decreased coronary flow reserve
• Coronary microvascular spasm (reproduction of symptoms and ischemic ECG changes on pharmacological provocation testing, without epicardial coronary artery spasm)
• Increased index of microcirculatory resistance
• Coronary slow flow phenomenon (TIMI frame count >25)

CAG, coronary angiography; CT, computed tomography; TIMI, thrombolysis in myocardial infarction. (Adapted from Crea F, et al. 2022.[16])

intracellular ROS and associated inflammatory reactions have been reported to be the mechanism of CMD.[218] In addition, activation of RhoA/Rho-kinase by ROS, inhibition of vasodilation by NO, and enhancement of vasoconstrictor activity by endothelin 1 (ET-1) have been reported to be involved in CMD.[16,219] In patients with epicardial coronary artery spasm and high IMR, inhibition of Rho-kinase reduces IMR, suggesting that Rho-kinase is involved in the pathogenesis of CMD.[138,142]

3.2 Epidemiology of Coronary MVS

MVS was first reported in Japan in 1998.[103,220] The diagnosis of MVS is based on the following findings; Intracoronary administration of ACh or ergonovine can cause myocardial ischemia (angina symptoms, ischemic changes on ECG, myocardial lactate production) and decreased coronary blood flow velocity (delayed contrast and increased TIMI frame counts) without significant epicardial coronary artery spasm.[10,55,101,220,221]

Coronary MVS is thought to cause supply ischemia without an increase in myocardial oxygen demand. In actual reports, MVS is more common in postmenopausal women, who often present with angina only at rest during the night or early morning, but also with exertional angina.[220] Cases of ECG ST-segment elevation on exertion have also been reported.[222] MVS is more common in women than in men in Europe and the USA, and is associated with chest pain both at rest and on exertion.[157,223] MVS can cause angina pectoris by itself, but it has also been suggested that MVS contributes to myocardial ischemia in VSA caused by epicardial coronary artery spasm, when myocardial ischemia occurs without significant epicardial artery spasm in the coronary spasm provocation test.[104] Epicardial coronary artery spasm combined with MVS is more common in women, and a history of chest pain lasting >30 min, in addition to typical angina symptoms, is more common in women.[104] Although the prognosis of patients with MVS is not bad, some cases of MI have been reported.[46,105,112,224]

The prevalence of MVS in INOCA and MINOCA has been reported (**Table 9**). The rates of coronary sinus blood lactate measurement in coronary spasm provocation tests vary from study to study, but MVS has been reported to be present in 13–53% of patients diagnosed with INOCA,[55,105,157,225–227] and in 16–54% of those diagnosed with MINOCA.[16,46,226,228,229] MVS may also cause ischemia in unstable angina caused by organically stenotic lesions in the coronary arteries, and may modulate the pathogenesis of IHD in general.[230]

3.3 Diagnosis of Coronary MVS

Patients suspected of coronary MVS have: (1) typical anginal pain or angina equivalent symptoms at rest or on exertion;[55,117,221] (2) MI with no apparent causative lesion in the coronary artery;[229,231] and (3) the epicardial coronary arteries presenting non-obstructive coronary arteries (<50% diameter) or FFR >0.80.[81,224,232,233]

Because coronary MVS cannot be confirmed by CAG[234] it is not an absolute diagnosis but rather a presumption.[55,221] Reports from Japan have shown that coronary spasm is induced not only by ACh but also by ergonovine,[156,235] and both drugs can be used for the diagnosis of coronary MVS.

The diagnosis is made when patients with suspected coronary artery dysfunction undergo ACh or ergonovine provocation test and the reproduction of chest symptoms is accompanied by the appearance of transient ischemic ECG changes but without significant epicardial coronary artery spasm[10,55,236] (**Figure 9**). Hence, the diagnosis cannot be made when there is (1) no reproduction of chest symp-

Table 9. Incidence of MVS in INOCA/MINOCA			
INOCA	**MVS**	**MINOCA**	**MVS**
Ohba K, et al, 2012[105]	13%	Montone RA, et al, 2018[46]	35.1%
Ong P, et al, 2014[157]	24.2%	Vidal-Perez R, et al, 2019[228]	25%
Ong P, et al, 2018[225]	30%	Pirozzolo G, et al, 2020[229]	54%
Probst S, et al, 2021[226]	53%	Probst S, et al, 2021[226]	29%
Suzuki S, et al, 2021[227]	32%	Crea F, et al, 2022[16]	16%

INOCA, ischemia with non-obstructive coronary artery disease; MINOCA, myocardial infarction with non-obstructive coronary arteries; MVS, microvascular spasm.

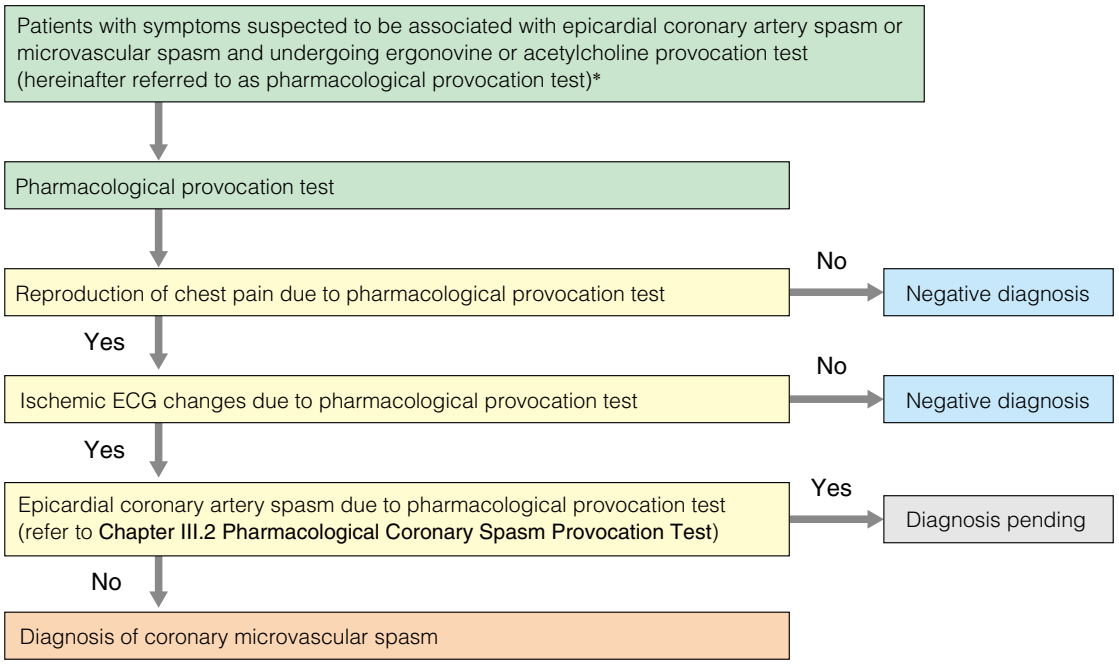


Figure 9. Diagnostic criteria for coronary microvascular spasm. *Coronary microvascular spasm cannot be diagnosed in patients with coronary artery diameter stenosis of 50% or more, even if the pharmacological provocative test is positive.

toms, (2) no appearance of transient ischemic ECG changes, and (3) significant epicardial coronary artery spasm. Coronary MVS is considered negative in the absence of significant epicardial coronary artery spasm and either chest symptoms or ischemic ECG changes. If significant epicardial coronary artery spasm is found, the diagnosis of coronary MVS is pending and the diagnostic criteria for CSA are followed.

It has been reported that the frequency of coronary MVS comorbid with epicardial coronary artery spasm is high and that re-administration of ACh in the setting of suppressed epicardial coronary artery spasm with nitroglycerin can diagnose coexisting coronary MVS.[13] Although that report was from a multicenter study, it is not included in this guideline because it was based on 95 patients, and we await the results of future studies.

A change from lactate uptake to production in the coronary circulation is evidence of ischemia instead of ischemic ECG changes,[10,105,221,224] and lactate measurement in the coronary sinus is likely to be recommended in the future for the diagnosis of coronary MVS. Recently, the COVADIS international criteria indicated abnormal coronary flow reserve, abnormal coronary microvascular resistance, and coronary artery slow flow as evidence of abnormal coronary microvascular function.[10] Coronary flow reserve can be measured by Doppler-wire[105,237] or thermodilution using a pressure wire.[81,238,239] CFR and coronary microvascular resistance[81,239,240] do not provide evidence of coronary MVS. The same is true for TIMI frame counts,[10,221] which indicate coronary slow flow. Doppler-wire is not currently commercially available and cannot be used,[105,144,241,242] but real-time measurement of blood flow velocity by Doppler-wire during ACh or ergonovine provocation test allows calculation of coronary blood flow during the provocation test, and thus coronary MVS can be estimated.[105] However, there are no diagnostic criteria for coronary blood flow to diagnose coronary MVS by pharmacological provocation test.

The COVADIS group has advocated a protocol of coronary microvascular function testing prior to ACh-provocation test.[81,239] On the other hand, as will be discussed in detail in **Chapter III.7**, in Japan it is common practice to refrain from administering drugs that affect coronary vascular function before the ACh-provocation test.

4. Coronary Spasm After Drug-Eluting Stent Implantation

4.1 Pathophysiology and Epidemiology

The pathophysiological mechanisms of persistent or recurrent angina after percutaneous coronary intervention (PCI) include (1) flow-limiting epicardial obstruction, such as in-stent restenosis, stent thrombosis, and progression of coronary atherosclerosis in coronary segments distinct from those treated with index PCI, and (2) coronary vasomotion abnormalities including epicardial or microvascular spasm, and CMD.[243] **Table 10** gives the recommendation and evidence for coronary spasm provocation testing in symptomatic post-PCI patients. Although the coronary hyperconstricting response to ACh occurs near the edges of the stent,[244] the degree of this response is enhanced in segments implanted with 1st-generation DES, compared with those with bare-metal stents (BMS).[245,246] The DES-induced coronary hyperconstricting response has been reported for both 1st- and 2nd-generation DES,[247,248]

Table 10. Recommendation and Level of Evidence for Coronary Spasm Provocation Test in Symptomatic Post-PCI Patients

	COR	LOE
In patients with persistent or recurrent angina after PCI, performing a spasm provocation test with acetylcholine or ergonovine should be considered if coronary angiography excludes significant coronary stenosis	IIa	C

COR, Class of Recommendation; LOE, Level of Evidence; PCI, percutaneous coronary intervention.

which is an important clinical issue as some serious cases exist among these reports. According to a Japanese report, significant hyperconstricting response was observed in 30 (71.2%) of 42 patients implanted with a 1st-generation DES who underwent ACh-induced spasm provocation test at follow-up.[249] In a report examining the relationship between the degree of neointimal coverage by coronary angioscopy and coronary endothelial function assessed by intracoronary ACh infusion, less neointimal coverage was associated with an enhanced hyperconstricting response distal to the stent after 1st-generation DES implantation.[250] Mechanistically, both poor neointimal coverage and the presence of intrastent thrombus were identified as independent factors contributing to the hyperconstricting response, suggesting the importance of endothelial dysfunction.[250]

Subsequently, 2nd-generation DES, which were clinically implemented in Japan around 2010, showed a decrease in the DES-induced coronary hyperconstricting response compared with 1st-generation DES.[251,252] A report comparing the hyperconstricting response to ACh in segments implanted with and without 2nd-generation DES in the same patients at 6–8 months after PCI showed that there was no significant difference between the two.[253] Also, cardiovascular events related to coronary spasm after PCI have been reported to be the lowest with 2nd-generation DES compared with BMS and 1st-generation DES (BMS 2.9%, 1st-generation DES 3.2%, 2nd-generation DES 0.4%), and the use of 2nd-generation DES and statins have been identified as independent factors contributing to the avoidance of cardiovascular events.[254] In addition, when PCI was performed in patients with VSA diagnosed with a previous spasm provocation test using ergonovine, 1st-generation DES significantly increased cardiovascular events in patients with comorbid VSA compared with those without, and both BMS and 2nd-generation DES showed no significant difference between patients with and without comorbid VSA.[255] Moreover, a pathological study showed that 2nd-generation DES had a higher rate of stent coverage and less inflammation and fibrin deposition than 1st-generation DES,[256] which may contribute to the reduced hyperconstricting response to 2nd-generation DES.

An important pathological mechanism of the DES-induced coronary hyperconstricting response is the activation of Rho-kinase,[111] a molecular switch in vascular smooth muscle contraction, as well as endothelial dysfunction described earlier. Rho-kinase activation inhibits myosin light chain phosphatase in vascular smooth muscle, resulting in inhibition of myosin light chain dephosphorylation and subsequent smooth muscle hypercontraction.[111] The involvement of Rho-kinase in the coronary hyperconstricting response after DES implantation has been demonstrated in a porcine model,[257] and in patients with CAD.[258] Intracoronary infusion of fasudil, a Rho-kinase inhibitor, attenuates the DES-induced coronary hyperconstricting response. In a porcine model exploring the effects of DES components (antiproliferative drugs, polymers, and metal stents) on the coronary hyperconstricting response, polymers induced the response via inflammatory changes at the stent edges and by Rho-kinase activation.[259] In addition, DES implantation induced formation of adventitial vasa vasorum (VV), and histologically developed inflammatory changes and Rho-kinase activation, suggesting an association between adventitial VV and DES-induced coronary hyperconstricting response.[260] Furthermore, increased inflammatory accumulation in perivascular adipose tissue (PVAT) was seen on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography after DES implantation in a porcine model.[261] On the other hand, DES implantation induced lymphangiogenesis in a porcine model, and lymphatic ligation after DES implantation exacerbated the coronary hyperconstricting responses and histologically demonstrated prolonged adventitial inflammation, which were associated with Rho-kinase activation.[262] Taken together, these findings suggest that inflammation is indeed important for Rho-kinase activation as a pathological mechanism of the DES-induced coronary hyperconstricting response.[263] Regarding therapeutic intervention of Rho-kinase activity, long-term treatment with nifedipine, a long-acting CCB, suppressed the DES-induced coronary hyperconstricting response through inhibition of inflammatory responses, microthrombus formation, and Rho-kinase activity in a porcine model.[264]

4.2 Treatment

In the Nifedipine on Coronary Vascular Function after Drug-Eluting Stent Implantation (NOVEL) study,[265] 100 patients with stable CAD who underwent implantation of an everolimus-eluting stent (EES), a 2nd-generation DES, were randomly assigned to receive either conventional treatment alone or additional long-acting nifedipine, and the patients underwent ACh-induced spasm provocation test 8–10 months after DES implantation. The results of the NOVEL study showed a significant reduction in coronary hyperconstricting responses to ACh in the nifedipine group compared with the control group. In addition, nifedipine-treated patients showed a decrease in serum levels of high-sensitivity C-reactive protein and an increase in those of adiponectin at follow-up, suggesting a relationship between the anti-inflammatory effect and the benefit of long-term nifedipine treatment.

On the other hand, in another study, 52 patients who underwent EES implantation for a single-vessel lesion were assigned to the β-blocker (bisoprolol 73%) or CCB (amlodipine 77%) group, and the positive rates of ACh-induced spasm provocation test at 9 months and major adverse cardiac events (MACE: composite of all-cause death, nonfatal MI, unstable angina, cerebrovascular disease, and coronary revascularization) at 24 months were investigated. The positive rate was similar in both groups (26.9%), but the incidence of MACE was significantly lower in the β-blocker group than in the CCB group, although all MACE were coronary revascularization (3.8% vs. 19.2%, P=0.01).[266] However, this study lacked statistical power due to the small sample size, so further study is warranted.

