Coronary vasospastic angina (CVsA) plays an important role in myocardial ischemia including stable angina, acute coronary syndromes, and sudden cardiac death. Inflammation status from either endothelium or adventitia can cause endothelial dysfunction. Thereafter, the endothelial dysfunction further induces vascular smooth muscle hypercontraction through the enhanced rho-kinase with the resultant clinical event. With better understanding of the interactions between inflammation, endothelium, and smooth muscle cells, we and other investigators have provided new insights into the basic pathophysiology of CVsA. Apart from calcium channel blockers, nitrates, and the rho-kinase inhibitor fasudil, anti-inflammatory treatment is helpful in some patients with refractory CVsA. Additional studies are needed to clarify the mechanisms of recurrent CVsA.

Key Words: Angina • Coronary vasospasm • Inflammation

HISTORY OF CORONARY VASOSPASM (CVsp)

In 1959, Prinzmetal and his colleagues described a syndrome characterized by angina at rest with transient ST-segment elevation in patients with diseased coronary arteries, which is different from that seen in classic angina. In these circumstances where the heart burden is not increased, the angina must be due to a reduction in coronary blood flow. Prinzmetal proposed the term “variant angina” and suggested that it was caused by spasm of a major coronary artery, because it was relieved promptly by administration of nitroglycerin. With the advent of coronary angiography, it became apparent that variant angina was caused by CVsp and it may occur at the site of a coronary stenosis or in normal coronary arteries, the so-called “variant of the variant” or “coronary vasospastic angina (CVsA)”.

Recently, many investigators found that much of the underlying cause of CVsA is associated with ST-segment depression rather than ST-segment elevation. Therefore, the term “variant angina” is usually denoted as angina with transient ST-segment elevation.

CLINICAL CHARACTERISTICS OF CVsA

CVsA is different from typical atherosclerotic angina in the pathophysiology. CVsp, however, might be induced by exercise, particularly in the morning in some patients with variant angina, and might cause exercise-induced angina with ST-segment depression in some patients with stable effort angina (Figure 1). The authors postulated that the spastic arteries are not normal, in that the spastic arteries cannot dilate fully in response to exercise as in normal coronary arteries. There are daily, weekly, monthly, and circadian variations in the incidence of CVsA.

Circadian variation in the incidence of attacks in patients with CVsA

CVsA occurs usually at rest, particularly from midnight to early morning. Yasue et al. compared coro-
nary arteriograms recorded in the early morning with those recorded in the afternoon in patients with variant angina. In the early morning, the tone of the major coronary artery was increased and its diameter was small. Under such conditions, mild exercise could induce CVsp resulting in attacks; the administration of nitroglycerin dilated the artery markedly. In contrast, in the afternoon, the major coronary artery was usually already dilated, and its tone was low on the control coronary arteriograms. Under such conditions, exercise could induce little coronary vasoconstriction and no attacks usually occurred except in patients with severe organic stenosis, in whom only a mild spasm could occlude the artery and result in angina attacks. To record quantitatively the difference in the tone in the major coronary arteries observed in the early morning and in the afternoon, Yasue et al. measured the diameter of the major coronary artery on both the control coronary arteriograms and the coronary arteriograms taken after nitroglycerin administration. The percentage increase in diameter of the major coronary artery after nitroglycerin administration was significantly greater in the early morning than in the afternoon. This may be one of the reasons that there is a circadian variation in the exercise capacity of most patients with variant angina. A pathology study illustrated the complexity of the local neural events that modulate the tone of the coronary arteries. The occurrence of CVsA in the early morning has been noted to be associated with rapid eye movement. Therefore, a rapid elevation of sympathetic activity during augmented parasympathetic activity has been suggested to be related to the occurrence of CVsA in the early morning.

