Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina (Coronary Spastic Angina) (JCS 2008)

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Preface: In formulating the guidelines

Coronary spasm is defined as a condition in which a relatively large coronary artery running on the surface of the heart transiently exhibits abnormal contraction. If a coronary artery is completely or nearly completely occluded by spasm, transmural ischemia occurs in the region perfused by the artery, which in turn causes anginal attacks with ST elevation on the ECG. If a coronary artery is partially occluded or diffusely narrowed by spasm, or if it is completely occluded by spasm but sufficient collateral flow has developed distally, non-transmural ischemia occurs, causing anginal attacks with ST depression on the ECG. These pathological conditions are collectively termed vasospastic angina (also termed coronary spastic angina), as a type of angina pectoris caused by coronary spasm. Variant angina pectoris, characterized by ST elevation during anginal attacks, is another type of vasospastic angina. Coronary spasm has been shown to play key roles in the onset of not only variant angina pectoris but also rest angina pectoris, effort angina pectoris, acute myocardial infarction, and other related conditions. The mechanism of involvement of coronary spasm in the onset of acute coronary syndrome is now being elucidated.

In drawing up the present guidelines, cases of vasospastic angina were categorized into three classes as described below. Please note that no evidence levels are established for the guidelines, since no large-scale clinical studies of this condition have been performed.

Classification of Recommendations

Class I: The benefits and efficacy of a method of evaluation or treatment have been demonstrated or are widely approved.

Class II: Some discrepancy exists in findings or opinions regarding the benefits and efficacy of a method of evaluation or treatment.

Class IIa: As judged from available findings and opinions, a method of evaluation or treatment is likely to be beneficial and effective.

Class IIb: As judged from available opinions, neither the benefits nor the efficacy of a method of evaluation or treatment have been well established.
Class III: A method of evaluation or treatment has been demonstrated to be useless and possibly harmful at times, or its harmfulness has been widely agreed upon.

The primary goal of formulating the present guidelines is to establish a definition of vasospastic angina, and to provide diagnostic criteria for this condition. These guidelines are composed of standards generated on the basis of a great deal of evidence. Individual patients have their own specific clinical features, and you are encouraged to use the guidelines with this fact in mind.

The present guidelines provide guidance on the diagnosis and treatment of patients with vasospastic angina for physicians in clinical practice. The final decisions regarding diagnosis and treatment should be made by the attending physicians after the pathologic condition of each patient has been individually determined. In addition, even if a diagnosis or treatment not in conformity with the guidelines is implemented, it should be noted that determination of treatment by attending physicians based on the specific conditions and circumstances of their patients should take precedence over the guidelines, and that the present guidelines provide no grounds for argument in cases of legal prosecution.

We hope that these guidelines will be useful in the diagnosis and treatment of patients with vasospastic angina by cardiologists and all other physicians.

I Overview

1 Definition and pathology

1 Characterization of coronary spasm in ischemic heart disease

(1) Characterization of coronary spasm in terms of the etiology of angina pectoris

In coronary spasm, sudden excessive coronary vasoconstriction produces a transient reduction of blood flow, resulting in myocardial ischemia (supply ischemia/primary angina). Although coronary spasm occurs mainly in large coronary arteries running on the surface of the heart, it is also known to occur in the coronary microvasculature of the myocardium. Coronary spasm is not always preceded by elevations of blood pressure and heart rate, which increase myocardial oxygen consumption. In this regard, coronary spasm is a pathological condition that is clearly distinguishable from demand ischemia/secondary angina represented by effort angina pectoris.

Coronary spasm develops in sclerotic lesions of varying severity. Even when no stenotic lesions are visible on coronary angiography, intravascular ultrasound (IVUS) reveals clear atherosclerotic lesions in locations consistent with regions of coronary spasm. Reduction of blood flow due to coronary spasm activates platelets and the coagulation system, causing vascular smooth muscle cell proliferation. It has in fact been revealed by evaluation using quantitative coronary angiography that the locations of coronary spasm induced in provocation tests were particularly susceptible to progression of arteriosclerosis.

(2) Characterization of coronary spasm in acute coronary syndrome

It was reported as early as the 1970s that coronary spasm can trigger not only angina pectoris but also myocardial infarction. There have been patients with acute myocardial infarction in whom emergent coronary angiography revealed extremely mild organic stenosis, as well as patients with complete coronary occlusion which exhibited recanalization after administration of nitrates alone. Recently, unstable angina, acute myocardial infarction, and sudden ischemic cardiac death have been referred to collectively as acute coronary syndrome. This is because these diseases share the pathological finding of rapid progression of coronary lesions, i.e., disruption of coronary atheroma (plaque) and the resulting thrombus formation. Coronary plaques are observed in the form of local thickening of the intima, and are structurally characterized by the accumulation of foamy macrophages forming a lipid core covered by a fibrous cap of connective tissue and smooth muscle cells. It has been hypothesized that if a tear occurs in this cap, the highly thrombogenic plaque content becomes exposed to the blood flow and rapidly forms thrombi that obstruct the vascular lumen. Plaques more likely to be ruptured are termed vulnerable plaques; they are often characterized by high lipid content and a thinned fibrous cap, and tend to be large.

It has been suggested that coronary spasm is a cause of rupture of vulnerable plaques. Investigations of coronary lesions in autopsies have demonstrated that spasm causes endothelial cell derangement and fibrous cap rupture, resulting in the protrusion of the plaque content exposed to the vascular lumen, where thrombi are
produced. In addition, coronary spasm is accompanied by hypercoagulation, decreased fibrinolytic activity, and activation of platelets and adhesion molecules, resulting in a thrombophilic state in acute coronary syndrome. Although plaque stabilization (prevention of rupture) and antithrombotic therapy are important in the prevention and treatment of acute coronary syndrome, prevention of coronary spasm is also important, particularly in Japanese, in whom the prevalence of coronary spasm is higher than in western countries.