5. Pediatric Disease, Coronary Sequelae in Kawasaki Disease and Vasospastic Angina

5.1 VSA in Children

Pediatric VSA is a rare disorder and described only in case reports. A literature search from 1985 to 2021 revealed 31 cases, and the reports were increased from the 2000s (**Table 11**,[267–279] **Figure 10**[267–279]). The age of onset ranged from 6 to 19 years, with a median age of 13 years, and boys were twice as likely to have the disease as girls. Symptoms occurred either at rest or with exercise, with the rest state accounting for more than 2/3 of cases. Symptoms included anterior chest pain, chest discomfort, and syncope, possibly accompanied by epigastric pain or nausea. This condition occurred rarely as toothache, AMI, or ventricular fibrillation.[271–273] Background of the patients included concomitant moyamoya disease, NO-related genetic mutations, and decreased reactive vascular index, a measure of systemic vascular endothelial function.[274–276] VSA or drug-induced coronary spasm was reported in patients with cardiomyopathies such as muscular dystrophy.[280]

Diagnosis is often based on symptoms, ECG changes during attacks (ST-segment elevation or ST depression in ≥2 leads), or improvement of symptoms with nitrate use. ST-segment elevation/depression coinciding with chest pain in Holter ECG may also be a clue to the diagnosis. Provocation testing with intracoronary ACh administration, hyperventilation, or exercise is used for the diagnosis (see **Chapter III.2**).[277] Provocation testing should be performed in collaboration with a cardiologist. Blood tests may show positive myocardial troponin and elevated cardiac enzymes. Treatment with oral or intravenous nitrates and calcium antagonists often improves the condition.[276,278,279] In cases of refractory VSA, symptoms may persist and require continuous intravenous administration of nitrates, calcium antagonists, or magnesium sulfate. The conditions of cardiogenic shock necessitate intensive management to maintain hemodynamics.[281] An implantable cardioverter defibrillator (ICD) device was used to treat cases of ventricular fibrillation and cardiac arrest.[282] Autopsy of refractory cases has revealed coronary artery occlusion due to thickening of the coronary artery wall in multivessel lesions.[271,274]

5.2 History of Kawasaki Disease and VSA

Kawasaki disease (KD) is an acute febrile illness of children under 5 years of age, and is a vasculitis of medium-sized vessels with unknown cause. Inflammation in the acute phase of the disease induces coronary artery damage,

Table 11. Summary of Case Reports of VSA in Children

	(1985–2021)
No. of reports	31
Sex*	Male 20 Female 10
Age of onset (years)	13 (6–19)
Onset of chest pain	
At rest	22 (71%)
Exercise - at rest	3 (10%)
Exercise	6 (19%)
Syncope	4 (13%)
Myocardial infarction	4 (13%)
Ventricular fibrillation · Cardiopulmonary resuscitation	7 (23%)
Death	2 (6%)
Positive myocardial troponin	9 (30%)
Positive acetylcholine-induced test	18 (58%)
Family history (cardiac disease)	5 (16%)

*1 case of no information available. VSA, vasospastic angina. (Collated from references[267–279])

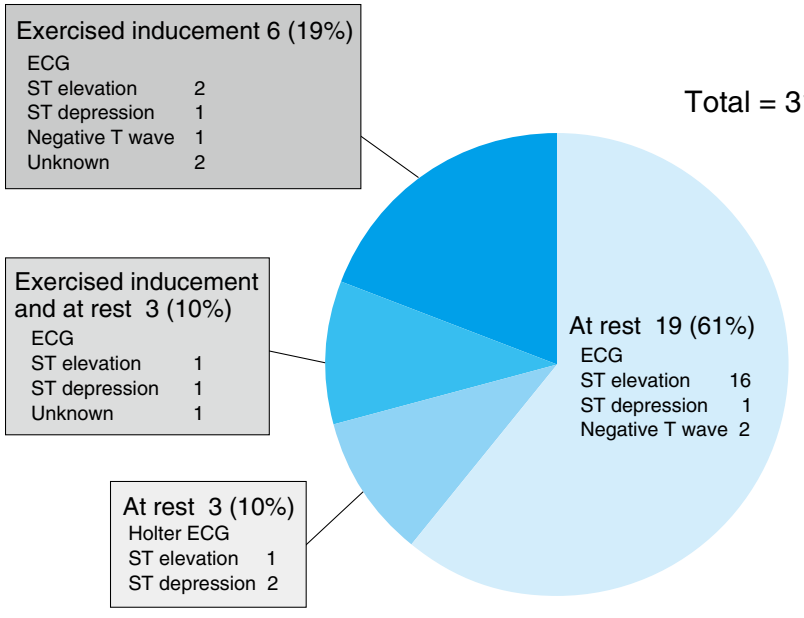


Figure 10. Onset of chest pain and ECG changes in childhood-onset VSA. There were 22 cases (71%) of onset at rest, 3 at rest or during exercise, and in 6 cases it was triggered by exercise. Resting onset was seen early in the morning and while sleeping. The most common ECG abnormality was ST-segment elevation. (31 cases from 1985 to 2021.[267–279])

resulting in coronary artery aneurysms in approximately 20% of untreated patients. Recently, treatment with intravenous immunoglobulin reduced the incidence of coronary sequelae to 2–3%.[283] The occurrence of VSA in patients with a history of KD is rare, although 1 case in KD patient at rest and 1 during exercise were included in reports of VSA.[284–286] In reports of VSA during pregnancy and delivery, a patient with a history of KD was included.[287] Endothelial dysfunction in the epicardial coronary arteries has been reported in patients with KD-related coronary sequelae, but it is unknown whether endothelial dysfunction causes VSA in KD.[288–290] There are also reports showing reduced MBF in cases of regressed coronary aneurysms after KD, even in the absence of significant stenosis of the epicardial coronary arteries.[291] CMD in patients with a history of KD is an issue that should be addressed in the future.

III. New Insights Into Diagnosis

1. Diagnostic Criteria

Until 2008, VSA was diagnosed in Japan according to diagnostic criteria independently adopted by each institution.[292] The "Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008 and 2013)"[1,2] unified the diagnostic criteria for VSA, referring to previous reports and other findings.[1,2] Yasue et al. state that VSA can be diagnosed even without performing CAG, provided that the anginal attacks disappear quickly upon administration of nitroglycerin and that any 1 of the following 5 conditions is met: (1) attacks occur at rest, particularly in the night and early morning; (2) marked diurnal variation is observed in exercise tolerance (in particular, reduction of exercise capacity in the early morning); (3) attacks are accompanied by ST elevation on ECG; (4) attacks are induced by hyperventilation (hyperpnea); and (5) attacks are suppressed by CCBs but not by β-blockers.[293] The 2013 revision of the Guideline was based on this statement,[2] which is also reflected in the international standardization initiatives on the diagnostic criteria for VSA that have been developed since that revision.[9,294] There was no change in the outline of the 2013 revised guideline, which established reference items within the diagnostic criteria and set 3 grades of diagnostic criteria; "Definite", "Suspected", and "Unlikely".[2] However, whether to include "diffuse coronary spasm" in the positive diagnostic criteria for the pharmacological coronary spasm provocation test has been debated since the 2013 revision, as further accumulation of relevant evidence is needed. This focused update applies "diffuse coronary spasm" as a positive diagnostic criterion for CAG based on domestic and international evidence. The diagnostic criteria for VSA are provided below, and the diagnostic algorithm is shown in **Figure 11**.[17,167,295–297]

1.1 Diagnostic Criteria for "Definite/Suspected" VSA

If any 1 of the following conditions and 1 of the following requirements are met, Definite/Suspected VSA is considered present. If none are met, the condition is judged Unlikely to be VSA. Clinically, both Definite and Suspected VSA are diagnosed as VSA.

1.1.1 Conditions

Any 1 of (1)–(3)

(1) Spontaneous attacks.

(2) Positive for nonpharmacological coronary spasm provocation test (e.g., hyperventilation test and exercise test).

(3) Positive for pharmacological coronary spasm provocation test (e.g., ACh and ergonovine).

1.1.2 Requirements

Definite VSA: The patient is considered to have Definite VSA when ischemic change is clearly observed on the ECG during attacks (*1), when the ECG findings are borderline but a clear finding of myocardial ischemia or coronary spasm is obtained in examinations (*2) and the patient has a history and symptoms during attacks that are consistent with VSA; or when, if there is no ECG change during attacks or if ECG examination has not been performed, ≥1 of the reference items is met, and examinations (*2) reveal a clear finding of myocardial ischemia or coronary spasm.

Suspected VSA: The patient is considered to have Suspected VSA when the ischemic change on ECG during attacks is borderline, and no clear finding of myocardial ischemia or coronary spasm is obtained in any examination; (*2), or when, if there is no change on the ECG during attacks or ECG examination has not been performed, ≥1 of the reference items apply, and a clear finding of myocardial ischemia or coronary spasm cannot be demonstrated on any examination.

*1: Ischemic change is defined as a transient ST elevation ≥0.1 mV, an ST depression ≥0.1 mV, or a new appearance of negative U waves, recorded in ≥2 contiguous leads on the 12-lead ECG. If the ischemic ECG change is prolonged, the patient should be treated as directed in the guidelines for management of acute coronary syndrome.[17]

*2: Examinations include the pharmacological coronary spasm provocation test during cardiac catheterization and hyperventilation test.

At the time of the 2013 guideline revision, whether to include diffuse coronary spasm in the positive diagnostic criteria for coronary spasm on CAG during pharmacological coronary spasm provocation testing using ACh or ergonovine was inconclusive. However, several domestic and international reports included diffuse coronary spasm as a positive diagnostic criterion.[9,101,106,112,157] In this guideline focused update, the positive diagnostic criteria for coronary spasm were changed and defined as follows, together with the previous findings:[167,295–298] "transient, total, or subtotal focal occlusion (>90% stenosis) of a coronary artery with signs/symptoms of myocardial ischemia (anginal pain and ischemic ECG change) or 90% diffuse vasoconstriction induced in ≥2 contiguous segments of a coronary artery".

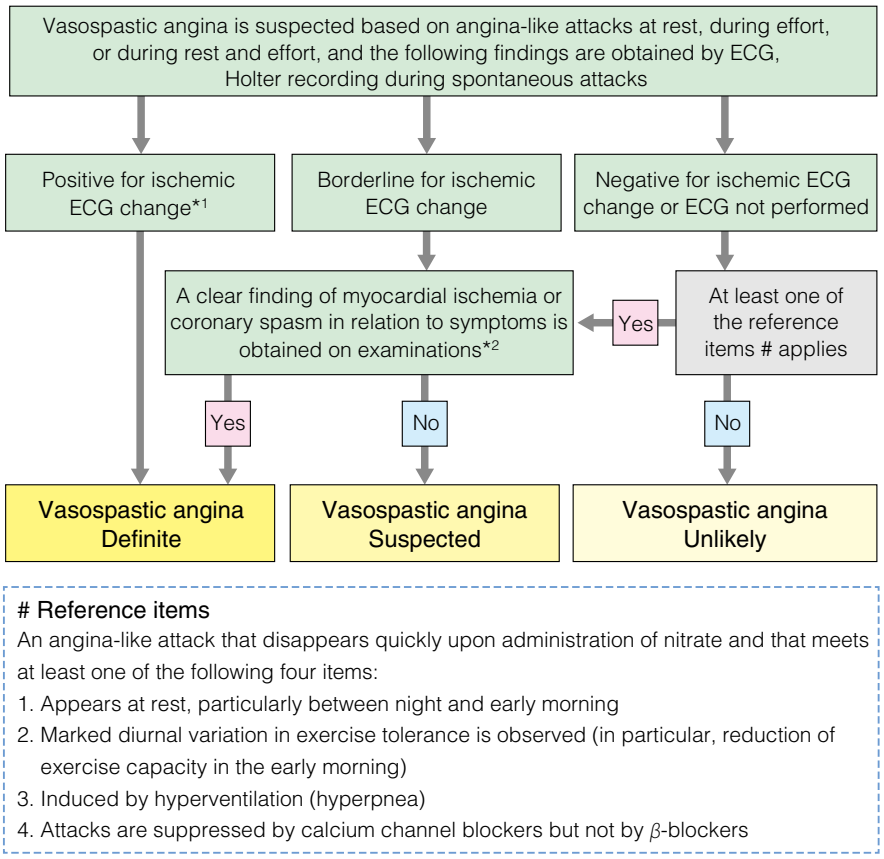


Figure 11. Diagnostic algorithm of vasospastic angina. *1: Ischemic change is defined as a transient ST elevation of 0.1 mV or more, an ST depression of 0.1 mV or more, or a new appearance of negative U waves, recorded in at least two contiguous leads on the 12-lead ECG. If the ischemic ECG change is prolonged, patients should be treated as directed in the guidelines for the management of acute coronary syndrome.[17] *2: Examinations include the pharmacological coronary spasm provocation test during cardiac catheterization and hyperventilation test. A positive finding for coronary spasm on coronary angiography in the acetylcholine- or ergonovine-induced coronary spasm provocation test is defined as "transient, total, or sub-total focal occlusion (>90% stenosis) of a coronary artery with signs/symptoms of myocardial ischemia (anginal pain and ischemic ECG change) or 90% diffuse vasoconstriction induced in two or more contiguous segments of a coronary artery".[167,295–297]

1.1.3 Reference Items

An angina-like attack that disappears quickly upon administration of nitrate, and that meets at least 1 of the following 4 items:

(1) Appears at rest, particularly between night and early morning.
(2) Marked diurnal variation in exercise tolerance (in particular, reduction of exercise capacity in the early morning).
(3) Induced by hyperventilation (hyperpnea).
(4) Attacks are suppressed by CCBs but not by β-blockers.

2. Pharmacological Coronary Spasm Provocation Test

2.1 Overview

The pharmacological coronary spasm provocation test during cardiac catheterization involves the selective intracoronary injection of ACh or ergonovine followed by CAG. The "Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2013)"[2] and the "JCS 2018 guideline on diagnosis of chronic coronary heart diseases"[18] already included an overview of this provocation test, and new findings since then are added here. The provocation test aims to prove coronary spasm in patients with rest angina or rule out coronary spasm in patients with chest pain but without significant coronary artery stenosis. The patients with indication for this provocation test also include some cases of exertional angina pectoris and myocardial infarction (see **Chapter I.1.3**). Both the sensitivity and specificity of the provocation test for detecting coronary spasm are high, ranging from 80% to 90%. The sensitivity is reduced in patients with low activity of VSA or patients treated with an antispastic drug before the provocation test. Patients with multivessel coronary spasm have a poor long-term prognosis. On August 25, 2017, an additional indication for "OVISOT® FOR INJECTION 0.1 g" was approved, and the ACh provocation test was officially covered by Japanese health insurance in 2018. Rest angina is common in Japan, and CAG often proves the presence of coronary

spasm.[299,300] The representative pharmacological provocation tests for coronary spasm include ACh[167] or ergonovine[301] provocation tests. In addition, adequate informed consent must be given before any invasive provocation test is performed in indicated cases.

2.2 ACh Provocation Test

ACh has a vasodilating effect by releasing NO from the endothelium and simultaneously also strongly contracts the vascular smooth muscles. Clinical studies in patients with variant angina have shown that selective injection of intracoronary ACh provokes coronary spasm with high sensitivity and specificity.[167,295,296] Because many institutions have reported similar results, especially in Japan,[297] this test has been established as a provocation test to diagnose coronary spasm as a pathogenesis of angina pectoris. With this provocation test, it is important to note that, especially in patients with highly active coronary spasm or multivessel coronary spasm, the provoked coronary spasm may be severe and extensive, and prolonged, which may cause critical conditions such as hypotension, cardiogenic shock, severe arrhythmia, and cardiac arrest. In such cases, intracoronary infusion of nitrate (nitroglycerin or isosorbide dinitrate) is necessary to release the spasm. The administration of drugs to raise blood pressure (noradrenaline) is necessary for hypotension, and serious arrhythmias should be treated immediately.

a. Standard Method of the ACh Provocation Test[167,295–297,302,303]

① **Control CAG of the Left and Right Coronary Arteries:** Perform CAG with the appropriate projection that ensures the best separation of the branches of each coronary artery. After ACh injection, repeat CAG in the same projection.

② **Insertion of Temporary Pacing Electrode Into the Right Ventricle:** Perform backup pacing (40–50 beats/min) because ACh administration, especially into the right coronary artery, may cause transient severe bradycardia.

③ **Injection of ACh Into the Left Coronary Artery:** Inject 20, 50, and 100 μg of ACh dissolved in 37°C saline (concentration adjusted to obtain 5 mL solution volume for each quantity of ACh) into the left coronary artery over 20 s. Perform CAG 1 min after the start of each injection. If ischemic changes appear on the ECG or chest pain, perform CAG at that time. Doses of ACh should be given at 5-min intervals.