**Acute coronary syndrome**

There is general consensus in the medical commu-
nity that intracoronary thrombus plays a major role in the pathogenesis of acute myocardial infarction. Yasue et al. found that CVsp was presumed to be responsible for the acute myocardial infarction because the culprit artery was patent without delay of visualization in 17.9% of patients in the early phase of acute myocardial infarction. Our report also found that the responsible coronary arteries were patent in 12% of patients with acute myocardial infarction (Figure 2). There was infarct-related CVsp involvement in 95% in these patients. This may be explained by the spontaneous resolution of either spasm or thrombus, or both. Oshima et al. reported that CVsp causes intracoronary thrombus formation, supporting the concept that CVsp is one of the primary factors contributing to acute myocardial infarction. Therefore, CVsp appears to play a role in the production of acute myocardial infarction in these patients.

Most of the patients with CVsA present as angina with ST-segment depression and/or T-wave inversion on electrocardiogram, which is an acute coronary syndrome. If there is no cardiac enzyme elevation, we define the cardiac event as an unstable angina because most of the CVsA occurs at rest. Angiographically normal or near-normal coronary arteries occurs in 25% of patients with acute coronary syndrome irrespective of the provocative agents. The CVsp can be induced in 50-60% of these patients. After initial management (i.e. oxygen, aspirin, nitroglycerin, and/or morphine) for acute coronary syndrome, follow-up electrocardiograms are important to indicate the role of CVsp for the acute coronary syndrome. If there is a normalized ST-segment after the initial management, the CVsp may play a role in acute coronary syndrome.

Intracoronary administration of methylergonovine

Provocative testing for CVsp is required to clarify its role in the pathogenesis of angina pectoris, especially in patients without significant obstructive coronary artery disease (CAD). To ensure a valid provocative test, vasodilators (calcium antagonists and nitrates) must be withdrawn for at least 24 hours, except sublingual nitroglycerin if necessary. The nitroglycerin solution must be well prepared before starting intracoronary methylergonovine testing, in part to abolish intracoronary methylergonovine-induced CVsp immediately through the intracoronary route (50-1000 µg). There have been several agents or procedures, including ergonovine maleate, methylergonovine maleate, acetylcholine or hyperventilation reported that induce CVsp in patients with CVsA. Intracoronary ergonovine administration has been a popular method to induce CVsp during angiographic study because of its high sensitivity and specificity. This test was administrated using a step-wise dose of ergonovine (1, 5, 10, and 30 µg) every 3 minutes;
the drug was first introduced into the right coronary artery and subsequently into the left coronary artery. CVsp was defined as a decrease of > 50% or 70% in the diameter of an arterial lumen with concurrent chest pain and/or ischemic ST-T changes during the provocation testing. Recently, the Japanese Circulation Society published a guideline to define a positive indicator on a provocative test as a decrease of > 90% in the diameter of an arterial lumen, with concurrent chest pain and/or ischemic ST-segment changes during the provocation test. However, Yasue et al. suggested that there are no limits on the degree of lumen diameter reduction required to diagnose CVsp since ischemia must accompany the changes of vessel size in a period of time. Although there are different criteria in vessel diameter, the angina and/or ischemic electrocardiographic changes during provocation testing are necessary in defining a positive provocation test result. After a CVsp had been diagnosed, the administration of intracoronary ergonovine was stopped and 50-1000 µg of intracoronary nitroglycerin was administered. The ergonovine maleate and acetylcholine are not available in Taiwan. Therefore, only methylergonovine maleate was used in the CVsp provocative testing in our studies, with the same intracoronary dose regimen as in ergonovine maleate. Although it is useful in the diagnosis of CVsA, safety is still a major concern. The contraindications for intracoronary methylergonovine testing included pregnancy, severe hypertension (systolic blood pressure > 180 mm Hg), moderate to severe aortic stenosis and uncontrolled ventricular arrhythmia. Some studies have reported complications of intravenous injection of ergonovine in patients who underwent cardiac catheterization, including ventricular tachycardia, ventricular fibrillation, and death. The importance of intracoronary nitroglycerin rather than intravenous or sublingual route in relieving provocative CVsp is emphasized. Since Hackett et al. introduced the intracoronary route for provocation testing in 1987, the general consensus has been that the intracoronary rather than the intravenous route is safer because of negligible drug recirculation and avoidance of effects on branches with critical stenosis. Recently, a Japanese multicenter study found that intracoronary ergonovine provocation testing induces ventricular tachycardia/ventricular fibrillation in 0.8% of patients with CVsA, which is similar to our prior study. They concluded that spasm provocation tests have an acceptable level of safety; the evaluation of spasm type may provide useful information for the risk stratification of CVsA patients. Consistent with the Japanese study, there was no mortality reported in our prior study. Because ventricular tachycardia or ventricular fibrillation is a possible complication following intracoronary methylergonovine administration, its use outside the cardiac catheterization laboratory is not recommended.

