—Review—

# Variant Angina and Coronary Artery Spasm: The Clinical Spectrum, Pathophysiology, and Management

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**Abstract**

Variant angina is a form of angina pectoris that shows transient ST-segment elevation on electrocardiogram during an attack of chest pain. Ischemic episodes of variant angina show circadian variation and often occur at rest from midnight to early morning. Ischemic episodes also occur during mild exercise in the early morning. However, they are not usually induced by strenuous exercise in the afternoon. Other important clinical features of variant angina include the high frequency of asymptomatic ischemic episodes and the syncope that sometimes occur during the ischemic episodes. Syncope is due to severe arrhythmias, including ventricular tachycardia, ventricular fibrillation, and high-degree atrioventricular block. Coronary artery spasm is the mechanism of ischemic episodes in variant angina. The incidence of coronary artery spasm shows a racial difference and is higher in Japanese than in Caucasians. Coronary arteriograms are normal or near-normal in most Japanese patients with variant angina. Deficient basal release of nitric oxide (NO) due to endothelial dysfunction, and enhanced vascular smooth muscle contractility with the involvement of the Rho/Rho-kinase pathway are reported to play important roles in the pathogenesis of coronary artery spasm. Other precipitating factors of coronary artery spasm include imbalance in autonomic nervous activity, increased oxidative stress, chronic low-grade inflammation, magnesium deficiency, and genetic susceptibility. The genetic risk factors associated with coronary artery spasm include gene polymorphisms of endothelial NO synthase (NOS), paraoxonase, and other genes. Calcium channel blockers are extremely effective in preventing coronary spasm. The long-acting nitrate, nicorandil, and Rho-kinase inhibitor are also useful for inhibiting coronary artery spasm. Because variant angina can lead to acute myocardial infarction, fatal arrhythmias, and sudden death, early treatment is important. The prognosis of patients with variant angina is favorable, if early complications can be overcome. However, because coronary artery spasm cannot be suppressed in some patients, even with multiple medications, medications to suppress intractable coronary artery spasm must be developed.
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**Key words:** variant angina, coronary artery spasm

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Variant angina was first described by Prinzmetal et al.[1] as a variant form of angina pectoris in which chest pain is accompanied by a transient ST-segment elevation on electrocardiogram. The development of ambulatory electrocardiographic monitoring and coronary arteriography permitted the investigation of the clinical features and pathophysiology of variant angina and revealed it to be caused by spasm of the coronary artery[2–4]. This review discusses the clinical spectrum, pathophysiology, and management of variant angina and coronary artery spasm.

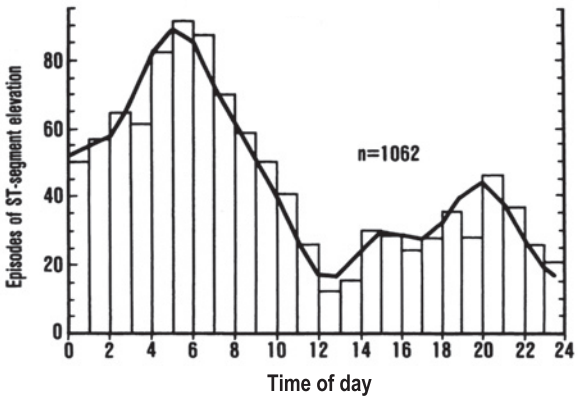


Fig. 1 Circadian variation in the episodes of ST-segment elevation in patients with variant angina.

## Clinical Spectrum of Variant Angina

Prinzmetal et al.[1] reported that the clinical presentation of variant angina differed from that of classic effort angina. They reported that the pain of variant angina occurs at rest or during ordinary activity and is not brought on by exercise. Electrocardiogram during attacks of pain shows ST-segment elevations with reciprocal depressions[1]. Ambulatory electrocardiographic monitoring of patients with variant angina has revealed a circadian variation in ischemic episodes[4,5]. Ischemic episodes with transient ST-segment elevation often occur at rest from midnight to early morning **(Fig. 1)** with a peak frequency at 5 o'clock in the morning. Although Prinzmetal et al.[1] reported that the pain of variant angina occurred at rest or during ordinary activity and was not brought on by exercise, Yasue et al.[5,6] have reported that anginal attacks also occur during mild exercise in the early morning. However, anginal attacks are rarely induced by strenuous exercise in the afternoon. Therefore, exercise capacity shows a circadian variation in most patients with variant angina[5,6]. Another important clinical feature of variant angina is the frequency of asymptomatic ischemic episodes and syncope that sometimes occur during the ischemic episodes. One study has revealed that 82% (872 of 1,062 episodes) of ischemic episodes were asymptomatic and that syncope occurred in 12.5% (30 of 240 patients) of patients with variant angina[4].