④ **Injection of ACh Into the Right Coronary Artery:** Inject 20 or 50 μg (each in 5 mL solution) into the right coronary artery over 20 s. The timing of CAG is the same as for the left coronary artery.

⑤ **Left and Right CAG After Nitrate Administration:** Inject the nitrate into each coronary artery, and perform CAG while the coronary artery is maximally dilated.

No principle states in which coronary artery to start the provocation test, the left or the right coronary artery, but the left coronary artery is often the first from the viewpoint of the number of coronary branches to be evaluated for the provoked spasm because the contralateral coronary spasm provocation test cannot be performed after nitrates administration for the release of provoked coronary spasm.

A small dose (20 μg) of ACh often provokes coronary spasm in patients with a high number of spontaneous attacks and high disease activity. In cases in which the incidence of hypotension or severe bradycardia during spontaneous attacks and extensive and severe ischemia is expected, starting with a smaller dose (10 μg) is recommended.

Because the half-life of ACh is extremely short, unlike spasm induced by ergonovine, the provoked coronary spasm spontaneously relieves in many cases. In other words, coronary spasm provoked by intracoronary infusion of ACh often does not require nitrate administration and does not affect the provocation test on the contralateral coronary artery, making it useful in the diagnosis of multivessel coronary spasm.[296] Because multivessel coronary spasm attacks are often severe and are one of the prognostic factors in cases of variant angina,[296,304] accurate diagnosis and treatment are important to improve the prognosis of these patients.

b. Sensitivity and Specificity of ACh Provocation Test[167,297,305,306]

Investigations in patients with atypical angina pectoris[167,303] showed that ACh-provoked spasm was observed in 112 of 121 patients (93%) and in 144 (89%) of 162 coronary arteries (sensitivity, 89–93%) which coronary spasm was predicted to occur based on ECG at the time of the attack. ST-segment elevation was observed in 66% of the induced attacks, ST depression in 31%, and negative U waves in 3%. In more than 2/3 of patients, >50 μg of ACh was required to provoke coronary spasm in both the left and right coronary arteries. On the other hand, a study of patients with atypical chest pain without significant coronary artery stenosis[167] demonstrated no provoked coronary spasm by ACh in 86 patients (specificity, 100%), and mild to moderate vasoconstriction and vasodilation was observed in some cases. A study in patients with severe coronary artery stenosis >90% showed that 4 of 16 patients with stable effort angina and 11 of 16 patients with a history of MI presented total or subtotal occlusion after provocation, consistent with the site of the stenosis.[305] The diagnostic significance of this provocation test was high in patients without significant stenosis, but the specificity was low in patients with severe stenosis, suggesting that diagnostic significance was reduced. Investigations have shown that in Japanese patients, diffuse as well as focal coronary spasm is often prevalent. Whether or not to include diffuse coronary spasm as a positive diagnostic criterion for the spasm provocation test was inconclusive because of the lack of evidence accumulation at the time of formulation of the "Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2013)".[2] Considering the current status of reports from Japan and overseas, this focused update includes diffuse coronary spasm as a diagnostic criterion.

2.3 Ergonovine Provocation Test

Ergonovine has a potent contractile effect on vascular smooth muscle by stimulating serotonin and α receptors. An investigation found that intravenous ergonovine-induced coronary spasm was almost the same as spontaneous attacks in patients with variant angina,[307] and the clinical use of ergonovine was initiated, but a death with a high dose of intravenous ergonovine was reported.[308] Later, the usefulness of the intracoronary ergonovine provocation test was confirmed, and the selective, lower-dose intracoronary ergonovine provocation test became a popular alternative to the conventional intravenous ergonovine provocation

test.[309,310] Many institutions in Japan reported data on the ergonovine provocation test, resulting in it being established as a pharmacological coronary spasm provocation test, as with the ACh-provocation test. The frequency of coronary spasm provoked by intravenous administration of ergonovine in variant angina ranges from 48% to 85%, but there are few reports on the diagnostic accuracy of intracoronary injection of ergonovine in variant angina. As with ACh, it is essential to note that this provocation test can induce severe coronary spasm in patients with high disease activity or with multivessel coronary spasm and that the provoked coronary spasm can be prolonged, resulting in critical conditions such as hypotension, cardiogenic shock, severe arrhythmias, and cardiac arrest. In such cases, it is necessary to quickly relieve the coronary spasm by intracoronary injection of nitrate (nitroglycerin or isosorbide dinitrate). Drugs to raise blood pressure (noradrenaline) should also be administered for hypotension. Severe arrhythmia should be treated immediately. However, ergonovine is not currently covered by Japanese health insurance.

a. Standard Method of the Ergonovine Provocation Test[307–313]

① **Control CAG of the Left and Right Coronary Arteries:** Perform CAG in the appropriate projection that ensures the best separation of the branches of each coronary artery. After the ergonovine injection, perform CAG in the same projection again.

② **Injection of Ergonovine Into the Left Coronary Artery:** Inject 20–60 μg of ergonovine dissolved in saline into the left coronary artery over a few minutes (≈2–5 min). Perform CAG 1–2 min after the start of each injection. If ischemic changes appear on the ECG or chest pain, perform CAG at that time. If the provocation test is negative, perform the provocation test in the right coronary artery 5 min later.

③ **Injection of Ergonovine Into the Right Coronary Artery:** Inject 20–60 μg of ergonovine dissolved in saline into the right coronary artery over a few minutes (≈2–5 min). The timing of CAG is the same as for the left coronary artery.

④ **Left and Right CAG After Nitrate Administration:** Inject the nitrate into each coronary artery, and perform CAG while the coronary artery is maximally dilated.

The provocation test can be started from either the left or right coronary artery. Coronary spasm provoked by ergonovine is less likely to release spontaneously than spasm provoked by ACh and often requires nitrates to relieve the spasm.[314]

In some cases, multivessel coronary spasm can be diagnosed by performing a contralateral provocation test after release of the provoked coronary spasm with nitrate, and the ergonovine provocation test can be performed in the contralateral coronary artery if the patient is hemodynamically stable.[304] Multivessel coronary spasm is one of the prognostic factors in patients with VSA, and accurate diagnosis of multivessel coronary spasm is essential to improve the prognosis. In cases of continuous administration of ergonovine, CAG is performed during drug administration to confirm whether coronary spasm occurs.

The dose of ergonovine used for intracoronary administration differs among institutions, and there is currently no standardized dosage for this method.[303] Based on previous reports, most institutions use a dosage of at least 20–60 μg for both right and left coronary arteries, and the continuous ergonovine administration method is recommended to avoid single administration for safety reasons. Continuous ergonovine administration requires a smaller dose and may further reduce complications. A small dose should be started when the ergonovine provocation test is performed to evaluate the severity of variant angina.

Investigations on the pharmacological coronary spasm provocation tests using ergonovine, serotonin, and ACh in patients with VSA suggest that each drug may provoke coronary spasm at a different site.[314,315] Therefore, a negative result for a coronary spasm provocation test cannot entirely exclude the presence of coronary spasm. Considering the period of drug discontinuation before the provocation test or the activity of angina pectoris, treatment, including CCBs, should be initiated if there is a strong suspicion of VSA based on the clinical symptoms, even if the provocation test for coronary spasm is negative.

2.4 Indication Criteria

Table 12 shows the indication criteria for pharmacological

Table 12. Recommendations and Levels of Evidence for Pharmacological Coronary Spasm Provocation Tests[2,18,106,148,149,156,157,167,295–297,301,307,310–312,316–318]

	COR	LOE
It is recommended to perform pharmacological coronary spasm provocation tests for patients with suspected vasospastic angina based on symptoms but not diagnosed with coronary spasm by noninvasive evaluation	I	B
Pharmacological coronary spasm provocation tests should be considered for patients diagnosed with coronary spasm by noninvasive evaluation and for whom the effect of medical therapy is inconclusive or inadequate	IIa	B
Pharmacological coronary spasm provocation tests may be considered for patients who have been diagnosed with coronary spasm by noninvasive evaluation and in whom medical treatment has been effective	IIb	B
It is not recommended to perform pharmacological coronary spasm provocation tests for patients without symptoms suggestive of vasospastic angina	III (No benefit)	C
Pharmacological coronary spasm provocation tests should not be performed for patients with acute coronary syndrome for which coronary angiography is performed and in whom serious complications from induced coronary spasm are expected (e.g., severe cardiac dysfunction, congestive heart failure)	III (Harm)	C

COR, Class of Recommendation; LOE, Level of Evidence. (Adapted from JCS 2018 guideline on diagnosis of chronic coronary heart diseases.[18])

coronary spasm provocation testing, which is summarized in reference to the "Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2013)",[2] "JCS 2018 guideline on diagnosis of chronic coronary heart disease"[18] and other reports.[106,148,149,156,157,167,295–297,301,307,310–312,316–318]

2.5 Diagnostic Significance

2.5.1 Objectives of Testing

The objectives of provocation testing are to (1) prove coronary spasm in patients with rest angina and in some patients with effort angina, (2) determine the severity of rest angina, and (3) rule out coronary spasm in patients without significant stenosis in the coronary arteries.

2.5.2 Diagnostic Performance

The sensitivity and specificity of coronary spasm provocation testing are generally quite high, being in the 80–90% range.[167,301,310,317–319] However, coronary spasm may not be provoked in patients who have received drug therapy before provocation testing or in patients with infrequent spasm, even if ST elevation was confirmed by Holter ECG. Also, there are diurnal variations in the frequency of coronary spasm, and attacks only occur in the early morning in some patients.[319] Therefore, to increase the diagnostic accuracy of pharmacological coronary spasm provocation testing, it should be performed in the morning whenever possible, and drugs, such as calcium antagonists and long-acting nitrates, should be discontinued for at least 2 days before testing if possible.

On the other hand, coronary spasm associated with ECG changes may be induced even in patients without a history of chest pain, but the pathological significance of such spasm is challenging to judge. Furthermore, with pharmacological coronary spasm provocation testing, it is challenging to assess the pathological relevance of coronary spasm that shows no change on ECG and does not meet the positive diagnostic criteria, although certain changes are seen on CAG. Recent reports from Europe and Japan indicate that 200 μg in the left and 80 μg in the right coronary artery improves diagnostic performance; however, the accumulation of evidence is still insufficient.[157,320]

2.5.3 Results and Diagnostic Significance

Proof of coronary spasm in patients with rest angina and in some with effort angina justifies long-term administration of nitrates and calcium antagonists as a treatment for angina pectoris. It also provides information to guide treatment with other drugs, such as whether β-blockers (which can induce coronary spasm) should be administered. Regarding the severity of rest angina, patients with multivessel coronary spasm have a poor long-term prognosis.[296] An association between subclinical atherosclerotic lesions and prognosis has also been shown.[146] In such cases, the results of provocation testing may be used to guide decisions about drug doses and the duration of treatment. Excluding coronary spasm in patients with chest pain showing no significant stenosis in the coronary arteries is crucial, especially in the Japanese population, because angina stemming from coronary spasm is more frequent in Japan.[318] Coronary computed tomographic angiography (CCTA) has become popular recently and has a very high negative predictive value; therefore, excluding coronary stenosis in patients with chest pain is possible without performing CAG. However, the absence of coronary stenosis does not directly exclude a diagnosis of angina pectoris. It is also problematic to keep patients on long-term treatment with nitrates or calcium antagonists for chest pain without a definitive diagnosis of angina pectoris. It is crucial to perform coronary spasm provocation testing in patients with chest pain to determine the appropriate therapeutic strategy.

2.6 Contraindications

Pharmacological coronary spasm provocation testing is invasive, and extreme caution should be exercised when deciding the indications for this test. As listed in **Table 12**, (1) It is not recommended to perform pharmacological coronary spasm provocation tests for patients without symptoms suggestive of vasospastic angina, and (2) Pharmacological coronary spasm provocation tests should not be performed for patients with acute coronary syndrome for which coronary angiography is performed and in whom serious complications from induced coronary spasm are expected (e.g., severe cardiac dysfunction, congestive heart failure). If performing the pharmacological coronary spasm provocation test in the acute setting, ruling out other pathologies such as plaque rupture and SCAD with certainty and adequate consideration of safety are required. In addition, the use of ACh requires confirmation of the presence of contraindicated comorbidities (see "OVISOT® FOR INJECTION 0.1 g" package insert). Although there is a retrospective study examining the safety of ACh use in patients with bronchial asthma, the evidence is limited.[321]

2.7 Complications

When coronary spasm provocation testing is performed, severe and extensive coronary spasm may be induced, and the induced vasospasm may be prolonged, especially in patients with frequent attacks or multivessel coronary spasm. As a result, hypotension, cardiogenic shock, severe arrhythmia, and cardiac arrest may occur. In such cases, an immediate alleviation of the coronary spasm by intracoronary infusion of nitrate, administration of vasopressors to maintain blood pressure, and immediate countermeasures for serious arrhythmia may be necessary. A recent investigation of complications in 17,700 patients undergoing coronary spasm provocation testing by intracoronary administration of ACh or ergonovine showed that serious procedural complications had a frequency of 0.89%, including 1 death (0.006%) and 2 cases of acute MI (0.01%).[322]

3. IVUS, OCT

CAG has been widely used in the study of VSA. Advances in in vivo imaging, such as IVUS and OCT, have allowed observation of the coronary artery wall itself in vivo and determination of the pathophysiology and etiology of VSA based on its morphological characteristics. Approximately 10 years have passed since the publication of the "Guidelines for diagnosis and treatment of patients with vasospastic angina" (2013 revision),[2] and many findings on morphological features have been reported using in vivo imaging.

3.1 IVUS

IVUS has revealed that coronary arteries with spasm do not display significant stenotic lesions on CAG, but mild atherosclerosis is present.[323,324] In addition, spasm sites frequently show negative remodeling with a reduced diameter compared with peripheral control vessel diameters.[325–327] There are 2 morphological types of coronary spasm: focal and diffuse. The intima–media complex of the former is significantly thicker than that of the latter, suggesting that focal coronary spasm can be induced under relatively advanced atherosclerosis.[328,329]

Patients with focal spasms had fewer calcified lesions than those without spasms, although there were no significant differences in atherosclerotic lesion indices, such as plaque area and plaque angle.[325,328] A study using virtual histology-IVUS, which uses signal processing of IVUS images to classify the histological characteristics of plaques into 4 colors, reported no difference in histological characteristics between patients with and without coronary spasm in a provocation test.[330]

3.2 OCT

OCT can discriminate 3 layers of the coronary artery wall and identify the change in each arterial wall layer before and after a provocation test. Since 2010, when OCT became available in Japanese clinical settings, many findings on the detailed morphological features of coronary spasm have been reported. Exploration of the spasm site in patients with VSA without significant stenosis on CAG via OCT revealed organic lesions in more than half of the cases.[36] The morphology of the lesions varies widely, including layered plaque,[331–333] intimal tears,[36] thrombi,[37,334] coronary artery dissection,[335,336] macrophage accumulation,[337] and vasa vasorum/intraplaque neovessels[338] (**Table 13**, **Figure 12**). Therefore, in institutions skilled in the operation and reading of OCT, it should be considered when the involvement of organic lesions in the intima and tunica media of the vessel is suspected. Thickening of the tunica media,[339,340] associated intimal bumps, and distorted lumen morphology have been observed even in patients without organic lesions[341,342] (**Figure 13**). Furthermore, an attempt has been made to determine the complexity of the lumen caused by an intimal bump, using the shoreline development index to find the site of the spasm without a provocation test.[341]

3.2.1 Mechanisms of Coronary Spasm From OCT

Although no change in the intimal area occurs before or

Table 13. Recommendations and Levels of Evidence for IVUS/OCT in Patients With Suspected Coronary Spasm

	COR	LOE
Observation for the presence of atherosclerotic lesions in the coronary spasm site may be considered using IVUS[323–325,328,330]/OCT[36,37,331–338]	IIb	C
Searching for mechanisms of coronary spasm using IVUS[325–329]/OCT[339–343] may be considered	IIb	C

COR, Class of Recommendation; IVUS, intravascular ultrasound; LOE, Level of Evidence; OCT, optical coherence tomography.