In theory, the diagnosis of CVsp must be made on the coronary angiographic findings during the attack. However, it is not practical to perform coronary angiography during an attack in every patient, and this step is unnecessary. During coronary angiography, adequate doses (50-1000 µg) of intracoronary nitroglycerin administration help cardiologists differentiate spontaneous CVsp from fixed obstructive CAD. Angina pectoris that is relieved promptly after nitroglycerin may be diagnosed as CVsA even without angiographic evidence, if one of following characteristics is noticed: 1) the attack occurs at rest, particularly from midnight to early morning; 2) there is marked circadian variation of exercise capacity, the attack easily induced by exercise in the morning but not by even vigorous exercise in the afternoon; 3) the attack is associated with ST-segment elevation on the electrocardiogram; 4) the attack is induced by hyperventilation; or 5) the attack is suppressed by calcium antagonists, but not by beta-blockers.

Prevalence of CVsp

In the Japanese population, CVsp frequency appears to be greater than that in Western populations, and the diagnosis of variant angina (angina with transient ST-segment elevation) is made in a high percentage (10% to 70%) of patients with anginal symptoms referred to Japanese medical centers. Our prior investigation also found that 27% of angina patients who underwent coronary angiography and had CVsA (angina with and without transient ST-segment elevation) in patients who had angina and no significant obstructive CAD, the prevalence of CVsp was around 50%. In patients who had acute coronary syndrome and no significant obstructive CAD, the prevalence of CVsp was estimated to be 57%, which is similar to data from Germany. The diagnosis of CVsp depends on angiographic
protocols and provocations tests, which varies from laboratory to laboratory. Premedication with spasmolytic drugs such as nitroglycerin or calcium antagonists, avoidance of coronary constrictors, and daily or monthly variation of disease activity may lead to a failure to diagnose CVsp. Therefore, an estimate of the prevalence of CVsp in different populations remains to be defined. Although the racial difference in coronary constrictor response has been strongly suggested, the underestimation of CVsp worldwide is an important issue in the current percutaneous coronary intervention era.

**Risk factors for the development of CVsA**

Cigarette smoking was found to be an unequivocal risk factor for CVsA in the literature (adjusted odds ratio of 2.41). Similarly, our investigation has found a multivariate-adjusted odds ratio of 2.58, which is similar to other studies. In our recent study, synergistic interaction was verified between smoking and high-sensitivity C-reactive protein (hs-CRP) in the development of CVsp. This interaction was linear and monotonic among smokers. In nonsmokers, however, hs-CRP had a threshold effect on CVsp development. A decreased odds ratio to 2.12 was observed when hs-CRP was added into the multivariate analysis between smoking and CVsp, suggesting that hs-CRP was an important covariate of CVsp. Further analysis showed that the relationship between hs-CRP and CVsp differs between men and women. The non-threshold model in men and a threshold model in women provide evidence that more smokers in men (life-style) and age (induction time) contribute to the natural history of CVsp development. In addition, we also found that hypertension is a negative predictor for CVsp, which suggests that the pathogenesis of CVsp differs from that of coronary atherosclerosis.