## Diagnostic criteria

At present, vasospastic angina is diagnosed in Japan using criteria independently adopted by individual institutions. In this background, the present guidelines are established to unify the diagnostic criteria with reference to previous reports and other findings. Yasue et al. state that vasospastic angina can be diagnosed even without performing coronary angiography, provided that anginal attacks disappear quickly upon administration of nitroglycerin, and that any one of the five conditions shown below is met: (1) attacks appear at rest, particularly between 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 the ECG; (4) attacks are induced by hyperventilation (hyperpnea); (5) attacks are suppressed by calcium channel blockers but not by β-blockers. In the present guidelines, reference items based on that opinion are included in the diagnostic criteria established for three grades: “Definite,” “Suspected,” or “Unlikely”. The diagnostic criteria for vasospastic angina are provided below. A diagnostic flow chart is shown in **Figure 1**.

### Diagnostic criteria for “Definite/Suspected” vasospastic angina

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

**Conditions (any one of the three below)**
1. Spontaneous attacks
2. Positive non-drug-induced coronary spasm provocation test (e.g., hyperventilation test and exercise test)

**Reference items**

An angina-like attack that disappears quickly upon administration of a nitrate, and that meets at least one of the following four items:
1) Appears at rest, particularly between night and early morning,
2) Marked diurnal variation in exercise tolerance is observed (in particular, reduction of exercise capacity in the early morning),
3) Induced by hyperventilation (hyperpnea),
4) Attacks are suppressed by calcium channel blockers but not by β-blockers.

(*) 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 new emergence 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 management of acute coronary syndrome.

(**) Examinations include the drug-induced 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 occlusion (>90% stenosis) of a coronary artery with signs/symptoms of myocardial ischemia (anginal pain and ischemic ECG change).”

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**Figure 1  Flow chart of diagnosis of vasospastic angina (VSA)**

VSA is suspected based on angina-like attacks at rest, during effort, or during rest + effort, and the following findings are obtained by ECG, Holter recording during spontaneous attacks:

- Positive for ischemic ECG change (*)
- Borderline for ischemic ECG change
- Negative for ischemic ECG change or ECG not performed

A clear finding of myocardial ischemia or coronary spasm in relation to symptoms is obtained on examinations (**)?

Yes

- VSA Definite

No

- VSA Suspected

- At least one of the following reference items applies

VSA Unlikely
3. Positive drug-induced coronary spasm provocation test (e.g., acetylcholine provocation test and ergonovine provocation test)

Requirements
A. “Definite vasospastic angina”
   The patient is considered to have Definite vasospastic angina when ischemic change is clearly observed on the ECG during attacks (*); when the ECG findings are borderline but a clear finding of myocardial ischemia or coronary spasm is obtained in examinations (**) and he/she has a history and symptoms during attacks that are consistent with vasospastic angina; or when, if there is no ECG change during attacks or if ECG examination has not been performed, at least one of the following reference items is met, and examinations (**) reveal a clear finding of myocardial ischemia or coronary spasm.

B. “Suspected vasospastic angina”
   The patient is considered to have Suspected vasospastic angina when the ischemic change on ECG during attacks is in the borderline, and no clear finding of myocardial ischemia or coronary spasm is obtained in any examination (**); or when, if there is no change on the ECG during attacks or ECG examination has not been performed, one or more of the following reference items apply, and a clear finding of myocardial ischemia or coronary spasm cannot be demonstrated on any examination (**).

(*) 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 new emergence 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 management of acute coronary syndrome.

(**) Examinations include the drug-induced 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 occlusion (>90% stenosis) of a coronary artery with signs/symptoms of myocardial ischemia (anginal pain and ischemic ECG change).”

Reference items
An angina-like attack that disappears quickly upon administration of a nitrate, and that meets at least one of the following four items:
1) Appears at rest, particularly between night and early morning.
2) Marked diurnal variation in exercise tolerance is observed (in particular, reduction of exercise capacity in the early morning).
3) Induced by hyperventilation (hypopnea).
4) Attacks are suppressed by calcium channel blockers but not by β-blockers.

2 Etiology and epidemiology

1 Etiology

(1) Environmental factors

(1) Smoking
A large number of coronary risk factors have been identified, including hypertension, lipid abnormalities, smoking, diabetes mellitus, and obesity. Of these, smoking is a well-recognized risk factor for coronary spasm. In fact, many reports have shown that a high percentage of patients with vasospastic angina in Japan are tobacco smokers. Smoking is a controllable factor in preventing the development of coronary spasm; smoking cessation programs are thus indispensable in the treatment of coronary spasm.

(2) Drinking
Patients with vasospastic angina in Japan include many habitual drinkers. Alcohol promotes the urinary excretion of magnesium, which in turn is likely to lead to tissue magnesium deficiency. It has been shown that many patients with vasospastic angina have magnesium deficiency, and it has been reported that intravenous administration of magnesium prevents hyperpnea-related attacks of coronary spasm. Alcohol restriction is thus required in patients with vasospastic angina.

(3) Lipid abnormalities
It has been reported that patients with vasospastic angina often have abnormalities of lipid metabolism and glucose metabolism as complications. It has been suggested that oxidative stress may be associated with abnormalities of triglyceride metabolism, HDL cholesterol level reduction, and impaired glucose tolerance.