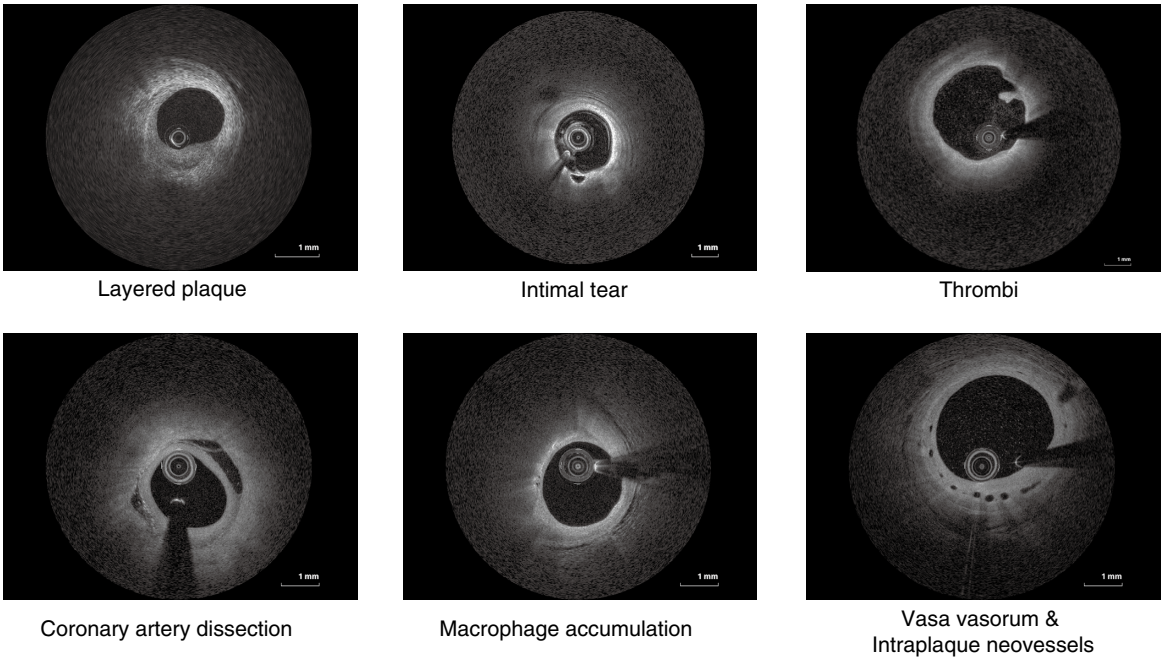
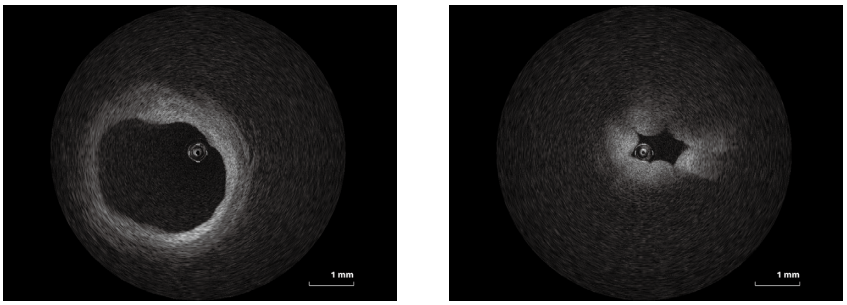


Figure 12. Organic lesions at the spasm site on optical coherence tomography in patients with vasospastic angina without significant stenosis on coronary angiography. Provided by the Department of Cardiovascular Medicine, Wakayama Medical University.



Intimal bumps and thickening of the tunica media (pre provocation)

Thickening of the tunica media (provocation)

Figure 13. Thickening of the tunica media, associated intimal bumps, and distorted lumen morphology observed on optical coherence tomography of patients with vasospastic angina. Provided by the Department of Cardiovascular Medicine, Wakayama Medical University.

after coronary spasm, a significant increase in the area and thickness of the tunica media has been reported.[339,340] Moreover, vasoconstriction occurs in asymptomatic patients with VSA, resulting in changes in intimal morphology.[341] This finding suggests that hypercontraction of the tunica media, which is composed of vascular smooth muscle, plays an important role in the vascular structural changes of coronary spasm.[343] Animal studies have shown that inflammation in the tunica media and hypercontraction of smooth muscle in the tunica media can be explained by a molecular mechanism centered on Rho-kinase,[344] and that VSA cases also show inflammation consistent with the site of coronary spasm,[32] which is consistent with this observation.

3.2.2 Involvement of Vasa Vasorum

The VV is a network of blood vessels, 30–200 μm in diameter, that surround larger blood vessels and can be evaluated in vivo using OCT.[345] The VV is mainly responsible for supplying oxygen and nutrients to the vessel wall and is classified as adventitial (AVV), which runs in the adventitia, and intraplaque neovessels (IPNVs), which run within plaque.[346] VVs are reported to proliferate in VSA, with AVVs increasing in diffusely spastic VSA, and IPNVs increasing in focally spastic VSA.[112] Moreover, VSA with myocardial bridging (myocardial bridge) results in a loss of AVV at the site of myocardial bridging.[347] However, the relationship between VVs and the phenotype of VSA remains unclear, and future studies are warranted.

3.2.3 Involvement of Layered Plaque

Organic abnormalities are found in more than half of cases of VSA.[36] Of these, many cases have been reported to have layered plaque.[331] Such stratified plaques are considered to be healed after asymptomatic rupture or erosion and are thought to form as a result of the fibrous component replacing the initial thrombus that was generated during the healing process.[348,349] Thus, the main constituent components of layered plaques are the fibrous and flat thrombus components. One hypothesis for why layered plaques are more common in VSA is that thrombi develop and heal from intimal tears induced by coronary spasm, resulting in the formation of layered plaques,[331] but this theory has not yet been fully elucidated.

4. Coronary Angioscopy

Coronary angioscopy (CAS) is an intravascular imaging modality that allows direct visualization of the vascular luminal surface in full-color, real-time images through a lens. Although evaluation of cross-sectional vessel images, as with IVUS and OCT, is not available with CAS, CAS enables detailed observation of the color tone, irregularities, and mobility of the luminal surface, which helps to evaluate intimal injuries, thrombus, etc.[350,351]

Because coronary spasm is diagnosed by CAG, CAS is not essential for clinical diagnosis of VSA and is instead mainly used for research purposes to clarify the pathophysiological mechanism.

The number of CAS reports on VSA is limited because CAS is approved for clinical use only in Japan. In this section, the CAS findings in VSA are summarized.

When coronary spasm sites are observed by CAS, intimal irregularities, thrombus, and yellow plaques are found at a frequency of ≈40%.[352] In a recent report, thrombi were observed in coronary spasm-induced sites with about 30% frequency, whereas thrombus adherence was not seen in non-induced sites.[353]

Three mechanisms for the presence of thrombus in spasm sites have been proposed: (1) plaque rupture caused by external forces from coronary spasm,[38,354] (2) intimal erosion due to hyperconstriction or hyperextension of the intima by severe or repeated coronary spasm,[339] and (3) coronary spasm itself promotes thrombus formation by increasing platelet aggregation and activation of blood coagulation.[33,355]

Another study demonstrated that a strong vasoconstrictive response to intracoronary ACh infusion occurs distal to 1st-generation DES with poor neointimal coverage and in-stent thrombi.[250] However, 2nd-generation everolimus-eluting stents demonstrated less thrombus adhesion and less vasoconstriction response to ACh than 1st-generation DES, and the degree of neointimal coverage was comparable.[356] These reports suggest that there is an association between intracoronary thrombus and an endothelium-

dependent vasoconstrictive response.

Although thrombi are often found in the early stages of vascular healing after stenting,[357] thrombi in the chronic phase could be a predictor of future cardiovascular events.[358] Because the presence of thrombus suggests endothelial dysfunction at the site, endothelial dysfunction may play a significant role in coronary spasm.

A previous study has investigated the CAS and OCT findings of the 2 coronary spasm types; focal spasm, which shows localized transient vessel narrowing, and diffuse spasm, which is diffuse vasoconstriction in >2 adjacent AHA coronary segments.[359] In that study, yellow plaques and mural thrombi were more frequently observed at the focal spasm site than at the diffuse spasm site, and in addition the plaque volume and lipid content were larger at the focal spasm site.[359]

These results indicate that focal spasm could be related to a local hypersensitivity reaction due to atherosclerotic changes,[323,339,360,361] whereas diffuse spasm could be attributed to disturbances of vasomotion.[359] Therefore, in patients with focal coronary spasm, administration of aspirin or statins in addition to CCBs and nitrites may be considered to prevent future cardiovascular events.[146,359,362] It has been reported that patients with yellow plaques in the chronic phase after DES implantation have a poorer prognosis.[363] Thus, careful attention to patients presenting focal coronary spasm with yellow plaques may be required. Because differences in the features and the progression of arteriosclerosis have been found between focal and diffuse spasm, the mechanism may also differ between these two types of spasm. These have not yet been fully elucidated, and further research is warranted.

5. CT, MRI, Nuclear Medicine Examinations

5.1 Significance of Noninvasive Imaging in the Diagnosis of VSA

Recommendations for noninvasive imaging in patients with suspected VSA are shown in **Table 14**.[364]

Table 14. Recommendations and Levels of Evidence for Noninvasive Imaging in Patients With Suspected Vasospastic Angina

	COR	LOE
CCTA should be considered to rule out obstructive coronary artery disease in patients with suspected vasospastic angina.	IIa	C
^{123}I-BMIPP myocardial scintigraphy may be considered in patients with suspected vasospastic angina[364]	IIb	C

^{123}I-BMIPP, ^{123}I-β-methyl-p-iodophenyl-pentadecanoic acid; CCTA, coronary computed tomography angiography; COR, Class of Recommendation; LOE, Level of Evidence.

5.1.1 Coronary Computed Tomography Angiography (CCTA)

Even when a patient has symptoms suspicious of VSA, it may be difficult to exclude obstructive CAD by symptoms and ECG. CCTA has a high negative predictive value for obstructive CAD and is useful for ruling it out.[365] The ESC guidelines recommend invasive angiography or CCTA to evaluate underlying CAD in patients with characteristic episodic resting anginal symptoms and ST-segment changes that are relieved by nitrates or CCBs.[6] Therefore, it is reasonable to consider CCTA to rule out obstructive CAD in cases of suspected VSA.

On the other hand, it is difficult to diagnose VSA with CCTA, considering the impracticality of CCTA imaging during an attack of coronary spasm and the fact that coronary arteries are usually dilated with nitroglycerin during CCTA imaging to improve coronary artery visualization. In the absence of obstructive CAD on CCTA, the need for evaluation of INOCA, including VSA, should be carefully considered. It should also be noted that obstructive CAD may be accompanied by VSA, so the presence of obstructive CAD on CCTA does not exclude VSA.

In addition, β-blockers are sometimes used during CCTA to improve coronary artery visualization by controlling the patient's heart rate, but, in general, there is concern that β-blockers may exacerbate coronary spasm.[366] Caution should be exercised in the use of β-blockers when testing patients whose history is highly suggestive of VSA and whose risk is considered high, such as patients with a history of syncope or frequent resting anginal symptoms. Because calcium antagonists such as verapamil and diltiazem, which are used to treat VSA, can also be expected to decrease heart rate, consideration may be given to take these medications instead of β-blocker administration during CCTA.

5.1.2 Myocardial Scintigraphy

In the "Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina)" (JCS 2013),[2] ^{123}I-MIBG (^{123}I-metaiodobenzylguanidine) myocardial scintigraphy, ^{201}Tl (^{201}thallium) myocardial scintigraphy combined with hyperventilation stress test or exercise stress test, and ^{123}I-BMIPP (^{123}I-β-methyl-p-iodophenyl-pentadecanoic acid) myocardial scintigraphy were all Class IIb recommendations and may be considered in patients with suspected VSA.[2] Reports from 1980 to 2018 on the diagnostic performance of these tests for VSA have been summarized.[364] ^{123}I-BMIPP myocardial scintigraphy is reported to have a relatively high diagnostic performance with sensitivity of 72.5% and specificity of 82.7%, whereas ^{123}I-MIBG myocardial scintigraphy (sensitivity 61.9%, specificity 79%) and ^{201}Tl myocardial scintigraphy (exercise stress: sensitivity 56.6%, specificity no data; hyperventilation stress: sensitivity 64.9%, specificity 54.5%) had relatively insufficient diagnostic performance.[364] Although VSA was diagnosed as coronary spasm provoked by the intracoronary administration of ACh or ergonovine in these reports on diagnostic performance, it should be noted that the diagnostic criteria for VSA have not been standardized, the sample size of these studies were small, and biases were not fully eliminated.[364] Considering that little research has been conducted on these testing methods in recent years, we have not included in this focused update version of the Guideline the recommendations for ^{123}I-MIBG myocardial scintigraphy and ^{201}Tl myocardial scintigraphy combined with hyperventilation stress test or exercise stress test. The following outlines ^{123}I-BMIPP myocardial scintigraphy.

5.1.3 ^{123}I-BMIPP Myocardial Scintigraphy

^{123}I-BMIPP myocardial scintigraphy is a procedure to image myocardial fatty acid metabolism. The administered ^{123}I-BMIPP, as with free fatty acids in the blood, is taken

Table 15. Recommendations and Levels of Evidence for Noninvasive Imaging in the Diagnosis of Microvascular Angina

	COR	LOE
Evaluation of myocardial perfusion with ^{13}N-ammonia PET should be considered in patients with stable chronic chest pain but no significant stenosis in the epicardial coronary arteries[88,173]	IIa	B
Evaluation of myocardial perfusion with stress myocardial perfusion MRI may be considered in patients with stable chronic chest pain but no significant stenosis in the epicardial coronary arteries[370–372]	IIb	B

COR, Class of Recommendation; LOE, Level of Evidence; MRI, magnetic resonance imaging; PET, positron emission tomography.

up by cardiac myocytes and becomes ^{123}I-BMIPP-CoA, which is mainly incorporated into the intracellular lipid pool and partly translocated into mitochondria.^{123}I-BMIPP is a branched-chain fatty acid with a methyl group at the β position of the carboxyl group, and it accumulates temporarily in the myocardium, which produce images reflecting fatty acid metabolism.

Beta-oxidation of fatty acids accounts for almost two-thirds of myocardial energy metabolism. However, in the presence of myocardial ischemia, the substrate for energy metabolism shifts from fatty acids to glucose. In addition, the impairment of myocardial fatty acid metabolism associated with ischemia persists for a while after coronary reperfusion (ischemic memory).[367–369] By performing ^{123}I-BMIPP myocardial scintigraphy during this period, the myocardial fatty acid metabolic impairment associated with myocardial ischemia can be detected without a stress test. Therefore, ^{123}I-BMIPP myocardial scintigraphy may be useful in the diagnosis of VSA, but it should be noted that it is difficult to differentiate it from ischemia due to obstructive CAD. The diagnostic sensitivity is not high (72.5%) enough to rule out VSA with negative results. In addition, the degree of accumulation of ^{123}I-BMIPP is influenced by the severity of ischemia and the time between the ischemic attack and imaging; thus care must be taken in the interpretation.

^{123}I-BMIPP myocardial scintigraphy can play a role in the follow-up of therapy. Previous reports have shown that in 75.5% of patients with VSA, the course of symptoms and the result of ^{123}I-BMIPP myocardial scintigraphy are consistent, but in the remaining 24.4% of patients there is a discrepancy;[364] thus further evidence should be accumulated regarding the prognostic impact of follow-up strategies using ^{123}I-BMIPP myocardial scintigraphy.