**Treatment and prognosis of CVsA**

Table 1 depicts the treatment strategies for CVsA patients. Calcium antagonists play a cornerstone role in the management of CVsA. Of importance, the long-acting calcium antagonist should be given before going to bed at night as CVsA occurs usually from midnight to the early morning. Usually, a high-dose long-acting calcium antagonist (e.g. nifedipine 80 mg/day, amlodipine 20 mg/day, diltiazem 360 mg/day, or verapamil 480 mg/day) is started. It may require 2 calcium antagonists (dihydropyridine and non-dihydropyridine) to relieve CVsA. While long-acting nitrates are also effective in preventing CVsA attack, the occurrence of nitrate tolerance may limit their use as a first-line approach. In contrast, β-blockers do not suppress, but rather may aggravate CVsp in patient with variant angina. Although platelets may play a role in precipitating or aggravating CVsp, intravenous prostacyclin or cyclooxygenase inhibitors have thus far not been shown to have beneficial effects. Recent clinical research shows that magnesium, antioxidants, rho-kinase (ROCK) inhibitor fasudil, and fluvastatin are also beneficial to treat CVsA. Addition-

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<td>Implantable cardioverter defibrillator</td>
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CVsA, coronary vasospastic angina; ROCK, Rho-associated coiled-coil containing protein kinase.
ally, the aggravating factors for CVsA such as cigarette smoking, catecholamines, muscarinic agonists, ergot alkaloids, prostaglandins, alcohol, emotional stress, and propanolol must be avoided. Coronary intervention plays a limited role in patients with CVsA and organic stenosis. In the current coronary stenting era, there are some reports of coronary stenting in the management of drug-refractory CVsA. Gaspardone et al. reported that coronary stent placement is effective in preventing angina attacks and methylergonovine-induced CVsp in 6 of 9 patients 6 months after stenting. They performed coronary stent placement in CVsA patients because of persistent angina attacks despite medical treatment (up to 960 mg diltiazem or 100 mg nifedipine and nitrates). Other reports also showed successful coronary stenting in the management of CVsA. However, their reports did not use the combination and maximal doses of 2 calcium antagonists in terms of aggressive medical therapy for CVsA. In theory, the coronary stenting is considered to be effective to abolish the CVsA in the absence of concomitant calcium antagonist treatment after coronary stenting. Calcium antagonists were still used after coronary stenting in these reports indicating that single-vessel or multi-vessel CVsp may develop at sites different from the initial stenosis. Therefore, Yuksel et al. suggested that before coronary stenting can be advocated as an established treatment resistant to maximal medical therapy, a randomized trial should be carried out. Nevertheless, approximately 20% of CVsA patients do not respond to treatment with 2 calcium antagonists plus a long-acting nitrates. Under the circumstances, coronary stenting in combination with adequate coronary vasodilators doses may be helpful in patients CVsA and severe organic stenosis. On the other hand, coronary interventions are contraindicated in patients with CVsA without severe organic stenosis. As coronary arteries treated with coronary interventions show time-dependent loss of endothelial-dependent and -independent vasomotor function, with imbalanced contraction/dilation capacity, the suggestion has been that cardiologists must keep CVsA in mind before performing coronary intervention. An implantable cardioverter defibrillator with aggressive medical therapy for CVsA was reported to be effective in patients who had syncope, ventricular tachycardia, or survived cardiac arrest outside the hospital.

The prognosis among Japanese patients with variant angina is better than that among western patients. The difference is probably due to the fact that the percentage of patients with multivessel disease or impaired left ventricular function or both was smaller, and the percentage of patients who received a calcium antagonist (diltiazem or nifedipine) as the initial treatment was higher in the Japanese series. By multivariate analysis, the intake of calcium antagonists, extent and severity of coronary artery disease, and multivessel CVsp were shown to be significantly independent predictors of survival without myocardial infarction. In Taiwanese patients who had CVsA and no significant obstructive CAD, the long-term prognosis was found to be good despite 11% of recurrent CVsA. The most common factors for recurrent CVsA are continued smoking and self-discontinuation of calcium antagonists. The occurrence of angina attacks is difficult to assess in individuals with CVsA because their frequency tends to fluctuate spontaneously and the attacks are not necessarily accompanied by symptoms. Based on the observation of recurrent angina pectoris, it appears reasonable to suggest that treatment should not be discontinued in cases of CVsA, even when the patients are asymptomatic.