(4) Stress (abnormal autonomic nervous system function)
Attacks of coronary spasm is induced by a wide variety of stimuli that act on receptors on coronary smooth muscle cells, including those due to abnormal autonomic nervous system function. In addition to its direct effect, i.e., the release of vasopressor neurotransmitters such as noradrenaline, platelet activation via the sympathethic nervous system also causes the release of serotonin,
a potent coronary constrictor. Many analyses focusing on heart rate changes have reported that in patients with vasospastic angina, as in those with other types of ischemic heart disease, parasympathetic nervous dysfunction tends to cause an imbalance in sympathetic and parasympathetic nerve, with predominance of sympathetic activity.

(2) Genetic factors

Since coronary diseases are often familial, and persons with no lifestyle-related risk factors can nevertheless develop them, it has been suggested that “genetic factors” may also be involved in their onset. In recent years, due to the remarkable advances in molecular biology, genes involved in the pathophysiology of various diseases have been cloned, and genom polymorphisms and variations have been identified; a great deal of research into multifactorial diseases has emerged, including that on lifestyle-related diseases, from molecular epidemiological perspectives. Single nucleotide polymorphism (SNP), in particular, is a form of polymorphism found in a large number of genes in the genome. It has been suggested that changes in the level of expression or function of protein molecules encoded by genes exhibiting SNPs may affect disease susceptibility. Analysis of the associations between SNPs and diseases is expected to elucidate the genetic factors involved in the pathophysiology of diseases, and enable their primary prevention by tailor-made medicine based on individual genetic features. In particular, coronary spasm occurs at higher incidence in Japanese than in Western individuals, and has been suggested to involve genetic factors. SNPs that have been identified as related to vasospastic angina include (1) the endothelial nitric oxide synthase (eNOS) gene Glu298Asp polymorphism, (2) the eNOS gene-786T/C polymorphism, (3) the eNOS gene intron 4b/a polymorphism, and (4) the phospholipase C-δ1 (PLC-δ1) missense mutation (R257H). Investigations using public databases have yielded reports on NADH/NADPH oxidase p22phox gene 242C>T polymorphisms (male), stromelysin-1 gene -1171/6A polymorphisms (female), and interleukin-6 gene -634C>G polymorphisms (female).

(1) Prevalence of vasospastic angina

To determine the prevalence of vasospastic angina, a survey was conducted on 2,251 consecutive patients with angina pectoris (average age of 65.2 years) hospitalized in 15 major cardiovascular medical institutions in Japan in 1998. Figure 2 shows the age group distribution of the disease in the study population. In Japan as well as Western countries, angina pectoris is more prevalent among males than females, and male prevalence increases with age. In females, the incidence of angina pectoris begins to rise at the average age of menopause, around 50 years, and sex-related differences in incidence no longer exist at above 80 years of age. In females, menopause represents a turning point in the onset of heart disease, and decreases in female sex hormones appear to play very important roles in this. Although the prevalence of vasospastic angina varies among institutions, about 40% of patients with angina pectoris studied had vasospastic angina. Analysis of the age group distribution of vasospastic angina revealed that prevalence tended to be higher in relatively young patients than in elderly ones (Figure 3).
(2) Race-related differences

Results of drug-induced coronary spasm provocation tests in Japan and Europe revealed higher incidences of coronary spasm in Japan than in Europe, although there were differences in both the route and dose level of administration of spasm inducers used.

Characteristics of cases of vasospastic angina reported in Japan and Western countries are summarized in Table 1. Although the female ratio is not high in either population, Japan has a lower female ratio than Western countries. Patients with a history of myocardial infarction, those with organic coronary stenosis, and those with multivessel diseases are prevalent among Western people. Reflecting these findings, left ventricular dysfunction is more prevalent in Westerners. In contrast to Westerners, Japanese patients with multivessel coronary spasm accounted for 8% of the study population. The mortality rate in patients with vasospastic angina is lower for Japanese; this is attributable to the fact that the incidence of myocardial infarction is higher in Westerners than in Japanese.

There is a report that coronary spasm was observed by provocation test early after the onset of myocardial infarction in 11 to 21% of Westerners and 69% of Japanese. Published reports have indicated that the percentage of cases of complete occlusion of culprit vessels in patients with myocardial infarction in the acute stage is significantly higher in Westerners (82%, 1,539/1,884) than in Japanese (64%, 296/465). This finding suggests that coronary spasm may be involved in the development of myocardial infarction in many Japanese patients.

### Table 1

<table>
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<th></th>
<th>Japan</th>
<th>Western countries</th>
<th>p</th>
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<tbody>
<tr>
<td>Total number of patients</td>
<td>752</td>
<td>586</td>
<td></td>
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<tr>
<td>Female ratio (%)</td>
<td>13</td>
<td>22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Past history of myocardial infarction (%)</td>
<td>7</td>
<td>24</td>
<td>&lt;0.0001</td>
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<tr>
<td>Organic coronary stenosis (%)</td>
<td>41</td>
<td>66</td>
<td>&lt;0.0001</td>
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<tr>
<td>Multivessel disease (%)</td>
<td>24</td>
<td>44</td>
<td>&lt;0.0001</td>
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<td>Left ventricular dysfunction (%)</td>
<td>6</td>
<td>34</td>
<td>&lt;0.0001</td>
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<td>Multivessel spasm (%)</td>
<td>8</td>
<td>0</td>
<td>&lt;0.0001</td>
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<td>3-year prognosis</td>
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<td></td>
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<tr>
<td>Myocardial infarction incidence rate (%)</td>
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<td>25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mortality rate (%)</td>
<td>3</td>
<td>11</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Pathophysiology