5.2 Significance of Noninvasive Imaging in the Diagnosis of Microvascular Angina

Recommendations for noninvasive imaging in the diagnosis of MVA are shown in **Table 15**.[88,173,370–372]

5.2.1 ^{13}N-Ammonia Positron Emission Tomography (^{13}N-Ammonia PET)

PET allows quantitative evaluation of MBF using tracers such as ^{15}O-water, ^{13}N-ammonia, and ^{82}rubidium (^{82}Rb). These are the most widely studied noninvasive quantitative methods of MBF to date and are considered the gold standard.[373]

Imaging in list mode is performed at the same time as or slightly before tracer injection, dynamic data are collected, and MBF is calculated using mathematical models such as compartment analysis. Pharmacological stress such as adenosine injection increases MBF due to endothelium-independent intramyocardial vasodilation. MBF reserve (MFR) is obtained by dividing MBF at pharmacologic stress by MBF at rest. MFR can be impaired in both epicardial coronary stenosis and CMD, but it can be used to evaluate coronary microvascular function in patients without significant stenosis of the epicardial coronary arteries. A reduction in MFR assessed by myocardial perfusion PET has been shown to be associated with cardiovascular events independent of the severity of coronary artery stenosis.[173] In addition, studies using myocardial perfusion PET to assess the severity of CMD have shown that patients with an MFR <2.0 have a higher 3-year incidence of cardiac events compared with patients with preserved MFR.[88]

In Japan, only the ^{13}N-ammonia PET scan is covered by health insurance for the diagnosis of IHD that cannot be diagnosed by other tests. However, ^{13}N-ammonia requires in-center synthesis using a small cyclotron, which limits the number of facilities where it can be performed.

5.2.2 Stress Myocardial Perfusion MRI

Stress myocardial perfusion MRI can provide a visual or semiquantitative assessment of reduced myocardial perfusion. Stress myocardial perfusion MRI has a high diagnostic performance for ischemia, and a meta-analysis using CAG with FFR as the standard has reported a diagnostic performance exceeding that of single-photon emission computed tomography (SPECT) and is comparable to PET (PET: sensitivity 84%, specificity 87%. MRI: sensitivity 89%, specificity 87%. SPECT: sensitivity 74%, specificity 79%).[374] Myocardial perfusion MRI is dynamic imaging of the myocardium with an intravenous bolus injection of gadolinium contrast agent to evaluate the dynamics of the first pass of the gadolinium. To assess myocardial ischemia, it needs to be combined with pharmacological stress using coronary vasodilators such as adenosine or adenosine triphosphate (ATP). In myocardium with preserved blood flow, the gadolinium contrast agent generates a high signal as it perfuses the myocardium, whereas myocardium with reduced blood flow has a slower onset of signal intensity and relatively low signal intensity. Typically, myocardial perfusion MRI scanned during coronary vasodilator stress shows a lower signal in the endocardial compared with the epicardial myocardium in patients with myocardial ischemia. When such findings suggestive of myocardial ischemia are obtained in patients without significant stenosis of the epicardial coronary arteries, the involvement of CMD is suspected.[375,376] The myocardial perfusion reserve index (MPRI), a semiquantitative measure of myocardial perfusion reserve, can be calculated from the time-signal intensity curves of resting and stress myocardial perfusion MRI. It has also been reported that the MPRI can be used to detect patients with CMD diagnosed by catheterization,[371] and has been shown to be associated with prognosis.[370,372]

A quantitative evaluation method for MBF using stress myocardial perfusion MRI has also been developed. It has

been reported that MBF quantitatively evaluated by stress myocardial perfusion MRI correlates well with MBF evaluated by PET, and is a promising method for evaluating CMD.[377] However, it requires a dual bolus approach of contrast agents or dual sequence and dedicated software, and is not yet widely used in clinical practice. Further accumulation of evidence is expected in the future.

Coronary vasodilators such as adenosine and ATP, which are used for pharmacological stress, are not covered by health insurance in Japan as drugs for stress myocardial perfusion MRI examinations, which is an obstacle to the widespread use of this testing method. In addition, arrhythmias such as AF are likely to worsen the image quality, and the gadolinium contrast agent cannot be used in patients with renal dysfunction (endstage renal disease with long-term dialysis, nondialysis cases with estimated glomerular filtration rate <30 mL/min/1.73 m^2, acute renal failure, etc.[378]). These are drawbacks to stress myocardial perfusion MRI. However, unlike PET, there is no radiation exposure, and when combined with myocardial delayed enhancement imaging, MI and other cardiomyopathies can also be evaluated in a single examination.

5.2.3 CCTA

CCTA has a high negative predictive value in the diagnosis of obstructive CAD and is performed mainly to rule it out in cases of suspected CAD.[365,379] Even in patients without obstructive CAD, if symptoms suggest myocardial ischemia, further evaluation is warranted because of the possibility of INOCA. On the other hand, one of the weaknesses of CCTA is that its positive predictive value for the diagnosis of obstructive CAD is not high enough.[365,380] Even if CCTA shows >50% stenosis, invasive CAG often does not show it. It is also difficult to evaluate whether the coronary artery stenosis detected by conventional CCTA alone is a functionally significant stenosis or not. Recently, FFRCT has emerged as an attractive method that can overcome these weaknesses. In addition, myocardial perfusion CT has made it possible to diagnose myocardial ischemia and to quantitatively evaluate MBF.

a. FFRCT (Fractional Flow Reserve-Computed Tomography)

FFRCT is a method of noninvasively estimating the FFR from conventional CCTA by post-hoc analysis. Based on 3D anatomical and physiological models of the coronary arteries created from conventional CCTA, fluid dynamics analysis is applied to simulate blood flow dynamics, and the estimated FFR values at each coronary artery segment are calculated as FFRCT values. The NXT study has shown improved specificity and positive predictive value with FFRCT compared with conventional CCTA when ischemia demonstrated by invasive FFR is used as the standard (CCTA: sensitivity 94%, specificity 34%, positive predictive value 40%, negative predictive value 92%. FFRCT: sensitivity 86%, specificity 79%, positive predictive value 65%, negative predictive value 93%).[381] When the quality of CCTA images is sufficient enough to analyze FFRCT, it has high diagnostic performance compared with SPECT and PET.[175]

In Japan, the HeartFlow FFR_{CT} (HeartFlow, Inc., Mountain View, California) was covered by health insurance in December 2018, but the number of facilities where it can be performed is limited.

b. Stress Myocardial Perfusion CT

CT perfusion (CTP) is a method of evaluating myocardial ischemia by observing the effect of intravenously injected iodine contrast medium on the myocardium, combined with pharmacological stress with coronary vasodilators such as adenosine and ATP. A meta-analysis using CAG with FFR as the standard reported that the diagnostic performance of stress CTP for ischemia is high (sensitivity 88%, specificity 80%), exceeding that of SPECT and comparable to PET and stress myocardial perfusion MRI.[374]

There are 2 types of CTP: static CTP, in which evaluation is based on image data from a single cardiac phase, and dynamic CTP, in which the first pass of contrast agent to the myocardium is imaged over time. A meta-analysis using CAG with FFR as the standard reported that both imaging methods have high diagnostic performance (static CTP: sensitivity 72%, specificity 90%; dynamic CTP: sensitivity 85%, specificity 81%).[382] Static CTP allows a relative reduction in radiation dose, whereas dynamic CTP is characterized by its ability to quantify MBF. Stress CTP is characterized by its ability to simultaneously evaluate CCTA for the presence of occlusive CAD, and its usefulness in the diagnosis of INOCA has been reported.[383] However, as with the stress myocardial perfusion MRI, coronary vasodilators such as adenosine and ATP, which are used for pharmacological stress, are not covered by health insurance in Japan as drugs for stress CTP.

5.3 Significance of Noninvasive Imaging in the Diagnosis of MINOCA

5.3.1 Cardiac MRI

CMR is useful to explore the underlying etiology of TP-NOCA (**Table 16**[384,385]). LGE imaging requires the administration of gadolinium contrast agent, whereas cine MRI and T2-weighted imaging are performed without contrast agents.

Cine MRI can obtain cine images with high spatial resolution and can detect regional wall motion abnormalities. It is possible to set an arbitrary imaging cross-section, and evaluation of the right ventricle, which is difficult to evaluate with echocardiography, is also possible.

On T2-weighted images, edematous tissue can be detected with high signal. Myocardium damaged by AMI, acute myocarditis, or takotsubo syndrome can all be depicted with high signal on T2-weighted images.

There are various LGE patterns depending on the etiology of myocardial injury. Usually, MI shows subendocardial or transmural LGE in a particular coronary artery territory.[386] Myocarditis, on the other hand, often shows mid-wall or epicardial LGE.[386] LGE is usually absent in takotsubo

Table 16. Recommendation and Level of Evidence for Cardiac MRI in the Diagnosis of MINOCA

	COR	LOE
Cardiac MRI with gadolinium contrast should be considered to explore the underlying etiology of TP-NOCA[384,385]	IIa	B

COR, Class of Recommendation; LOE, Level of Evidence; MINOCA, myocardial infarction with non-obstructive coronary arteries; MRI, magnetic resonance imaging; TP-NOCA, troponin-positive non-obstructive coronary arteries.

syndrome,[387] but has been reported as present in some cases in the acute phase.[388,389]

CMR with gadolinium contrast has been reported to distinguish the etiology in 87% of patients with TP-NOCA (acute myocarditis: 37%, takotsubo syndrome: 27%, AMI: 21%).[385] In a meta-analysis including 556 TP-NOCA patients, CMR with gadolinium contrast was reported to determine MI in 21% of patients and myocarditis in 33% of patients.[384]

6. Vascular Endothelial Function Test and Vascular Reactivity

6.1 Significance and Usefulness of Vascular Endothelial Function Tests in the Pathogenesis and Diagnosis of INOCA

Impaired production and release of NO due to vascular endothelial dysfunction plays an important role in the pathogenesis of coronary artery vasospasm. However, although vascular endothelial dysfunction is frequently observed in atherosclerosis, not all atherosclerosis results in coronary artery vasospasm. This is thought to be because the pathophysiology of coronary artery vasospasm involves multiple factors, such as genetic predisposition (e.g., eNOS gene polymorphisms), that directly contribute to endothelial dysfunction and abnormal increase in vascular smooth muscle tone. As discussed in detail in other chapters, INOCA includes epicardial coronary spasm as well as CMD. The primary pathogenesis of CMD is either (1) structural remodeling of the microvasculature or (2) microvascular functional abnormality, or a combination of both.[390] Typical features of structural remodeling are wall thickening in the lumen of arterioles and capillary rarefaction,[391] which reduces the vasodilatory ability of the microvasculature and limits maximum blood flow and oxygen supply. The following parameters are used to evaluate structural remodeling: decrease in CFR, assessed by coronary artery reactivity to endothelium-independent vasodilators such as adenosine; and increase in the IMR. Microvascular dysfunction is primarily an abnormality of arterioles with relatively larger diameters that act as resistance vessels.[390] The physiological effect of microvascular function is an endothelium-dependent vasodilatory response in resistance vessels that occurs with increased oxygen demand in tissues. Vascular endothelial dysfunction causes impaired vasodilation and, in some cases vasoconstriction.[392] Coronary endothelial function is invasively assessed by increasing coronary blood flow through the administration of ACh to coronary arteries. ACh acts as both vasoconstrictor and vasodilator.[393–395] As a vasoconstrictor, it binds to the muscarinic type-3 receptor (M3 receptor) on VSMCs and stimulates the intracellular release of calcium ions, inducing vasoconstriction. As a vasodilator, it binds to the M3 receptor on vascular endothelial cells, stimulates the release of calcium ions, and activates NO synthase, which results in calmodulin-dependent NO release; NO stimulates soluble guanylate cyclase (sGC) in vascular smooth muscle to increase cyclic guanosine monophosphate (cGMP), causing vasodilation. Thus, ACh predominantly induces either the vasoconstriction of vascular smooth muscle or vasodilation mediated by vascular endothelial cells. It has been reported that myocardial ischemia during exercise stress myocardial perfusion scintigraphy or at rest in INOCA patients correlates with endothelial dysfunction of the left anterior descending coronary artery as assessed by an intracoronary ACh test.[396,397] Microangiopathy due to structural remodeling of the microvasculature is often complicated by coronary endothelial dysfunction.[80]

There are 2 major noninvasive tests of peripheral vascular endothelial function currently used in clinical practice: flow-mediated endothelium-dependent vasodilation (FMD), and reactive hyperemia peripheral arterial tonometry (RH-PAT). The peripheral vascular endothelial function assessed by these tests is useful in prediction because it correlates positively with coronary endothelial function.[398,399] Other reports have shown that endothelial dysfunction in INOCA involves not only coronary arteries but also systemic arteries.[400–402] Coronary endothelial dysfunction in INOCA is associated with the urinary albumin/creatinine ratio, a marker of the renal microcirculation.[403] Additionally, a recent study reported on the response of resistance vessels to drugs using gluteal subcutaneous fat biopsies from patients with INOCA, including CMD, MVS, and VSA; the results showed decreased endothelium-dependent vasodilatory responses in peripheral arteries and increased responses to vasopressor substances.[404] Therefore, coronary artery disorder in INOCA is considered part of a systemic vascular disorder, and noninvasive tests of peripheral vascular endothelial function may predict INOCA. As an illustration, it has been reported that vascular endothelial dysfunction assessed by FMD or RH-PAT correlates with INOCA,[398,405,406] and that vascular endothelial dysfunction in patients with INOCA assessed by FMD and RH-PAT is a strong predictor before catheterization.[398,407] Likewise, previous studies have reported concomitant CMD and peripheral vascular endothelial dysfunction assessed by RH-PAT or FMD in patients with VSA.[143,408,409] In contrast, other studies have reported that RH-PAT and FMD do not correlate with CMD,[410,411] so further studies are required.

6.2 Usefulness of Assessing Peripheral Vascular Endothelial Function for Prognostication in INOCA Patients

Patients with CMD or VSA have a 4–5-fold risk of cardiovascular death and MI compared with patients without cardiac disease but similar conventional cardiovascular risk.[412] Among these patients, complications of CMD with coronary endothelial dysfunction have been reported to have a particularly poor prognosis;[412] therefore, risk assessment is important. Vascular endothelial function plays an important role not only in the regulation of vascular tonus, but also in vascular permeability, platelet function, the coagulation/fibrinolytic system, and smooth muscle proliferation. Thus, it involves INOCA as well as atherosclerosis development and acute coronary events. Coronary endothelial dysfunction has also been associated with the development of subsequent cardiovascular events in INOCA patients.[413,414] Furthermore, the assessment of peripheral vascular endothelial dysfunction in INOCA patients by noninvasive RH-PAT could also predict subsequent cardiovascular events.[415] Of the 2 available tests for peripheral vascular endothelial function in clinical practice, RH-PAT and FMD, a meta-analysis reported that their prognostic value was comparable, with a 1 SD (standard deviation) deterioration in measurements for either test doubling the risk of subsequent cardiovascular events.[416]

In summary, noninvasive assessment of vascular endothelial function is useful for predicting INOCA and the prognosis of INOCA patients. Additionally, the noninvasive nature of the tests allows for repeated testing and can be used for patient-specific monitoring (**Table 17**).

6.3 Significance of Vascular Endothelial Function in MINOCA

MINOCA encompasses the following pathological conditions: plaque disruption or erosion, coronary artery vasospasm, SCAD, CMD, and other type 2 MI that cause an imbalance of the oxygen demand–supply without obstructive CAD. As described above, endothelial dysfunction plays an important role in plaque disruption or erosion, coronary artery vasospasm, and microangiopathy, and these conditions are associated with peripheral vascular endothelial dysfunction as assessed by RH-PAT and FMD. Studies examining the association between SCAD and endothelial dysfunction have not yielded consistent results;[41,417,418] however, coronary endothelial dysfunction may be involved in the pathogenesis of MINOCA. Further studies are needed to determine whether tests of vascular endothelial function are useful in predicting the development of MINOCA and the prognosis of patients with MINOCA.