**INFLAMMATION AND CVsA**

**Determinants of CVsp: endothelium and smooth muscle**

There is no single mechanism that can explain the entire process of CVsA. In 1980s, the autonomic nervous system was found to play an important role in the pathophysiology of CVsA. In the 1990s, oxidative stress, deficiency of nitric oxide activity, respiratory alkalosis, magnesium deficiency and insulin deficiency were identified as other possible mechanisms for CVsA. In the late 1990s and early 2000s, mutation of the promoter in endothelial nitric oxide synthase gene and polymorphism of paraoxonase gene were found to be associated with CVsA. In another large Japanese cohort study, the nicotinamide adenine dinucleotide hydrogen/nicotinamide adenine dinucleotide phosphate hydroxide p22 phox gene is a susceptibility locus for CVsp in men, and the stromelysin-1 and interleukin-6 genes are susceptibility loci in women. In this study,
the inflammation gene was firstly identified to be associated with CVsp. These findings indicate that dysfunctional endothelium secondary to down-regulation of endothelial nitric oxide synthase and oxidative inactivation of nitric oxide is one of the major mechanisms responsible for CVsA. In addition, inflammation is indicated as a possible contributor in the development of CVsA. However, a deficiency of endothelial nitric oxide may not explain the complete mechanism of CVsA because all atherosclerotic coronary arteries are not necessarily associated with CVsp in spite of the deficiency of nitric oxide activity. In 2006, Kakket et al. found that spontaneous CVsp occurs in K<sub>ATP</sub> mutant mice, which arise from a smooth muscle-extrinsic process. They postulated that endothelial dysfunction with loss of K<sub>ATP</sub> channels and decreased nitric oxide production and/or bioavailability promotes smooth hypercontraction. Another possibility includes the sympathetic neurons, where opening of presynaptic K<sub>ATP</sub> channels decreases norepinephrine release, enhancing smooth muscle relaxation to dilate coronary arteries. A defect in these channels decreasing the threshold for norepinephrine release might be associated with CVsp. In 2011, Qipshidz et al. found that folic acid treatment attenuates acetylcholine-induced coronary vasoconstriction in hyperhomocysteinemic cystathionine beta synthase heterozygote mice. They suggested that CVsp is related to the regulation of endothelial nitric oxide synthase expression, nitric oxide availability, and tissue homocysteine.

In addition to deficient endothelial nitric oxide activity, hyperreactivity of the coronary smooth muscle seems to play an important role in the pathogenesis of CVsA. Shimokawa and colleagues developed swine models of CVsp and showed that ROCK activity is enhanced in coronary artery smooth muscle after wrapping the coronary artery with interleukin-1 beads. They also demonstrated that ROCKs expression and activity are enhanced at the inflammatory/arteriosclerotic coronary lesions. Recently, we found that ROCK activity in circulating neutrophils is a useful biomarker for the diagnosis and disease activity assessment in patients with CVsA. Some investigators found that decreased endothelial nitric oxide synthase activity increase ROCK activity in coronary arteries. These findings connect the activity of ROCK to endothelial nitric oxide and are in agreement with the clinical observations that spastic arteries are inflammatory and are supersensitive to both vasoconstrictor agonists and nitrates.