Transient ST-segment elevations with reciprocal depressions indicating transmural myocardial ischemia are typical electrocardiographic changes in variant angina. The ST-segment elevation corresponds to the distribution of the major coronary artery. Other electrocardiographic changes during attacks include a taller and broader R wave, disappearance of the S wave, and a taller T wave[1]. Negative U waves occasionally appear during attacks of variant angina and usually appear in the same leads that show ST-segment elevation. Negative U waves begin to appear when ST-segment elevation begins to resolve, then gradually become prominent and gradually disappear[7]. Severe arrhythmias, including ventricular tachycardia **(Fig. 2)**, high-degree atrioventricular block **(Fig. 3)**, and bradyarrhythmia, that cause syncope occasionally appear during an attack of variant angina[4]. Therefore, ambulatory electrocardiographic monitoring is useful for detecting electrocardiographic changes in patients with variant angina.

Yasue et al.[6] have suggested that angina pectoris induced by coronary artery spasm (vasospastic angina) can be diagnosed without performing coronary angiography if anginal attacks disappear quickly upon administration of nitroglycerin and if any 1 of the 5 criteria is met: 1) attacks appear 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) attacks are

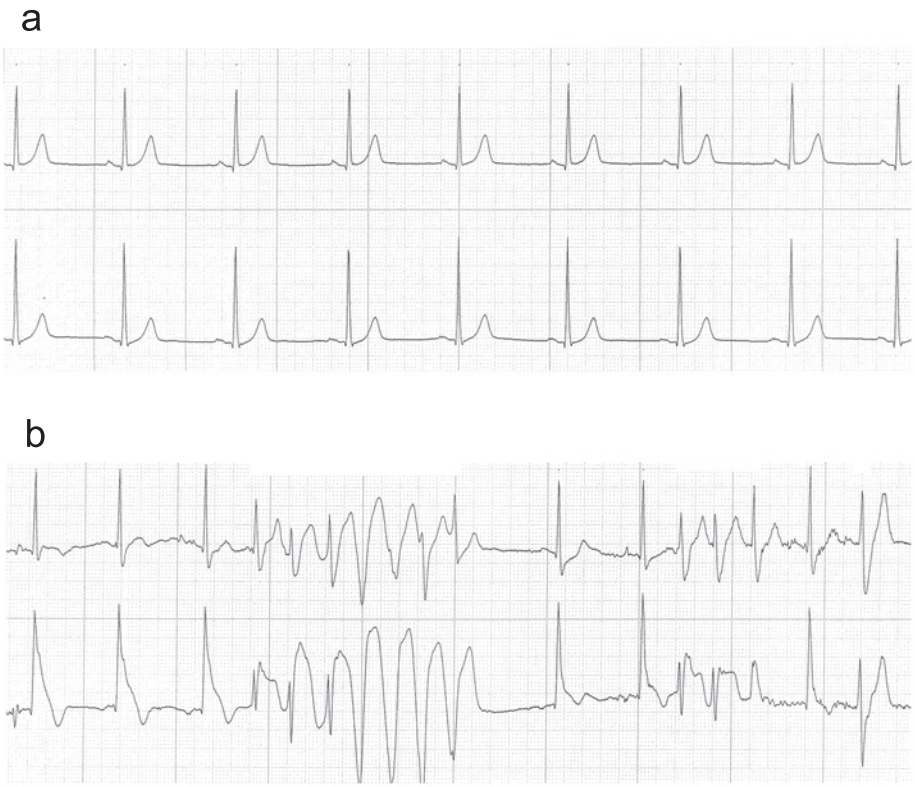


Fig. 2 Ambulatory electrocardiographic recordings in a patient with variant angina. Panel **a**: control recordings. Panel **b**: recordings during an attack showing ST-segment elevation and ventricular tachycardia.

accompanied by ST-segment elevation on electrocardiogram; 4) attacks are induced by hyperventilation; and 5) attacks are suppressed by calcium channel blockers but not by beta-blockers. Recently, the guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008) have included diagnostic criteria for vasospastic angina and a diagnostic flow chart[8].