6.4 Reference Values in the Testing of Peripheral Vascular Endothelial Function

There is ample evidence that vascular endothelial dysfunction plays a central role in various pathophysiologies, such as early and advanced atherosclerosis, coronary artery vasospasm, and microangiopathy; it has been proven to be predictive of cardiovascular events.[416] On the other hand, guidelines for reference values and diagnostic criteria of peripheral endothelial dysfunction have not been established because of differences in subjects, study designs, and measurement methods. In 2021, the Japanese Circulation Society and the Japan Society for Vascular Failure published diagnostic guidelines for the application of tests of vascular endothelial function in daily clinical practice, disease management, and treatment.[419] **Figure 14**[419] shows the reference values for the 2 noninvasive vascular endothelial function tests that can be used in clinical practice: FMD, by placing a tourniquet around the forearm, and RH-PAT, which measures finger arterial pulse waves. The reference values shown here are not those determined by studies to predict coronary artery vasospasm or INOCA, but those reviewed from reports examining vascular endothelial function and prognosis. The validity of these reference values needs to be studied further in the future.

Table 17. Recommendations and Levels of Evidence for Noninvasive Endothelial Function Tests

	COR	LOE
Vascular endothelial function testing may be considered for patients with suspected INOCA, including VSA and CMD	IIb	C
Vascular endothelial function tests may be considered for patients with INOCA to predict prognosis	IIb	C

CMD, coronary microvascular dysfunction; COR, Class of Recommendation; INOCA, ischemia and non-obstructive coronary artery disease; LOE, Level of Evidence; VSA, vasospastic angina.

7. Invasive Coronary Physiological Testing

7.1 Vasospasm and CMD in INOCA

INOCA is a concept that encompasses several different pathophysiologies, including VSA and CMD. Although active vasoconstriction is diagnosed by imaging to confirm the response to drugs (ACh, ergonovine), physiological testing is required to evaluate the dilatation function of

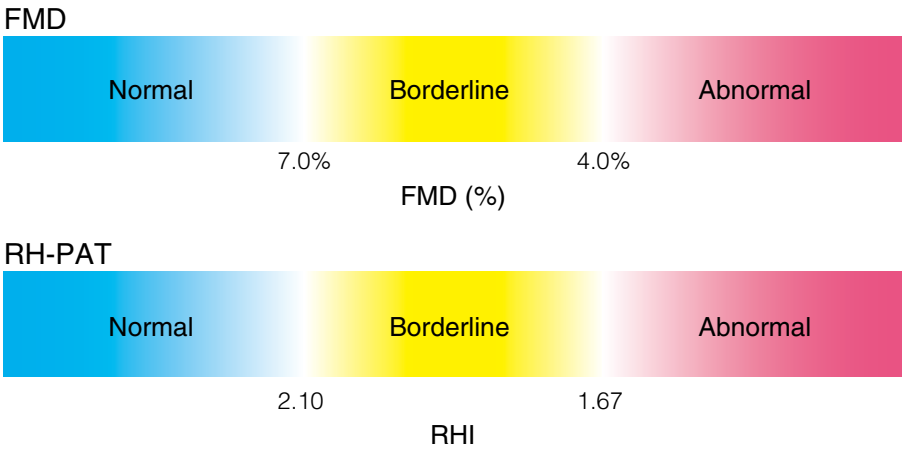


Figure 14. Reference values for the 2 noninvasive vascular endothelial function tests that can be used in clinical practice: flow-mediated endothelium-dependent vasodilation (FMD), by placing a tourniquet around the forearm, and reactive hyperemia peripheral arterial tonometry (RH-PAT), which measures finger arterial pulse waves. RHI, reactive hyperemia index. (Source: Physiological Diagnostic Criteria for Vascular Failure, Life Science Publishing, Published January 30, 2021.[419])

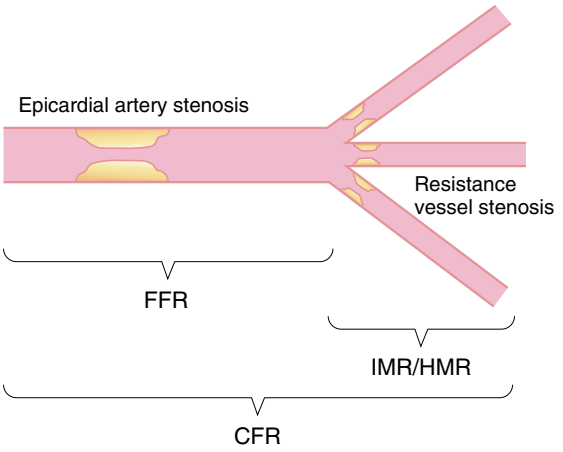


Figure 15. Physiological indices in coronary artery sites. CFR, coronary flow reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; IMR, index of microcirculatory resistance.

coronary arteries, especially coronary microvessels. Currently, CFR and IMR are used to evaluate the coronary microvascular dilation response. A low CFR and high IMR are the diagnostic criteria for MVA.[139]

7.2 Coronary Flow Reserve (CFR)

CFR is a measure of the reserve capacity of how much maximal hyperemic blood flow can increase relative to resting blood flow. It represents the ability of coronary blood flow to increase in response to increased myocardial oxygen demand. It is mainly regulated by resistance vessels (pre-arterioles, arterioles, pre-capillaries, and capillaries) that are $<500\,\mu$m in diameter.

CFR is an indicator of abnormalities in both the epicardial arteries and coronary microvasculature, and can be used as an indicator of the coronary microcirculation if there is no significant stenosis in the epicardial arteries. However, its interpretation requires caution because it is sensitive to many other influences besides coronary stenosis, including myocardial status, cardiac (pressure and volume) load status, blood pressure, and heart rate at the time of measurement.

Invasive measurement of CFR includes a Doppler method using a Doppler guidewire, and a thermodilution method using a guidewire with a temperature sensor, and noninvasive tests include transthoracic echocardiography, myocardial scintigraphy, and PET, etc. In INOCA evaluation, no difference in the detection rate of CMD by CFR has been found between studies using invasive and noninvasive tests.[139] Among the noninvasive tests, the detection rates have been reported to be higher in PET studies.

7.2.1 Standard for CFR Measurement by Thermodilution Method

By using a 0.014-inch guidewire with a pressure sensor and a temperature sensor, it is possible to measure CFR as well as FFR using the thermodilution method. The mean transit time (Tmn) is measured from the thermodilution curve in the guiding catheter and the thermodilution curve by the temperature sensor near the tip of the wire when room temperature saline is administered into the coronary artery. The Tmn is then measured again after maximum hyperemia is induced by administering a drug (adenosine, ATP, papaverine hydrochloride, nicorandil, etc.) that dilates the resistance vessels maximally.

According to the indicator dilution theory:

$$F = V/Tmn$$

where F indicates blood flow; V is vascular volume between the injection site and the measuring site; and Tmn, the mean transit time travelling from the injection site to the distal sensor.

Because CFR is the ratio of resting blood flow F-rest to maximal hyperemic blood flow F-hyperemia:

$$CFR = \text{F-hyperemia}/\text{F-res} = (\text{vessel volume V}/\text{Tmn-hyperemia})/(\text{vessel volume V}/\text{Tmn-rest})$$

Assuming the epicardial vascular volume V remains unchanged, CFR can be calculated as:

$$CFR = \text{Tmn-rest}/\text{Tmn-hyperemia}$$

7.2.2 Standard for CFR Measurement by the Doppler Method

The Doppler guidewire comprises a 0.014-inch guidewire with an ultrasound transducer onto its tip to measure coronary flow velocity using Doppler. To accurately measure coronary flow velocity, the transducer is placed in a straight section of an epicardial coronary artery, at a sufficient distance from either stenosis or vessel curve to avoid the influence of them, and the ultrasound beam direction is set as parallel as possible to the direction of coronary flow. Intracoronary nitrate is administered to maintain constant vessel area at the measurement site, and after confirming that a good flow velocity profile has been obtained, the time-averaged peak velocity (APV) at rest is measured. The APV is measured again during maximal hyperemia. Assuming the vessel area at the measurement site is constant, the ratio of APV represents the ratio of coronary blood volume. CFR can be calculated as:

$$CFR = \text{APV at maximum hyperemia}/\text{APV at rest}$$

7.3 Index of Microcirculatory Resistance (IMR)

By measuring intracoronary pressure and coronary flow at the distal coronary artery, just before the myocardial perforator branch, blood vessel resistance distal to the measurement site can be obtained. There are 2 resistance indices: IMR, obtained by thermodilution method using a pressure and a temperature sensor,[420–423] and HMR (hyperemic microvascular resistance), obtained by a wire with a pressure and Doppler sensor.[144,424] IMR and HMR are used as specific indices of coronary microcirculatory resistance compared with CFR (**Figure 15**).

7.3.1 Standard for IMR Measurement

A pressure guidewire with a temperature sensor is used to calculate IMR by simultaneously measuring distal coronary pressure (Pd) and distal Tmn. The pressure and temperature sensors are placed at least 6 cm distal to the catheter tip. The recommended location in each coronary artery is the mid to distal two-thirds of the left anterior descending artery, just before the 4PD-4AV bifurcation in the right

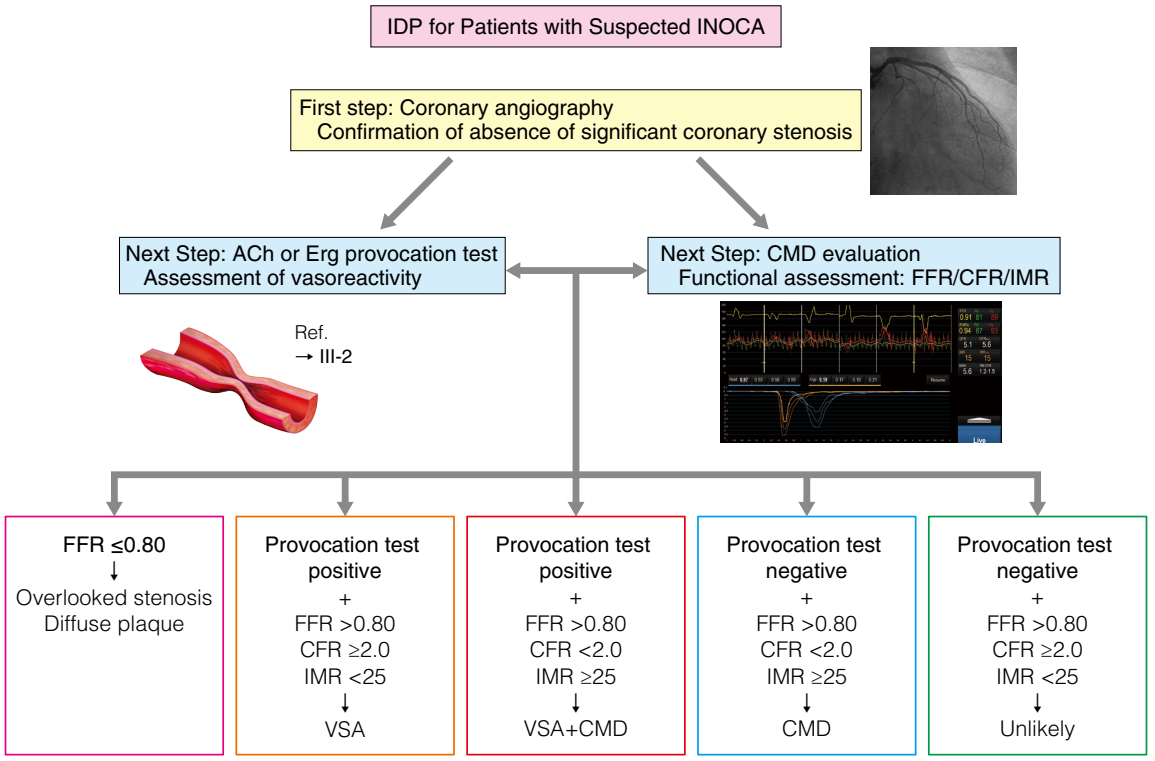


Figure 16. Comprehensive interventional diagnostic procedures for INOCA. ACh, Acetylcholine; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; Erg, Ergonovine; FFR, fractional flow reserve; IDP, interventional diagnostic procedures; IMR, index of microcirculatory resistance; INOCA, ischemia with non-obstructive coronary artery disease; VSA, vasospastic angina.

coronary artery, and the branch with the largest perfusion area in the left circumflex artery.

$$\text{TMR (true microcirculatory resistance)} = Pd / F = Pd \cdot Tmn / V$$

Assuming that vascular volume V is constant, TMR can be approximated by IMR as follows:

$$IMR = Pd \cdot Tmn$$

7.4 Comprehensive Diagnostic Procedures for VSA and CMD in INOCA (Figure 16)

Both a low CFR and high IMR are used to diagnose CMD. In a report of CFR and IMR measurements following an ACh-provocation test as an evaluation for INOCA,[142] a positive ACh-provocation was found in 68%, low CFR (<2.0) in 35%, and high IMR (≥18) in 40%. Many of these coexisted: VSA complicated by low CFR in 37%, high IMR in 48%, and VSA, low CFR and high IMR in 22%. On the other hand, in Europe and the USA, the recommended diagnostic procedure for INOCA is to measure CFR and IMR first, followed by ACh-provocation.[101,102] In this diagnostic procedure, 52% of INOCA cases were diagnosed as MVA alone (CFR <2.0, IMR ≥25), 17% as VSA alone, and 21% as a combination of both. In cases excluding VSA (epicardial artery spasm and MVS), 25% had high IMR (≥25), 24% had low CFR (<2.0), and 9% had a combination of both.[141]

The different diagnostic procedures (CFR/IMR first, or ACh-provocation test first) resulted in a similar number of negative (noncardiac) determinations (11–16%), but the CFR/IMR first strategy resulted in a lower ACh-provocation positive rate (diagnosed as VSA) (37% vs. 68%) and more cases being diagnosed as MVA alone (52% vs. 16%). Differences in diagnostic procedures may affect the diagnosis of INOCA endotypes and should be noted (**Figure 16**).

7.5 Physiological Indices and Prognosis

Stratification of pathophysiology by physiological indices has been shown to be useful in predicting subsequent prognosis in INOCA. The COVADIS group, defined the diagnostic criteria for MVA as myocardial ischemia in the absence of obstructive CAD associated with low CFR (<2.0 by invasive measurement or <2.5 by noninvasive measurement), MVS, high IMR (>25), and presence of slow flow (TIMI frame count >25). It was reported that events occurred in 7.7%/year during observation, but no sex or racial differences were observed.[14]

In a report measuring CFR and IMR following an ACh-provocation test, VSA with high IMR (≥18) was high risk for events.[142]

The CorMicA study, which examined the effect of incorporating of IDPs into the INOCA comprehensive diagnosis and subsequent treatment strategy in a prospective, randomized fashion, showed IDP contributed to

Table 18. Recommendations and Levels of Evidence for Physiological Evaluation in INOCA Patients		
	COR	LOE
If INOCA is suspected, physiological evaluation by measuring CFR and IMR should be considered[11,14,81,101,102,141,142]	IIa	B
CFR and IMR to predict prognosis in INOCA cases should be considered[86,425–428]	IIa	B

CFR, coronary flow reserve; COR, Class of Recommendation; IMR, index of microcirculatory resistance, INOCA, ischemia and non-obstructive coronary artery disease; LOE, Level of Evidence.

improvement in angina symptoms and QOL.[11,81] However, the CorMicA study focused mainly on measurements in the left anterior descending coronary artery, and further research is needed.

In a retrospective study measuring FFR, CFR, and IMR for the evaluation of FFR-negative intermediate stenosis, the group with low CFR (≤2.0) and high IMR (≥23) had the worst prognosis.[425] CFR and IMR are often reported to be a prognostic factor independent of FFR[86,426–428] (**Table 18**).