#### 1. Involvement of vascular endothelial cells

In patients with vasospastic angina, coronary spasm can be induced at high incidence without producing a change in systemic hemodynamics, by injecting acetylcholine directly into a coronary artery. Acetylcholine dilates blood vessels when the vascular endothelium is normal, but if there is endothelial detachment or injury, it contracts blood vessels. This occurs because nitric oxide (NO), a potent smooth muscle relaxant, is secreted from endothelial cells, provided that the vascular endothelium is intact. In the endothelium, NO is produced by eNOS, which releases NO upon activation by a wide variety of signals. On the other hand, eNOS becomes activated via calmodulin as a result of elevation of intracellular Ca\(^{2+}\) level by mechanical stimuli such as shear stress. The receptor-mediated vasodilation induced by vasoactive mediators such as acetylcholine, bradykinin, and serotonin activates receptors, G proteins, and phospholipase C (PLC) in vascular endothelium to produce inositol triphosphate (IP3) and release stored Ca\(^{2+}\) in cells. This receptor stimulation promotes Ca\(^{2+}\) inflow through ionic channels. Stimulation by physiological active substances such as acetylcholine, bradykinin, and insulin and mechanical stimuli such as shear stress also increase eNOS activity.

Nitrates are metabolized to NO in the body, which in turn stimulates the soluble guanylate cyclase in vascular smooth muscle to increase the level of cyclic guanosine monophosphate (cGMP) and dilate blood vessels. Because NO is produced and released from normal vascular endothelium, the hyperreactivity of coronary arteries in spasm to nitroglycerin is probably due to a lack of baseline production or release of NO from the endothelium in these arteries.

#### 2. Involvement of vascular smooth muscles

Details of the mechanism of contraction of vascular smooth muscle were recently elucidated. Specifically, in response to stimulation by constrictive vasoactive substances such as angiotensin II, G protein-coupled PLC in vascular smooth muscle cells is activated to produce IP3. IP3 opens Ca\(^{2+}\) channels on sarcoplasmic reticulum, a sarcoplasmic reticulum that stores Ca\(^{2+}\); to release Ca\(^{2+}\) into the cytoplasm, resulting in increase in intracellular Ca\(^{2+}\) concentration. Ca\(^{2+}\) channels are also present in the cell membrane. They open in response to
a wide variety of stimuli, followed by Ca\(^{2+}\) inflow from outside the cells. The Ca\(^{2+}\) release from the sarcoplasmic reticulum and Ca\(^{2+}\) inflow from outside the cells result in increased intracellular Ca\(^{2+}\) levels, and calcium ions bind to calmodulin to form Ca\(^{2+}\)/calmodulin complexes. These complexes bind to the catalytic subunit of myosin light chain kinase (MLCK) to convert MLCK from its inactive to its active form. Phosphorylation of the myosin light chain (MLC) by active MLCK activates Mg\(^{2+}\)-ATPase in the head of myosin, by actin, and vascular smooth muscle contracts. Subsequently, as the intracellular Ca\(^{2+}\) concentration falls, Ca\(^{2+}\) dissociates from calmodulin, and MLCK becomes inactivated. As a result, the activity of myosin light-chain phosphatase (MLCPh) becomes dominant, MLC undergoes dephosphorylation, and vascular smooth muscle relaxes.

The phosphorylation of MLC is promoted and suppressed by MLCK and MLCPh, respectively. In addition, MLCPh has been shown to be suppressed by Rho-kinase. Rho-kinase is an important molecular switch that controls the contraction and relaxation of vascular smooth muscle independently of intracellular Ca\(^{2+}\) concentration. Upon stimulation by a vasopressor substance, Rho, a low-molecular-weight G protein, is activated via the G protein-coupled receptor, and Rho-kinase, one of its target proteins, is activated. The activated Rho-kinase phosphorylates the myosin-binding subunit (MBS) of MLCPh to inhibit its activity. As a result, the balance of MLCK/MLCPh activity is lost, phosphorylation of MLC is promoted, and vascular smooth muscle undergoes excessive contraction.

### II Diagnosis

#### Subjective symptoms and physical findings

**1. Subjective symptoms**

(1) Characterized by vague pain that cannot be indicated by a single finger, with a sensation of compression, a pressing sensation, and a sensation of tightness in the precordium, especially in the center of the subternal region. Occasionally, symptoms develop in the upper abdomen.

(2) Appears at rest, with pain persisting for several to about 15 minutes. The pain often radiates to the neck, jaws, left shoulder, and elsewhere, occasionally accompanied by symptoms such as numbness and weakness of the left shoulder and upper arm.

(3) Anginal attacks due to coronary spasm often persist longer than effort anginal attacks due to organic stenotic lesions, and are sometimes accompanied by cold sweats and disturbance of consciousness including syncope.

(4) Can be induced by hyperpnea and drinking of alcohol.

(5) Fast-acting nitrates are remarkably effective against attacks of coronary spasm.

(6) Calcium channel blockers suppress attacks of coronary spasm.

(7) Attacks are often accompanied by arrhythmias; if they are complicated by complete atrioventricular block, ventricular tachycardia, or ventricular fibrillation, disturbance of consciousness or syncope is observed.

(8) Attacks of coronary spasm typically occur at rest between night and early morning. They are usually not induced by daytime exercise. Diurnal variation with a peak between night and early morning is observed; 67% of attacks are asymptomatic episodes of myocardial ischemia without subjective symptoms (Figure 4). Usually, attacks of vasospastic angina can be induced by even slight effort in the early morning, but are not induced by even strenuous effort in the afternoon or later in the day. Hence, diurnal variation is also observed in exercise tolerance in patients with vasospastic angina.

(9) Attacks of coronary spasm may occur frequently, i.e., several times every day, or may not occur for several months to several years.