### Pathophysiology of Variant Angina

Prinzmetal et al.[1] suggested that the variant form of angina pectoris results from temporary occlusion of a large diseased coronary artery with a narrow lumen due to the increase in the tonus of the vessel wall. Subsequent studies indicated that coronary artery spasm is the mechanism of myocardial ischemia in patients with variant angina and occurs in coronary arteries that appear nearly normal on coronary arteriography as well as at sites of organic stenosis[2,3]. Yasue et al.[5] have reported that coronary arteriograms are normal or near normal in 70% of Japanese patients with coronary artery spasm. Representative coronary arteriograms exhibiting coronary artery spasm in a patient with variant angina are shown in **Figure 4**. Provocation methods have been developed to diagnose coronary artery spasm. Acetylcholine and ergonovine are usually used to provoke coronary artery spasm[6,9,10]. However, the provocation of coronary artery spasm can result in serious complications and should be performed only by experienced physicians and in a properly equipped angiographic laboratory[6].

Although the pathogenesis of coronary artery spasm has not been fully elucidated, endothelial dysfunction and enhanced vascular smooth muscle contractility are considered to be the major underlying mechanisms[6,11].

Nitric oxide (NO) is synthesized from L-arginine by endothelial NO synthase (NOS) in vascular endothelial cells. Under normal conditions, NO induces smooth-muscle relaxation and vascular dilatation in response to endothelium-dependent vasodilators[12]. Kugiyama et al.[13] have shown that

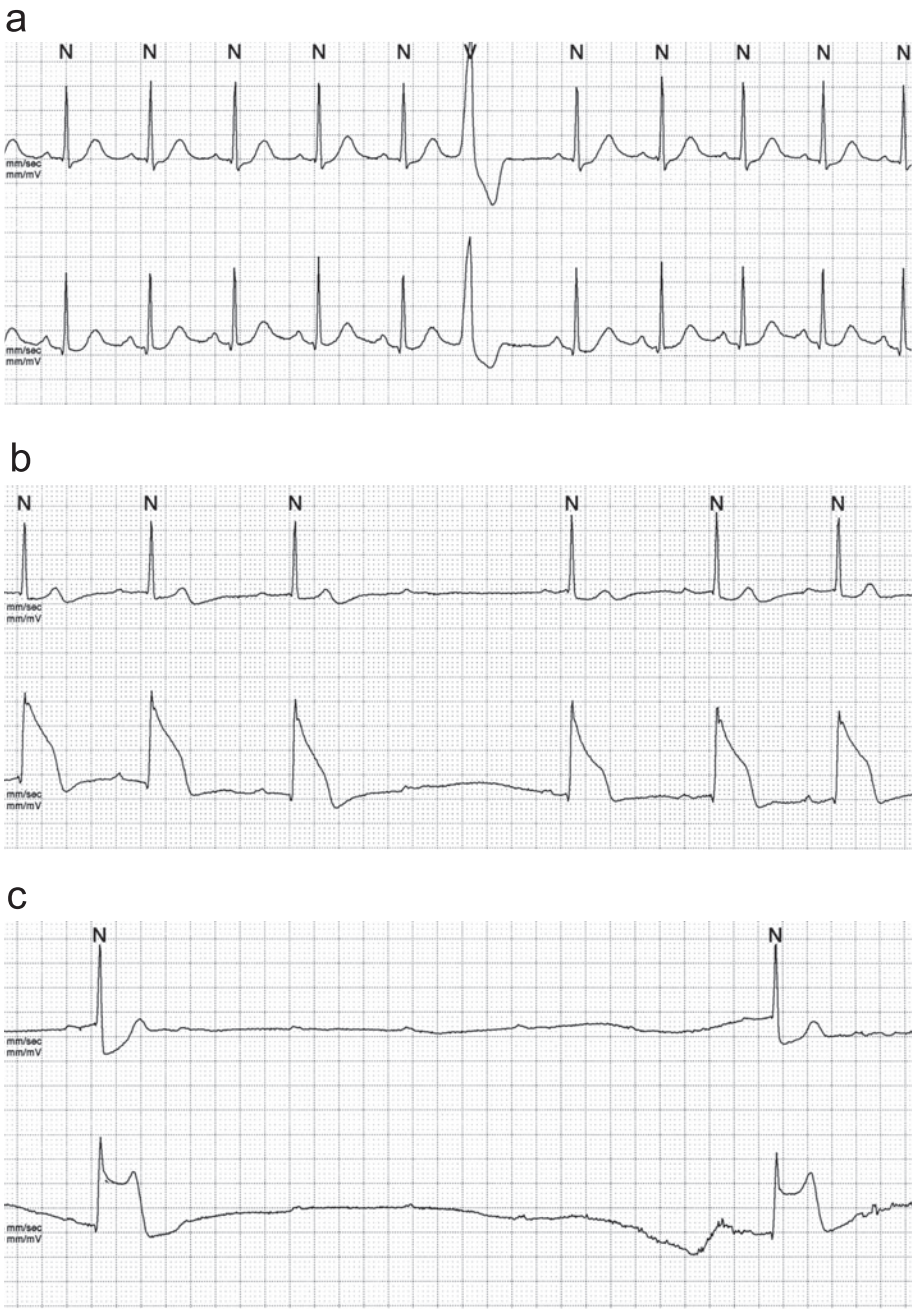


Fig. 3 Ambulatory electrocardiographic recordings in a patient with variant angina. Panel **a**: control recordings. Panels **b** and **c**: recordings during an attack, showing ST-segment elevation and second-degree atrioventricular (AV) block (panel b) and advanced AV block (panel c).