IV. New Insights Into Treatment

1. Daily Life Management

1.1 Cardiac Rehabilitation, etc.

1.1.1 Importance of Comprehensive Cardiac Rehabilitation in INOCA

Among patients with symptoms corresponding to angina pectoris, 50% have no significant fixed stenosis on CAG. The underlying mechanism for INOCA is epicardial or coronary MVS or CMD.[6,14,139] Coronary endothelial damage is one of the etiologies of VSA and CMD, and because IVUS often shows the presence of plaque coinciding with the site of spasm, the risk factors for INOCA are considered to be similar to those for atherosclerotic diseases[14,139] such as hypertension, diabetes, smoking, dyslipidemia, obesity, and lack of exercise. Comprehensive cardiac rehabilitation is recommended as Class 1 for INOCA as for IHD if there are no contraindications.[6,429,430] For both VSA and CMD, moderate to vigorous aerobic exercise at an anaerobic metabolic threshold level for at least 30 min should be performed at least 3 times each week (preferably daily).[6,429] Continuous full-body aerobic exercise such as brisk walking, jogging, or swimming for 140–180 min/week is recommended. Anginal attacks may occur during or immediately after exercise, with 2 possible mechanisms. One is coronary spasm due to exercise-induced hyperventilation and the other is due to CMD. In such cases, it is advisable to reduce the intensity of exercise and prolong the cool-down time to prevent hyperventilation. In CMD, β-blockers may be effective for exertional angina. Prominent risk factors of INOCA are smoking[431] and heavy alcohol consumption, and stress or cold.

In INOCA, the most important aspects of daily life management are smoking cessation, continuation of medical treatment, exercise, blood pressure control, weight control, dyslipidemia control, blood glucose control if diabetes mellitus is present (be careful of hypoglycemia during exercise), and moderation of alcohol consumption (**Table 19**).

Table 19. Recommendations and Levels of Evidence for Comprehensive Cardiac Rehabilitation in INOCA		
	COR	LOE
Comprehensive cardiac rehabilitation is recommended if there are no contraindications[6,429,430]	I	A
Moderate to vigorous aerobic exercise is recommended (≥30 min, at least 3 times per week)[6,429,430]	I	B
Smoking cessation is recommended[431]	I	A

COR, Class of Recommendation; INOCA, ischemia and non-obstructive coronary artery disease; LOE, Level of Evidence.

2. Pharmacotherapy

2.1 Fasudil (Rho-Kinase Inhibitor)

Coronary artery spasm is a local hyperreactivity mainly caused by an increase in contractility of vascular smooth muscle.[111] Phosphorylation of myosin light chain (MLC), which plays a central role in the regulation of vascular smooth muscle contraction and relaxation, is regulated by MLC kinase (MLCK) and phosphatase (MLCPh) activities (**Figure 17**).[432,433] In VSMCs, inositol triphosphate (IP3) generated by phospholipase C (PLC) in response to vasoactive substances triggers Ca^{2+} release from the intracellular sarcoplasmic reticulum. Simultaneously, the L-type Ca^{2+} channel on the VSMC plasma membrane opens and causes Ca^{2+} influx from outside the cell. Eventual increase in intracellular Ca^{2+} forms a complex with calmodulin, which activates MLCK. Phosphorylated MLCK then cross-reacts with actin, causing VSCMs to contract. When the intracellular Ca^{2+} levels decrease, Ca^{2+} dissociates from calmodulin, MLCK is inactivated, and MLCPh becomes dominant. Rho-kinase regulates VSMC contraction and relaxation in a Ca^{2+} concentration-independent manner. Stimulation by vasoconstrictive agents activates small GTPase Rho, which regulates MLC phosphorylation through its target, Rho-kinase. Activated Rho-kinase inactivates MLCPh by phosphorylating its myosin-binding subunit. Accordingly, the balance of MLCK/MLCPh activities becomes MLCK-dominant and MLC phosphorylation is promoted, resulting in hypercontraction of VSMCs.[434,435]

Thus, Rho-kinase is an important molecular switch that regulates the contraction and dilatation of vascular smooth muscle in an intracellular Ca^{2+} concentration-independent manner.[436] Fasudil, a Rho-kinase inhibitor, specifically and potently inhibits the Rho-kinase of VSMCs and releases coronary spasm.[437] Because the mechanism of vasodilatation by fasudil is completely different from that by nitrates, additional administration of fasudil after nitrates could

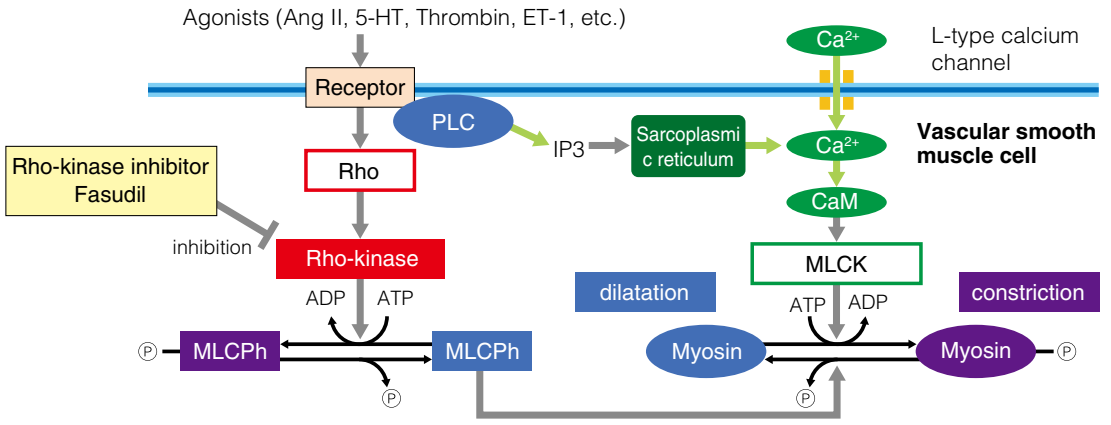


Figure 17. Regulation of vascular smooth muscle contraction and relaxation. 5-HT, 5-hydroxytryptamine; ADP, adenosine diphosphate; Ang, angiotensin; ATP, adenosine triphosphate; ET-1, endothelin 1; IP3, inositol triphosphate; MLCK, myosin light chain kinase; MLCPh, myosin light chain phosphatase; Ⓟ, phosphorus; PLC, phospholipase C.

Table 20. Recommendation and Level of Evidence for Intracoronary Administration of Fasudil for Release of Refractory Coronary Spasm

	COR	LOE
Intracoronary administration of fasudil should be considered to release refractory coronary spasm	IIa	B

COR, Class of Recommendation; LOE, Level of Evidence.

Table 21. Recommendation and Level of Evidence for Denopamine in Patients With VSA

	COR	LOE
Denopamine may be considered for VSA[450–452] (This is not covered by health insurance)	IIb	C

(This guideline is not intended to recommend off-label use) COR, Class of Recommendation; LOE, Level of Evidence; VSA, vasospastic angina.

promote an additive effect in coronary vasodilatation.[438] Although many case reports strongly suggest the usefulness of intracoronary administration of fasudil in patients with multidrug-resistant or refractory coronary spasms,[142,439–444] no randomized controlled trials or observational studies have objectively demonstrated that fasudil is superior to conventionally used vasodilators such as nitrates and nicorandil in the relief of coronary spasm. Meanwhile, in a retrospective observational study[445] that investigated the effect of fasudil on the slow-flow phenomenon, transient hypotension was observed in 22% of patients who received intracoronary fasudil (median dose of 18 mg, maximum dose of 30 mg) over 1–5 min under ECG monitoring. However, no serious complications such as death or MI occurred, indicating the safety of intracoronary administration of fasudil. Intracoronary administration of fasudil is being investigated as a therapeutic option for refractory coronary spasm that is intractable to conventional coronary vasodilators such as nitrates (**Table 20**).

2.2 Denopamine (Table 21)

CCBs and nitrates are useful treatment for VSA, but approximately 20% of patients are reported to be refractory to these drugs,[446] so other drugs have to be considered. In this context, adrenergic receptor agonists are an option, because autonomic nervous system involvement has been reported to be involved in the exacerbation and development of VSA.[447]

Denopamine, an oral adrenergic β_1 receptor selective stimulator developed in Japan for the treatment of chronic HF, is known to have a different mechanism of action from catecholamine preparations such as noradrenaline and dopamine because it does not have a catecholamine structure and has less excessive effects on pulse rate and blood pressure.[448] In addition, it has been reported that denopamine increases coronary blood flow through β_1-receptor stimulation and increases renal and femoral blood flow through α-receptor blockade.[448,449]

In clinical cases, the usefulness of denopamine for VSA without significant stenosis of the coronary arteries in which coronary spasm has been proven by spontaneous attacks or induction studies has been reported.[450–452] In 10 patients with VSA, administration of 40 mg of denopamine resulted in complete resolution of attacks in 7 cases, a significant decrease in the number of attacks and the use of nitroglycerin, and no exacerbations of attacks.[451] The usefulness of a low dose of 15 mg/day in the treatment of refractory VSA in combination with multiple drugs has also been reported.[452]

However, although denopamine has been effective in many case reports, it is possible that only effective cases have been reported, and there are no recent reports or reports on a large number of cases. Although denopamine may be effective in some cases, further studies, including dosage, are needed, and at this point, there is insufficient evidence of prophylactic efficacy.

Table 22. Recommendation and Level of Evidence for Aspirin in Patients With VSA

	COR	LOE
Aspirin is not recommended for patients with VSA without significant organic stenosis[454–460]	III (No benefit)	B

COR, Class of Recommendation; LOE, Level of Evidence; VSA, vasospastic angina.

Table 23. Recommendation and Level of Evidence for Kampo Medicines in Patients Wtih VSA

	COR	LOE
Kampo medicines may be considered for VSA[463,466–468] (This is not covered by health insurance)	IIb	C

(These guidelines are not intended to recommend off-label use)
COR, Class of Recommendation; LOE, Level of Evidence; VSA, vasospastic angina.

2.3 Aspirin (Table 22)

Low-dose aspirin is recommended for secondary prevention of not only ACS but also CCS because of its inhibitory effect on thromboxane A2 production by suppressing cyclooxygenase-1, thereby reducing thrombus formation.[17] On the other hand, it is a well-known fact that aspirin increases the risk of bleeding in primary prevention, even if cardiovascular events are prevented by aspirin, and the true benefit of low-dose aspirin is determined by its balance.[453]

High-dose aspirin has been reported to exacerbate symptoms of VSA,[454] and low-dose aspirin has been reported, including in meta-analyses.[455–459] An analysis of patients with VSA without significant coronary artery stenosis divided into aspirin-treated and non-aspirin-treated groups found that the incidence of MACE was similar in both groups.[455–458] A systematic review and meta-analysis[459] included 4 propensity-matched studies, 1 retrospective study, and 1 prospective multicenter study. A total of 3,661 patients with VSA without significant coronary artery stenosis were included in the meta-analysis, with and without aspirin. After 1–5 years of observation, no correlation was show between aspirin use and occurrence of MACE, nor MI or cardiac death. On the other hand, in a retrospective study of patients who developed ACS due to coronary spasm, the incidence of AMI and recurrent chest pain was significantly lower in the aspirin-treated group than in the non-treated group.[460] In addition, OCT has revealed thrombus-associated coronary plaque erosion at almost 25% of coronary spasm-inducing sites,[36] and the association between coronary spasm and coronary plaque erosion has also attracted attention. It has also been reported that coronary artery plaque erosion and subsequent thrombus formation may be induced by coronary spasm, leading to ACS.[461]

Antiplatelet therapy for VSA may be effective in preventing platelet activation after a coronary spasm attack and intracoronary thrombus caused by increased coagulability, and may be especially useful in patients with unstable angina due to coronary spasm or those with a history of ACS. However, the efficacy of antiplatelet agents has not been established at this time. On the other hand, VSA complicated by significant organic stenosis should be treated according to antiplatelet therapy in stable exertional angina.

2.4 Kampo Medicines (Table 23)

The association between CAD and anxiety and depression is well known. Accordingly, it has been reported that more patients with VSA have anxiety and depression than those with organic CAD.[462] The usefulness of kampo medicines used for anxiety and depression in VSA has been noted.

Shigyakusan has been reported as effective in the treatment of VSA associated with psychogenic symptoms including autonomic imbalance.[463] In that study, 2 patients with VSA and severe anxiety whose chest pain was not controlled by benidipine, isosorbide nitrate, or nicorandil were treated with shigyakusan and keishibukuryogan in small doses and their chest pain attacks completely disappeared, taking side effects into consideration.[463]

Keishibukuryogan has an action to improve peripheral circulation by dilating small arteries, resulting in improvement of blood flow and red blood cell stasis.[464,465] In addition, by producing endothelium-derived NO, it may improve vascular endothelial function and coronary spasm.[465] There is a case report of a patient with VSA refractory to efonidipine and unable to use nicorandil due to its side effects, who was completely prevented from chest pain for a long period of time with the use of keishibukuryogan.[466]

Other kampo medicines used for VSA include saibokuto for patients receiving nitrate medications, which may also improve symptoms.[467,468] Three cases have been reported in which a significant decrease in chest pain attacks and improvement in QOL were observed after additional administration of saibokuto to a patient with refractory VSA that was difficult to control with ≥2 coronary dilator drugs.[467]

Although kampo medicines including shigyakusan, keishibukuryogan, and saibokuto have been effective in many case reports, it is possible that only effective cases have been reported. There are no recent reports or studies of a large number of cases with comparator groups. Although it may be effective as an adjunctive therapy to standard drugs in some cases, further studies, including dosages, are needed.

3. Nonpharmacotherapy

3.1 ICD Implantation

3.1.1 Mechanism of Lethal Arrhythmias in VSA

The mechanism of lethal arrhythmias (ventricular tachycardia: VT/ventricular fibrillation: VF) in VSA is not well understood. It is thought that ischemia due to coronary spasm causes repolarization abnormalities,[469] and that myocardial scar formation due to ischemia in coronary spasm[470] is involved. In coronary artery ligation models, different mechanisms have been reported in the early acute phase (within 30 min of ischemia) and the late acute phase (within 12–48 h of ischemia).[471] The early acute phase mechanism is thought to be reentry associated with injured myocardium generated by ischemia,[472] while that of the late acute phase is assumed to be triggered activity via delayed afterdepolarization or early afterdepolarization.[473]

Table 24. Mortality Rate and Frequency of Appropriate ICD Therapy in VSA

Study (Author, Year)	Mean (median) observation period (years)	Mortality rate during the observation period					Frequency of appropriate ICD therapy
		Total	No history of cardiac arrest	History of cardiac arrest			
				Total	Without ICD	With ICD	
Ahn JM, et al, 2016[475]	(7.5)	8%	8%	13%	14%	4%	21%
Rodríguez-Mañero M, et al, 2018[476]	(4.9)	10%	NA	10%	40%	7%	27%
Vlastra W, et al, 2018[477]	7.5	3%	0%	9%	0%	13%	25%
Ogino Y, et al, 2021[478]	(4.2)	9%	NA	3%	NA	3%	20%
Tateishi K, et al, 2021[479]	3.2	15%	NA	11%	0%	20%	60%

ICD, implantable cardioverter defibrillator; NA, not available; VSA, vasospastic angina.

3.1.2 Frequency of Lethal Arrhythmias and Appropriate ICD Therapy in VSA

It has been reported that sudden cardiac death (SCD) may occur in patients with VSA, and is more frequent in cases refractory to medical therapy or with a history of out-of-hospital cardiac arrest.[148] In a questionnaire survey completed by 34 centers in Japan, 5,726 SCDs occurred over a 5-year period from 2014 to 2018, with 808 (14%) due to VSA.[474] Among SCDs due to VSA, 169 (21%) were resuscitated cardiac arrests (aborted SCD: ASCD), of which 117 (69%) had an ICD.

Although there are not many reports on prognosis and ICD availability in VSA (**Table 24**),[475–479] a recent systematic review[480] found that at a mean follow-up of 4.2 years, 6% of patients with VSA died, and the mortality rate was higher in patients with ASCD compared to patients without a history of cardiac arrest (9% vs. 5%). Among the ASCD patients, those who underwent an ICD implantation, had a lower mortality rate than those who did not (3% vs. 14%), and appropriate ICD therapy was observed in 17% of patients. It has been reported that death due to pulseless electrical activity can occur even in patients with an ICD, although this is not limited to patients with refractory VSA.[474]

Based on these considerations, it is reasonable to assign Class IIa to patients with pre-existing VT/VF, including ASCD, if they are refractory to medical therapy, and Class IIb even if medical therapy is effective (**Table 25**). In patients with a history of ASCD, the use of a wearable cardioverter defibrillator in the acute phase may also be considered.[481]

Table 25. Recommendations and Levels of Evidence for ICD Indication in VSA

	COR	LOE
ICD implantation should be considered in cases of pre-existing VT/VF, including out-of-hospital cardiac arrest associated with coronary spasm, when refractory to medical therapy[148,474–480]	IIa	B
ICD implantation may be considered in cases of pre-existing VT/VF, including out-of-hospital cardiac arrest associated with coronary spasm, when medical therapy is effective[148,474–480]	IIb	C

COR, Class of Recommendation; ICD, implantable cardioverter defibrillator; LOE, Level of Evidence; VF, ventricular fibrillation; VSA, vasospastic angina; VT, ventricular tachycardia.