**2. Physical findings**

In auscultation during attacks, gallop rhythms and systolic murmurs are sometimes heard. These are caused by decreased wall motion, mitral regurgitation, and other changes resulting from ischemia. If symptoms disappear upon administration of a fast-acting nitrate or similar agent, these findings may also disappear. Hypotension may occur during attacks. In addition, since the arrhythmias developing in association with attacks include complete atroventricular block, ventricular tachycardia, and ventricular fibrillation, they must be monitored for carefully.
2 Methods of evaluation

1 Non-invasive evaluation

(1) ECG and Holter recording

Class I
1. Two ECG records, obtained during an attack and after administration of fast-acting nitrate or just after symptom stabilization in cases in which vasospastic angina is strongly suspected based on subjective symptoms
2. Holter recording (multi-channel recording acceptable) for an extended period of time of 24 to 48 hours in cases in which vasospastic angina is strongly suspected based on subjective symptoms accompanied by syncope or palpitations without identifiable cause

Class IIa
Holter recording for 24 to 48 hours in cases in which it is difficult to record the ECG during attacks

Class IIb
1. ECG or Holter recording in patients in whom the likelihood of vasospastic angina is low, as judged from the patient’s age, subjective symptoms, and background
2. 12-lead ECG records targeting time periods in which attacks are prevalent (in cases in which hyperventilation and exercise tests cannot be performed)

Class III
None

(1) Standard 12-lead ECG
The ECG often exhibits normal findings in the absence of attacks. Hence, when symptoms occur frequently, a diagnosis can be established by recording the 12-lead ECG both in the presence and the absence of an attack. Typical ECG changes during attacks of vasospastic angina include ST elevation in leads corresponding to the culprit lesion and ST depression in contralateral leads. The diagnosis can be made because these findings normalize upon administration of a fast-acting nitrate. Many patients with vasospastic angina have moderate organic stenosis of the affected coronary arteries, and in some cases only ST depression is present in contiguous leads and the absence of ST elevation appears to depend on the severity of coronary spasm or ischemia. Other possible findings include the appearance of negative T waves in the culprit lesion during recovery from ischemia, and the new emergence of negative U waves during spasm.

* Criteria for positive ischemic ECG finding
If an ST elevation of 0.1 mV or more, an ST depression of 0.1 mV or more, or new emergence of negative U waves is recorded in at least two contiguous leads on the 12-lead ECG during an attack, ECG findings are considered indicative of ischemic change.

(2) Holter recording
In patients with vasospastic angina, chest pain develops in about 20 to 30% of episodes of ischemic ST change, and many events of coronary spasm are asymptomatic. Because attacks are prevalent between night and early morning at rest, the ischemic ST changes that occur during an attack are often unrecordable except in the hospitalization setting. In such cases, Holter recording is the most useful examination. If ischemia persists for
5 minutes or longer, chest pain is likely to be present; ECG recordings during symptomatic ischemic episodes should be evaluated in detail for characteristics of ST segment levels and the occurrence of arrhythmia. Attention to asymptomatic ST-T changes is also required.

(2) Exercise test

Class I
None

Class IIa
None

Class IIb
Exercise test in patients who are in stable condition and suspected of having vasospastic angina

Class III
Exercise test in patients who are in unstable condition and in whom acute coronary syndrome cannot be ruled out

If an exercise test in the early morning reveals at least one of the following findings, and the findings of ECG and exercise tolerance in the morning differ from those in the daytime, the patient’s condition may be vasospastic angina.

(1) Emergence of ST elevation of 0.1 mV or more in at least two contiguous leads during the exercise test
(2) Emergence of ST depression of 0.1 mV or more in at least two contiguous leads during the exercise test
(3) Emergence of negative U waves not observed at rest, during the exercise test

(3) Hyperventilation test

Class I
None

Class IIa
Hyperventilation test in patients suspected of having vasospastic angina with a low frequency of attacks

Class IIb
Hyperventilation test in patients suspected of having vasospastic angina with a high frequency of attacks

Class III
Hyperventilation test in patients suspected of having acute coronary syndrome

[Method]
1. It is desirable that the hyperventilation test be conducted at rest in the early morning after an interval of at least 48 hours from administration of vasoactive drugs.
2. Always monitor the 12-lead ECG during the hyperventilation and for 10 minutes after its completion.
3. Measure blood pressure every minute.
4. Place the patient in supine position and obtain the resting 12-lead ECG and blood pressure, and then provide an explanation of hyperventilation. Subsequently, promote vigorous hyperventilation (target: respiratory rate of 25 times/minute or higher) for 6 minutes, to the extent possible for the patient.
5. If the onset of an anginal attack or a significant ST-T change on the ECG is observed during artificial hyperventilation, discontinue it immediately.
6. In the event of an anginal attack, administer a fast-acting nitrate immediately.
7. Evaluation of ST level should be performed at 80 ms after the J point on the ECG.

Criteria for positive ECG finding of coronary spasm on hyperventilation test

If at least one of the following findings is obtained, a positive ECG finding of coronary spasm is considered present.

(1) Emergence of ST elevation of 0.1 mV or more in at least two contiguous leads during the hyperventilation test
(2) Emergence of ST depression of 0.1 mV or more in at least two contiguous leads during the hyperventilation test
(3) Emergence of negative U waves not observed at rest, during the hyperventilation test

(4) Evaluation of vascular endothelial function

Class I
None

Class IIa
None

Class IIb
Vascular endothelial function test in patients suspected of having vasospastic angina

Class III
None

(5) Myocardial scintigraphy

Class I
None

Class IIa
None

Class IIb

1. $^{121}$I MIBG myocardial scintigraphy
2. $^{121}$TI myocardial scintigraphy in combination with hyperventilation test or exercise test
3. $^{121}$BMIPP myocardial scintigraphy
Class III
Stress myocardial scintigraphy in patients suspected of having acute coronary syndrome

(6) Others
Class I
None
Class IIa
None
Class IIb
Cold pressor test or mental stress test in patients who are in stable condition and suspected of having vasospastic angina
Class III
Cold pressor test or mental stress test in patients suspected of having acute coronary syndrome

2 Invasive evaluation (cardiac catheterization)

A drug-induced coronary spasm provocation test is performed by intracoronary administration of acetylcholine or ergonovine. If increased diagnostic accuracy is desired, a washout period of 2 days or longer for any calcium channel blockers and nitrates should be included whenever possible.