**Role of inflammation**

In 1978, Lewis et al. first reported a patient who died of cardiogenic shock due to variant angina and localized pericarditis. They postulated that there was a link between inflammation and CVsA. In the mid and later 2000s, we showed that chronic inflammation was associated with CVsA, as evidenced by elevated peripheral leukocyte and monocyte counts, hs-CRP, interleukin-6, and adhesion molecules. It was demonstrated that the serum level of cortisol, one of the important stress hormones, causes coronary hyperreactivity through activation of ROCK in pigs in vivo. Cigarette smoking, a major risk factor for CVsA, is associated with low-grade inflammation. These findings suggest that there is increased inflammatory status in patients with CVsA and the inflammation may contribute to the occurrence of CVsp. An interaction between smoking and hs-CRP was recently reported by our group and the relationship between hs-CRP and CVsA differed between men and women. We also have recently demonstrated that ROCK activity in peripheral leukocyte independently predicts the presence and severity of CVsA and the level of ROCK activity correlates with plasma interleukin-6. These findings suggest that there is increased inflammatory status in patients with CVsA and the inflammation may cause endothelial dysfunction, ROCK activity accentuation and finally contribute to the vascular smooth muscle hypercontraction, the occurrence of CVsp.

Some investigators found that inflammatory clinical condition is associated with CVsA. Several reports have suggested a possible link between allergic disease and CVsA. The pathogenesis of bronchial asthma has been recently attributed to hyperreactivity of the airway caused by inflammation, and corticosteroids are considered to work by alleviating that inflammation. There is an analogy with the pathophysiology of CVsA and bronchial asthma; that is CVsp may be induced by arterial hyperreactivity caused by local inflammation in the coronary arterial wall and corticosteroids suppress the hyperreactivity by alleviating the inflammation in the vessel wall. In fact, Forman et al. reported a patient with CVsA complicated by sudden death in whom
mast cell infiltration was found at the site of angiographic documentation of CVsp, which indicates that CVsp can also occur as the result of adventitial inflammation in addition to endothelial inflammation. Some other studies also reported that focal infiltration of inflammatory cells was seen in the adventitia or plaque of the coronary artery in patients with CVsA.\(^{59}\) Even where there is no evident narrowing during angiography, diffuse intimal thickening or intimal bump by precursor medial contraction is demonstrated from optical coherence tomography.\(^{60,61}\) Nitric oxide availability is reduced under the circumstances of low-grade inflammation of atherosclerosis or diffuse intimal thickening.\(^{62}\) Endothelial nitric oxide synthase has been reported to be quantitatively associated with caveolin-1 in endothelial cells. The vascular relaxation in response to acetylcholine was also much larger in aortic rings collected from caveolin-1\(^{-/-}\) mice than in their wild-type littermates.\(^{63}\) Of note, isolated aortic rings from caveolin-1\(^{-/-}\) mice were unable to maintain a constant contractile tone, oscillating at 1 Hz frequency. These studies support the proposition that, in the basal condition, endothelial nitric oxide synthase becomes hyperactivated in the absence of caveolin-1. Based on the above analyses, it appears reasonable to speculate that CVsp is an early inflammatory coronary artery condition because of the presence of low-grade inflammation-related endothelial dysfunction with resulting diffuse intimal thickening and impaired nitric oxide production.\(^{64}\) Because the lack of normal nitric oxide activity does impact the normal vessel, the vessel tends to constrict in the presence of low-grade inflammation such as cigarette smoking, stress, airway disease, and allergy.

**CONCLUSION**

Identification of CVsp is important in our daily clinical practice because of a wide disparity between treatment strategies for fixed obstruction versus vasospasm of coronary arteries. Adequate doses of intracoronary nitroglycerin administration help cardiologists differentiate spontaneous CVsp from fixed obstructive CAD. However, cessation of cigarette smoking and adequate dose and timing of calcium antagonists are the cornerstone for CVsA therapy. Accumulating evidence suggests that inflammation substantially contributes to the development of CVsA. Clinical studies with antiinflammatory therapies further support the role of inflammation in CVsA. Release of inflammatory mediators, such as interleukin-6, histamine, or serotonin leads to nitric oxide availability reduction, endothelial dysfunction, and precursor medial contraction. The final common pathway in CVsp is vascular smooth muscle contraction by increased ROCK activity. With the understanding of interactions between inflammation, endothelium, and smooth muscle cells, we and other investigators have provided some insights into the basic pathophysiology of CVsp. More studies are needed to clarify the mechanisms of recurrent CVsA.

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