3.1.3 Risk Factors for Lethal Arrhythmias in VSA

Long-term survival in patients with VSA has been reported to be high with smoking cessation and calcium antagonist therapy, unless the patient has multivessel coronary spasm or organic coronary artery lesions.[482] On the other hand, in a study of 2,032 VSA patients, including 188 ASCD cases, younger age, hypertension, dyslipidemia, family history of SCD, multivessel coronary spasm, and coronary spasm in the left anterior descending branch were risk factors for ASCD.[475] The early repolarization (ER) pattern on ECG is also considered a risk factor for VT/VF; 64 (24%) of 265 patients with VSA showed the ER pattern, and the ER pattern was significantly more common in patients with pre-existing VF. Recurrence of VF was significantly more common in patients with pre-existing VF and the ER pattern.[483] A recent systematic review found that the risk of VF is approximately 5-fold higher in the presence of the ER pattern.[484] Conversely, in a report of 34 ER patients with a history of VF, 13 patients (38%) had VSA, and caution should be exercised with the combination of both diseases.[485] Furthermore, Brugada syndrome can be associated with VSA, and it has been reported that coronary spasm can induce VF by acting additively or synergistically on the arrhythmogenic component of Brugada syndrome.[486,487] Thus, ASCD cases among VSA patients should be thoroughly evaluated for coexistence of Brugada syndrome.

3.1.4 Method for Assessing the Risk of Developing Lethal Arrhythmias in VSA

Electrophysiologic studies (EPS) are used to assess the risk of VT/VF; the frequency of VT/VF induced by EPS has been reported to be significantly higher in patients with VSA.[488] It has also been reported that VT/VF is often induced by EPS in patients with a history of out-of-hospital cardiac arrest.[489] Although an arrhythmic substrate may be present in patients with VSA, especially in those with a history of out-of-hospital cardiac arrest, the significance of EPS for considering ICD indication has not been established.

Other tests, such as QT dispersion and T wave alternans (TWA), have been reported to be related to the occurrence of VT/VF. QT dispersion was reported to be greater in patients with VSA, with significantly greater QT dispersion in those with VT/VF than in those without VT/VF.[490] The same was reported for TWA, with a higher incidence

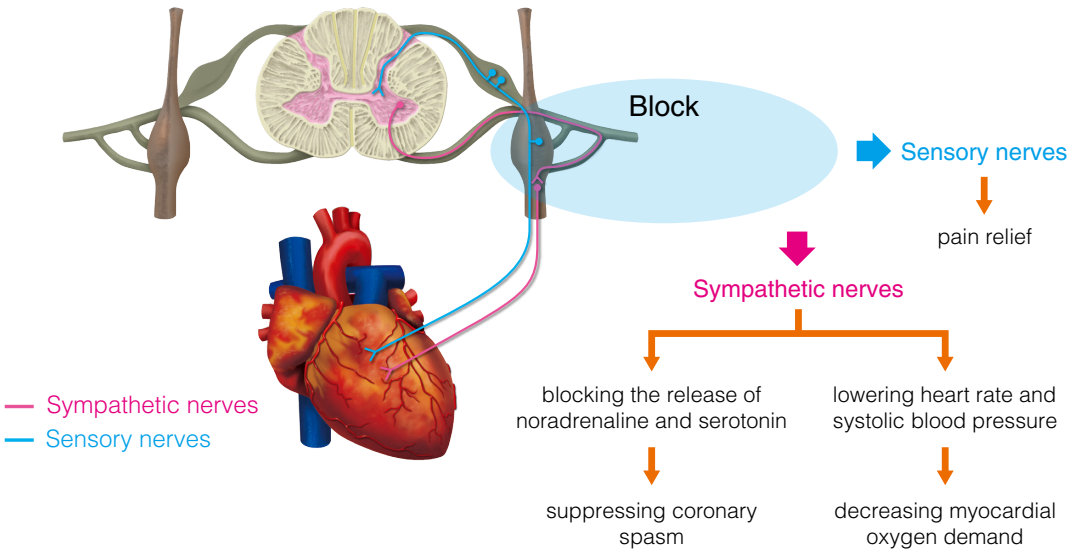


Figure 18. Effects of stellate ganglion block and thoracic sympathectomy for coronary spasm.

of TWA in patients with VSA and significantly greater variability in those with VT/VF compared to those without VT/VF.[491] Thus, QT dispersion and TWA may be related to VT/VF in patients with VSA, but there is not enough evidence to determine ICD indication.

3.2 Stellate Ganglion Block, Thoracic Sympathectomy

Autonomic dysfunction is thought to be involved in the pathogenesis of coronary spasm,[492] which occurs when vagal activity is high, such as late at night or at rest, and is induced by ACh, supporting the involvement of parasympathetic nerves.[295,361] In contrast, the increase in blood catecholamine levels during coronary spasm and the appearance of coronary spasm during nocturnal REM sleep indicate a decrease in vagal tone and an increase in adrenaline via the sympathetic nervous system, suggesting sympathetic involvement.[493,494] An imbalance between the sympathetic and parasympathetic nervous systems was believed to cause a predominance of sympathetic nervous system activity, which in turn affected coronary spasm.[495] Platelet aggregation via the sympathetic nervous system was thought to induce coronary spasm.[496,497] When anginal attacks occur during exertion or stress, increased myocardial oxygen demand may be involved in the coronary spasm.

Stellate ganglion block and thoracic sympathectomy have the following effects: (1) blocking noradrenaline binding to adrenergic α_1-receptors that constrict vascular smooth muscle, (2) blocking the release of serotonin caused by platelet aggregation via α_2-receptors, (3) decreasing myocardial oxygen demand by lowering heart rate and systolic blood pressure during thoracic sympathectomy, and (4) relieving pain by partially blocking the pain-sensing nerve pathway caused by ischemia (**Figure 18**). In addition, the antiarrhythmic effects through sympathetic nerve suppression and improvement of heart rate variability and QT time variability can potentially treat refractory or severe VSA.[498–500]

To date, most studies have demonstrated the benefit of stellate ganglion block and thoracic sympathectomy in refractory or severe VSA,[501–505] and randomized trials have been limited to a few single-center studies.[506] In the only prospective randomized study of the effect of thoracic sympathectomy on coronary spasm,[506] the study evaluated the effect of thoracoscopic thoracic sympathectomy on MACE for 24 months in 79 patients with drug-refractory VSA randomized to thoracoscopic thoracic sympathectomy or medical therapy. The rate of MACE at 24 months was significantly lower in the thoracic sympathectomy group than in the medical therapy group (16.22% vs. 61.90%, P=0.0001). The overall mortality rates were 0% and 14.29% in the thoracic sympathectomy group and medical therapy group, respectively (P=0.0001). The study included high-risk patients, among whom 60% and 50% had ST-segment elevation and fatal arrhythmia, respectively.

One problem with stellate ganglion block and thoracic sympathectomy is the possibility that the therapeutic effect may include a placebo effect.[507] Although controlled studies using a sham group are necessary to solve this problem, it is difficult to conduct such studies in patients with severe

Table 26. Recommendation and Level of Evidence for Stellate Ganglion Block and Thoracic Sympathectomy for Refractory or Severe VSA

	COR	LOE
Stellate ganglion block and/or thoracic sympathectomy may be considered for refractory or severe VSA[501,503,506] (This is not covered by health insurance)	IIb	C

COR, Class of Recommendation; LOE, Level of Evidence; VSA, vasospastic angina.

VSA who have a history of refractory or fatal cardiac accidents. Other issues include the dosage of anesthetic for stellate ganglion block,[507] whether thoracic sympathectomy should be performed bilaterally, and how long the effect lasts.[508]

Currently, despite strict lifestyle management such as smoking cessation and removal of mental stress as well as administration of multiple different types of coronary dilators, for cases of (1) fatal major vasospastic attacks, including frequent ICD shock therapy, or (2) frequent episodes of angina pectoris associated with increased sympathetic tone (frequently during the day and induced by stress or physical activity), a stellate ganglion block and/or thoracic sympathectomy may be considered one of the nonpharmacologic treatments (**Table 26**, **Figure 18**).

V. Providing Information to Citizens and Patients

Q1. What Is Vasospastic Angina?

Angina pectoris is a disease that causes chest pain when blood flow in the arteries that nourish the heart (coronary arteries) is reduced and the heart muscle (myocardium) is not supplied with sufficient oxygen (myocardial ischemia). Exertional angina pectoris is a disease in which the coronary arteries become extremely narrow due to atherosclerosis (coronary stenosis), and during exercise such as hurried walking or climbing stairs, myocardial ischemia occurs due to insufficient oxygen supply to the heart muscle, causing chest tightness. Vasospastic angina is a disease in which the coronary arteries temporarily contract excessively (spasm), resulting in a marked decrease in blood flow and subsequent myocardial ischemia. Unlike exertional angina, vasospastic angina tends to occur at rest, not during exercise (mainly at night during sleep and in the early morning at rest).

Q2. What Symptoms Does Vasospastic Angina Cause?

Symptoms of vasospastic angina often include a feeling of pressure, stuffiness, or tightness in the chest, which may manifest as severe chest pain with cold sweats or as weak, vague chest discomfort. The pain is mainly in the anterior chest area, but may extend to the back teeth, jaw, left shoulder, and left arm. It often lasts only a few minutes and resolves quickly with sublingual nitroglycerin. Temporary loss of consciousness (syncope) may occur after the patient is aware of chest pain. If the coronary spasm persists for a long time, myocardial infarction may occur and, in very rare cases, sudden death.

Although these symptoms often occur at rest during the night when the coronary arteries are prone to spasm, during sleep at night or after early morning awakening, they can also occur at rest during the daytime. Exertional angina occurs on exertion, whereas vasospastic angina is characterized by its occurrence at rest. Vasospastic angina can also occur only in the early morning with very light exertion, for example, when going to the bathroom after waking up or when going outside in the morning and breathing cold air.

Q3. How Is the Diagnosis of Vasospastic Angina Made?

Because the most decisive factor in diagnosing vasospastic angina is the history of the patient's symptoms, it is most important that the patient describe subjective symptoms in detail to the physician. The diagnosis is confirmed if a 12-lead electrocardiogram (ECG) is performed when chest pain occurs at rest during the night and early morning, and if ECG findings characteristic of myocardial ischemia are observed. However, it is not easy to record a 12-lead ECG at the onset of symptoms during the night or early morning unless the patient is in hospital. Ambulatory ECG

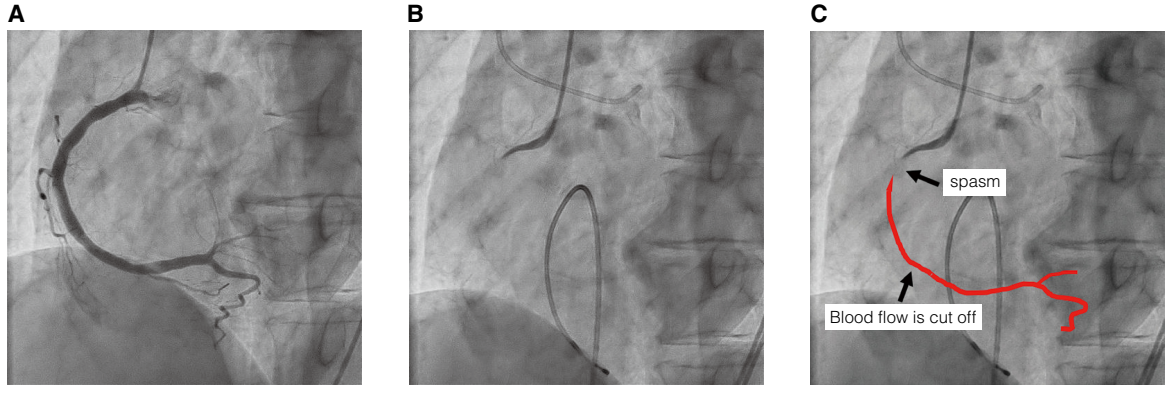


Figure 19. Coronary spasm provocation test during cardiac catheterization. (**A**) Coronary angiography shows no narrowing (stenosis) of the right coronary artery. (**B**,**C**) Coronary spasm provocation test showed chest pain and electrocardiogram showed ischemic findings. Coronary angiography showed complete occlusion of the proximal portion of the right coronary artery, and blood flow was cut off. A few minutes later, the chest pain subsided, the electrocardiogram normalized, the coronary artery spasm disappeared, and the patient again showed the findings in (**A**).

monitoring can be useful to detect myocardial ischemia if episodes of angina are frequent. However, patients who have symptoms infrequently, such as once every month to several months, are less likely to have an ECG recorded at the time of symptom onset.

The coronary spasm provocation test during cardiac catheterization is a useful method for the definitive diagnosis of vasospastic angina because it directly confirms that coronary spasm has occurred. During cardiac catheterization, a thin tube called a catheter is inserted into the artery and angiography (coronary angiography=imaging) of the coronary artery is performed to observe whether there are any narrowed areas (stenosis) in the coronary artery. Next, a special drug (acetylcholine or ergonovine) is injected into the coronary artery to observe whether or not a coronary artery spasm is induced (coronary spasm provocation test). If the coronary artery is transiently completely or incompletely occluded in the coronary spasm provocation test, the same chest symptoms as usual appear, and the ECG shows ischemic findings, then a definite diagnosis of vasospastic angina can be made. Most induced coronary spasms disappear within a few minutes (**Figure 19**). If myocardial ischemia at the time of symptom onset is confirmed by ECG, the diagnosis may be made by confirming the absence of coronary artery stenosis.

Q4. How Is Vasospastic Angina Treated?

Once vasospastic angina is diagnosed, a calcium-channel blocker, a drug that inhibits coronary spasm, is taken to prevent attacks. In addition, when chest pain appears, nitroglycerin is placed under the tongue and dissolved to quickly relieve symptoms. Coronary spasm prevention with calcium-channel blockers should be continued under medical supervision. Caution should be exercised because abrupt discontinuation of the drug often causes a rebound of symptoms. If angina attacks occur even with normal doses of therapy, the dose of calcium-channel blocker may need to be increased or long-acting nitrates may need to be added; 3–4 medications may be necessary to completely control attacks. Coronary spasms are more likely to occur at night or early the next morning after heavy drinking, so it is important to avoid excessive alcohol consumption and to remember to take your medication when drinking. Smoking is an important risk factor for coronary spasms, and quitting smoking is also important to prevent attacks.

Q5. What Is Microvascular Angina?

Microvascular angina is angina pectoris in which no narrowing (stenosis) or coronary spasm is seen in the large coronary arteries on coronary angiography, despite evidence of myocardial ischemia during chest pain. Microvascular angina causes myocardial ischemia due to coronary microvascular dilatation response disorder, in which coronary blood flow does not increase sufficiently due to abnormal coronary microvascular dilatation response, or coronary microvascular spasm, in which microvascular contractility is markedly increased. Unlike exertional angina pectoris or vasospastic angina, it is relatively more common in women (especially around menopause), and chest pain occurs not only during exertion but also at rest, and may last for 10 min or more. In many cases, sublingual nitroglycerin is not effective. Calcium-channel blockers and β-blockers are recommended for treatment, but if symptoms are not controlled, additional vasodilating agents such as angiotensin-converting enzyme inhibitors may be necessary.

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Appendix 2. Disclosure of Potential Conflicts of Interest (COI): JCS/CVIT/JCC 2023 Guideline Focused Update on Diagnosis and Treatment of Vasospastic Angina (Coronary Spastic Angina) and Coronary Microvascular Dysfunction (2020/1/1–2022/12/31)

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