coronary arteries constrict in response to $N^G$-monomethyl-L-arginine (L-NMMA), an inhibitor of NOS, in control subjects but show little or no response in patients with vasospastic angina. They have also reported that L-NMMA suppresses flow-dependent dilation of coronary arteries in control subjects but has no significant effect in patients with coronary artery spasm and that the dilator response to nitroglycerin is not impaired in spastic coronary arteries[14]. These reports suggest that endothelial dysfunction of coronary arteries, leading to the deficient basal release of NO, plays an important role in the pathogenesis of coronary artery spasm.

The contraction and relaxation of vascular smooth

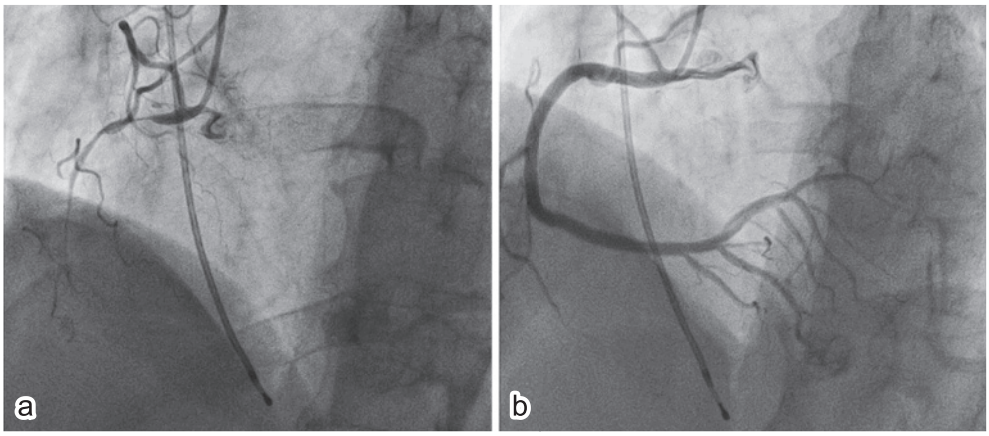


Fig. 4 Coronary angiograms in a patient with variant angina. Panel **a**: coronary artery spasm induced by intracoronary injection of acetylcholine into right coronary artery. Panel **b**: right coronary artery with no significant stenosis after intracoronary injection of nitroglycerin.

muscle are regulated by myosin light chain kinase and myosin light chain phosphatase via phosphorylation and dephosphorylation of the myosin light chain. RhoA and its down stream effector, Rho-kinase, are involved in the regulation of vascular smooth muscle contractility. Rho-kinase inhibits myosin light chain phosphatase, leading to the augmentation of myosin light chain phosphorylation and $Ca^{2+}$ sensitization in response to vasoconstrictor stimuli[11,15]. Shimokawa et al.[11,16] have presented evidence indicating that Rho-kinase is involved in the pathogenesis of coronary artery spasm. Intracoronary administration of fasudil and hydroxyfasudil, specific inhibitors of Rho-kinase, inhibit coronary artery spasm in a porcine model[17,18]. They have also reported that intracoronary fasudil inhibits acetylcholine-induced coronary artery spasm and related myocardial ischemia in patients with vasospastic angina[19]. Studies of the effects of the combination of intravenous fausdil and intracoronary nitroglycerine in patients with vasospastic angina have shown that fasudil further dilates the site of coronary artery spasm that had already been treated with nitroglycerine[20]. These clinical studies have demonstrated that the Rho/Rho-kinase pathway is involved in the pathogenesis of coronary artery spasm in humans.