For patients undergoing this examination, adequate informed consent must be obtained before invasive evaluation is performed.

1 Acetylcholine provocation test

Class I
Acetylcholine provocation test during coronary angiography performed in patients in whom vasospastic angina is suspected based on symptoms, but who have not been diagnosed with coronary spasm by non-invasive evaluation

Class IIa
Acetylcholine provocation test during coronary angiography performed in patients who have been diagnosed with coronary spasm by non-invasive evaluation, and in whom drug treatment is ineffective or insufficiently effective

Class IIb
Acetylcholine provocation test during coronary angiography performed in patients who have been diagnosed with coronary spasm by non-invasive evaluation, and in whom drug treatment has been proven to be effective

Class III
1. Acetylcholine provocation test during coronary angiography performed in patients without symptoms suggestive of vasospastic angina
2. Acetylcholine provocation test during coronary angiography performed in patients who are considered at high risk of suffering a life-threatening complication of induced coronary spasm (e.g., patients with left main coronary trunk lesions; those with multivessel coronary lesions, including obstructive lesions; those with severe cardiac dysfunction; and those with untreated congestive heart failure) (however, in cases in which the onset of severe cardiac dysfunction or congestive heart failure may be a consequence of coronary spasm, the criteria for Class IIb apply)
3. Acetylcholine provocation test during emergent coronary angiography performed in patients with acute coronary syndrome

In an acetylcholine- or ergonovine-induced coronary spasm provocation test, coronary spasm is defined as “transient, total, or sub-total occlusion (>90% stenosis) of a coronary artery with signs/symptoms of myocardial ischemia (anginal pain and ischemic ST changes).”

[Standard method of provocation test]

1. Insertion of a temporary pacing electrode in the right ventricle: Administration of acetylcholine, especially in the right coronary artery, may cause transient episodes of severe bradycardia. Perform backup pacing (40 to 50 bpm).

2. Control angiography of left and right coronary arteries: Perform angiography in an appropriate projection that ensures the best separation of the branches of each coronary artery. After injection of acetylcholine, perform angiography in the same projection again.

3. Injection of acetylcholine into the left coronary artery: Inject 20, 50, or 100 µg of acetylcholine in solution in 37°C physiological saline (concentration adjusted to obtain 5 ml solution volume for each quantity of acetylcholine) into the left coronary artery over a period of 20 seconds. Perform coronary angiography 1 minute after the start of each injection. In the event of an ischemic change on the ECG or chest pain, perform angiography at that time. Doses of acetylcholine should be given at 5-minute intervals.

4. Injection of acetylcholine into right coronary artery: Inject 20 or 50 µg of acetylcholine (each in 5 ml solution) into the right coronary artery over a period of 20 seconds. The timing of angiography is the same as for the left coronary artery.

5. Left and right coronary angiography after administration of nitrate: Administer a nitrate into each
coronary artery, and perform angiography while the coronary artery is maximally dilated.

(2) Ergonovine provocation test

Class I
Ergonovine provocation test during coronary angiography performed in patients in whom vasospastic angina is suspected based on symptoms, but in whom coronary spasm has not been diagnosed by non-invasive evaluation

Class IIa
Ergonovine provocation test during coronary angiography performed in patients who have been diagnosed with coronary spasm by non-invasive evaluation, and in whom drug treatment is ineffective or insufficiently effective

Class IIb
Ergonovine provocation test during coronary angiography performed in patients who have been diagnosed with coronary spasm by non-invasive or invasive evaluation, and in whom drug treatment has been proven to be effective

Class III
1. Ergonovine provocation test during coronary angiography performed in patients without symptoms suggestive of vasospastic angina
2. Ergonovine provocation test during coronary angiography performed in patients who are at high risk of suffering a life-threatening complication of induced coronary spasm (e.g., patients with left main coronary trunk lesions; those with multivessel coronary lesions, including obstructive lesions; those with severe cardiac dysfunction; and those with untreated congestive heart failure) (however, in cases in which the onset of severe cardiac dysfunction or congestive heart failure may be a consequence of coronary spasm, the criteria for Class IIb apply)
3. Ergonovine provocation test during emergent coronary angiography performed in patients with acute coronary syndrome

As with the acetylcholine provocation test, coronary spasm during the ergonovine provocation test is defined as “transient, total, or sub-total occlusion (>90% stenosis) of a coronary artery with signs of myocardial ischemia (anginal pain and ischemic ST changes).” In the present guidelines, it is recommended for reasons of safety that the ergonovine provocation test be conducted with intracoronary rather than intravenous administration.

[Standard method of provocation test]

Intracoronary administration

(1) Control angiography of left and right coronary arteries: Perform angiography in an appropriate projection that ensures the best separation of the branches of each coronary artery. After injection of ergonovine, perform angiography in the same projection again.

(2) Injection of ergonovine into the left coronary artery: Inject 20 to 60 µg of ergonovine in solution in physiological saline into the left coronary artery over a period of several minutes (about 2 to 5 minutes). Perform coronary angiography 1 to 2 minutes after completion of the injection. In the event of an ischemic change on the ECG or chest symptom, perform angiography at the time of its onset. In case of a negative result in the provocation test, proceed to the right coronary provocation test 5 minutes later.

(3) Injection of ergonovine into the right coronary artery: Inject 20 to 60 µg of ergonovine in solution in physiological saline into the right coronary artery over a period of several minutes (about 2 to 5 minutes). The timing of angiography is the same as for the left coronary artery.

(4) Left and right coronary angiography after administration of nitrate: Administer a sufficient dose of nitrate into each coronary artery, and perform angiography while the coronary artery is maximally dilated.

(3) Measurement of coronary blood flow

Class I
None
Class IIa
None
Class IIb
Used for supplementary diagnosis in the drug-induced coronary spasm provocation test in patients suspected to have vasospastic angina

Class III
Used for supplementary diagnosis in the drug-induced coronary spasm provocation test in patients with severe organic stenosis

(4) Measurement of coronary sinus lactate levels

Class I
None
Class IIa
None
Class IIb
Measurement of coronary sinus lactate levels during a drug-induced coronary spasm provocation test
A catheter is placed in the coronary sinus, and coronary spasm is induced with acetylcholine or a similar agent. Coronary venous blood and blood from the base of the aorta or coronary arterial blood is drawn before and after the induction, and lactate metabolism in the myocardium is examined. Upon the development of ischemia, myocardial lactate consumption decreases; as the ischemia increases in severity, a shift to lactate production occurs. Although lactate consumption decreases during coronary spasm, whether the shift to lactate production occurs depends on the severity of ischemia, the site where the ischemia occurs, and other factors. This parameter is also considered useful as a marker of the onset of myocardial ischemia in the diagnosis of coronary microvascular spasm.

(5) Coronary angioscopy

Coronary angioscopy in patients with vasospastic angina is usually performed for the purpose of investigating the pathological condition or mechanism of onset of vasospastic angina, rather than for diagnostic purposes.

(6) Intravascular ultrasound (IVUS)

The major role of IVUS in the diagnosis of vasospastic angina is to elucidate its pathological condition and etiology based on its morphological (and sometimes functional) features.

### III Treatment

#### 1 Management of daily life (Correction of risk factors)

**Class I**
- Smoking cessation
- Blood pressure control
- Maintenance of ideal body weight
- Correction of impaired glucose tolerance
- Correction of lipid abnormalities
- Avoidance of excessive fatigue and mental stress
- No or moderate drinking

**Class IIa**
- None

**Class IIb**
- None

**Class III**
- None

---

#### 2 Drug therapies

**Nitrates**

**Class I**
- Sublingual administration, spraying in the oral cavity, or intravenous administration during an attack

**Class IIa**
- Administration of long-acting nitrates for prevention of coronary spasm

**Class IIb**
- None

**Class III**
- Administration of nitrates within 24 hours after taking an agent to treat erectile dysfunction

Nitrates are metabolized to NO in the body, which in turn activates guanylate cyclase to increase cGMP, resulting in relaxation of vascular smooth muscle. Nitrates also suppress the activity of Rho-kinase via NO and thereby relax smooth muscle. Nitrates exert effects in the treatment of coronary spasm by a mechanism of action different from that of calcium channel blockers; it is therefore desirable that patients be treated with the combination of a calcium channel blocker and nitrate or monotherapy with either drug alone based on the condition of individual patients.

**Calcium channel blockers**

**Class I**
- Administration of calcium channel blockers for vasospastic angina

**Class IIa**
- None

**Class IIb**
- None

**Class III**
- None

Calcium channel blockers that suppress Ca^{2+} infl ow into vascular smooth muscle cells are highly effective in preventing coronary spasm, and are deemed drugs of first choice for the treatment of vasospastic angina. They can be used safely, without adverse reactions, at usual doses.
### 3 Nicorandil

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<th>Class</th>
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<tbody>
<tr>
<td>I</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>Administration of nicorandil for vasospastic angina</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Administration of nicorandil within 24 hours after taking an agent to treat erectile dysfunction</td>
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### 4 β-blockers

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<tbody>
<tr>
<td>I</td>
<td>None</td>
<td></td>
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<tr>
<td>IIa</td>
<td>Concomitant use of β-blockers for vasospastic angina with significant stenosis of coronary artery</td>
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<tr>
<td>IIb</td>
<td>Concomitant use of β-blockers for vasospastic angina without significant stenosis of coronary artery</td>
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<tr>
<td>III</td>
<td>Monotherapy for vasospastic angina without significant stenosis of coronary artery</td>
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### 5 Other drugs possibly effective in suppressing coronary spasm

#### (1) Vitamins and antioxidants

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<td>IIa</td>
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<tr>
<td>IIb</td>
<td>Administration of vitamin E preparations for vasospastic angina</td>
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#### (2) Estrogens

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<td>I</td>
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<tr>
<td>IIa</td>
<td>None</td>
<td></td>
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<tr>
<td>IIb</td>
<td>Administration of estrogens for vasospastic angina in postmenopausal women</td>
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#### (3) Steroids

<table>
<thead>
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<td>I</td>
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<tr>
<td>IIa</td>
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<tr>
<td>IIb</td>
<td>Administration of steroids for vasospastic angina</td>
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<tr>
<td>III</td>
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#### (4) Fasudil

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<tr>
<td>IIa</td>
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<tr>
<td>IIb</td>
<td>Administration of fasudil for vasospastic angina</td>
<td></td>
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<td>III</td>
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### 3 Concomitant percutaneous coronary intervention

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<tr>
<td>I</td>
<td>None</td>
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<tr>
<td>IIa</td>
<td>Percutaneous coronary intervention performed in combination with adequate administration of coronary dilators for vasospastic angina with severe organic stenosis</td>
<td></td>
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<tr>
<td>IIb</td>
<td>None</td>
<td></td>
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<tr>
<td>III</td>
<td>Coronary intervention performed for vasospastic angina without severe organic stenosis</td>
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### 4 Issues related to coronary spasm

#### 1 Intractable vasospastic angina

Although attacks of vasospastic angina can usually be relieved or suppressed with coronary vasodilators such
as nitrates and calcium channel blockers, in some patients vasospastic angina is intractable and resists these drugs, and attacks cannot be relieved or suppressed. A Ministry of Health, Labour and Welfare (MHLW)-commissioned study was undertaken by a research task force (10ko-5) to determine the incidence of intractable vasospastic angina. In that study, intractable vasospastic angina was defined as angina pectoris that cannot be controlled even with the administration of two types of coronary vasodilators. According to the report by the task force, vasospastic angina was found in 921 (40.9%) of 2,251 patients with angina pectoris reported from 15 institutions nationwide in Japan; in 126 of these patients (13.7%) the condition was intractable. The patients with intractable vasospastic angina were characterized by younger age at the time of onset, and included high proportions of tobacco smokers and normotensive patients than the group of patients with treatable vasospastic angina.

For patients in whom control of coronary spasm with calcium channel blockers or nitrates is not possible, oral drugs that can control the other mechanism of action are required. It is strongly hoped that further advances will be made in research into the mechanisms of coronary spasm and the development of prophylactic medications. Reported non-drug treatments include the use of an implantable cardioverter defibrillator (ICD) for ventricular tachycardia and ventricular fibrillation during coronary spasm attacks in intractable vasospastic angina, but no agreement exists concerning the validity of this treatment. If ischemic attacks can be prevented with drug therapy, use of an ICD is not considered indicated. If the patient’s condition is intractable and attacks cannot be prevented, ICD may be considered. Further investigation is needed to develop appropriate treatment strategies for patients with intractable coronary spasm.

Some possibilities have been suggested regarding the mechanism of onset of myocardial ischemia based on abnormalities of the coronary microcirculation. They include (1) steal phenomenon resulting from reduction in coronary microvessel diastolic function or uneven vasodilation in the left ventricular wall, and (2) coronary microvascular spasm. In patients with what is termed microvascular angina, it has been reported that both decreased blood flow in a particular region of the left ventricle or the subendocardial region and myocardial ischemia occur in the high-rate atrial pacing test, hand-grip stress test, or adenosine stress test. These types of impairment of metabolic vasodilation in the coronary microvessels can cause myocardial ischemia during exercise (effort angina pectoris). It is thought that if coronary microvascular hypercontraction (spasm) occurs, angina pectoris not accompanied by an increased myocardial oxygen demand, i.e., rest angina pectoris, develops.

Because coronary microvascular spasm cannot be detected on angiography, its occurrence must be indirectly detected from the results of a provocation test. If symptoms of angina are induced despite the absence of spasm in the major coronary arteries during a coronary spasm provocation test with administration of acetylcholine or ergonovine into the coronary arteries, and at the same time direct or indirect findings of myocardial ischemia, such as clear reduction of coronary blood flow rate, emergence of ischemic changes on the ECG, and myocardial lactate production, appear, then coronary microvascular spasm is diagnosed.

During and after coronary artery bypass grafting, coronary spasm is likely to develop because endogenous vasopressor substances are produced as a result of anesthesia, surgical invasion, and cardiopulmonary bypass, and also because exogenous catecholamine and vasoconstrictors are administered. Furthermore, because hemodynamics are unstable in the perioperative period, coronary spasm can have serious, even life-threatening consequences in some cases. Perioperative coronary spasm develops suddenly, causing a broad range of signs of myocardial ischemia. Intraoperative and postoperative coronary spasm tends to be repetitive, and are sometimes accompanied by elevated pulmonary arterial pressure; careful monitoring is therefore essential with variety of devices. Because myocardial damage due to inadequate cardioplegia and graft blood flow insufficiency also lead to signs of myocardial ischemia during surgery, it is necessary to distinguish between these pathological conditions and coronary spasm.

In addition to coronary spasm, spasm of the graft itself is a potential problem following coronary artery bypass grafting. The ergonovine provocation test significantly alters the diameters of great saphenous vein grafts, but does not alter those of internal thoracic artery grafts. In addition, it has been reported that radial artery and gastroepiploic artery grafts are more likely to exhibit spasm than internal thoracic artery grafts.

Takotsubo cardiomyopathy is a transient myocardial...
damage of acute onset nature resembling acute coronary syndrome. It is characterized by sudden chest pain and chest symptoms as well as ECG changes such as ST elevation, abnormal Q waves, and negative T waves, is often triggered with physical or mental pain and stress, and occurs at relatively high incidence in elderly women. Its pathological features include slightly elevated levels of myocardial enzymes that are inconsistent with the severity of left ventricular wall motion abnormalities, and typical wall motion abnormalities unrelated to significant coronary stenotic lesions (i.e., left ventricular apical ballooning, abnormal dilation of the left ventricular wall at the papillary muscle attachments, and excessive contraction at the cardiac base), that are observed during the acute phase but improved in the chronic phase.

Details of the etiology of Takotsubo cardiomyopathy remain unclear. In early reports from Japan and several retrospective studies of cases subsequently compiled, coronary spasm was observed in spontaneous attacks and drug provocation tests in the chronic phase of this disease. Although the incidence of coronary spasm in patients with Takotsubo cardiomyopathy varied between 0 to 43% in different reports, it is believed that coronary spasm may play an important part in the development of myocardial damage in this population. However, Takotsubo cardiomyopathy differs from the common types of cardiomyopathy due to coronary spasm in pathological characteristics, patient characteristics, and causal factors. Reports from Western countries have suggested that whether coronary spasm is involved in the development of Takotsubo cardiomyopathy is unclear. Coronary spasm cannot be considered the cause of all cases of Takotsubo cardiomyopathy.