Other proposed precipitating factors of coronary artery spasm include imbalance in the autonomic nervous activity, increased oxidative stress, chronic low-grade inflammation, magnesium deficiency, and genetic susceptibility[6,21]. Autonomic nervous system activity may play an important role in the development of coronary artery spasm in patients with variant angina, because episodes of myocardial ischemia occur more frequently from midnight to early morning[22,23]. Yasue et al.[22] have reported that the enhanced activity of the parasympathetic nervous system, which occurs at rest, is involved in triggering attacks by stimulating the sympathetic nerve that induces coronary artery spasm by activating alpha receptors in the large coronary arteries. Another study has suggested that sympathovagal imbalance, sympathetic activation without parasympathetic augmentation, in the early morning plays an important role in causing coronary artery spasm[23]. Studies of heart-rate variability and the norepinephrine release in response to insulin infusion in patients with variant angina have suggested that increased vagal tone and hyperreactivity to adrenergic stimulation trigger coronary artery spasm[24].

Oxygen free radicals damage vascular endothelial cells and degrade NO, leading to vasoconstriction. Levels of oxidative-stress markers are increased[25], and concentrations of antioxidants (e.g., vitamin E) are decreased in patients with vasospastic angina[26]. Cigarette smoking is a major risk factor for vasospastic angina without significant coronary artery narrowing[27] and has been shown to increase

oxidative stress and to degrade NO[28].

Itoh et al.[29] have shown that plasma levels of C-reactive protein, a sensitive marker of inflammation, are higher in patients with coronary artery spasm than in those without. They have suggested that chronic low-grade inflammation causes coronary artery spasm via the impairment of endothelial function, reduction of endothelial NO activity, and activation of the RhoA/Rho-kinase pathway.

Magnesium deficiency is thought to be a contributing factor in the genesis of coronary artery spasm[30,31]. Magnesium may have a blocking effect on calcium channels and may prevent the contraction of vascular smooth muscle[32,33]. The infusion of magnesium suppresses anginal attacks induced by hyperventilation[32] or by intracoronary infusion of acetylcholine[33] in patients with vasospastic angina. Anginal attacks are closely related to alcohol ingestion in some patients with variant angina[34]. Habitual drinking may induce latent magnesium deficiency in patients with variant angina. The ingestion of alcohol probably accelerates urinary excretion of magnesium and reduces tissue magnesium content, thereby facilitating the development of coronary artery spasm[31].

The incidence of coronary artery spasm shows racial differences[6,21]. Japanese patients with recent myocardial infarction exhibit a 3-times greater incidence of spasm than those in Caucasians[35], suggesting that genetic factors are involved in the pathogenesis. Genetic mutations may increase the susceptibility to coronary artery spasm[6,21]. A missense Glu298Asp variant in exon 7[36] and a $T^{-786}\rightarrow C$ mutation in the 5'-flanking region[37] of the endothelial NOS gene are significantly associated with coronary artery spasm. Polymorphisms of the endothelial NOS gene reduce endothelial NO synthesis and predispose to coronary artery spasm[6,38]. Polymorphism of the paraoxonase gene Gln 192Arg (Q192R) is significantly associated with coronary artery spasm and may play a role in the genesis of coronary artery spasm by attenuating the suppression of oxidative stress[39]. Other reported genetic risk factors for coronary artery spasm include the R257H variant in the phospholipase C-δ1[40], 242C→T in the NADH/NADPH oxidase p22 phox gene in males and -1171/5A→6A in the stromelysin-1 gene and -634C→G in the interleukin-6 gene in females[41].

## Management of Variant Angina

Early treatment of variant angina is important to prevent complications, such as acute myocardial infarction, fatal arrhythmias, and sudden death[42,43]. The sublingual or intravenous administration of nitroglycerine or isosorbide dinitrate is effective for relieving attacks of variant angina.

Calcium channel blockers are extremely effective for preventing ischemic attacks[6,44,45]. A survey by Kimura and Kishida[44] on drug treatment of variant angina in Japan showed that calcium channel blockers were effective in 92.5% of patients. In this survey, the efficacy rates of nifedipine, diltiazem, verapamil, and nifedipine + diltiazem were 94.0%, 90.8%, 85.7%, and 100%, respectively. Recent studies have shown that both benidipine and amlodipine are highly effective for the treatment of variant angina[46,47].

Long-acting nitrates are useful for preventing ischemic attacks. However, intermittent usage with nitrate-free periods is recommended to avoid nitrate tolerance[6]. Nicorandil, a combination of an adenosine triphosphate-sensitive potassium channel opener and nitrates, is also useful for suppressing ischemic attacks in patients with variant angina[47]. The Rho-kinase inhibitor fasudil effectively inhibits, coronary artery spasm[19]. Intravenous fasudil further dilates sites of coronary artery spasm previously treated with intracoronary nitroglycerine in patients with vasospastic angina[20].

A combination of different classes of calcium channel blockers and nitrates or nicorandil or both is necessary for patients with variant angina that is resistant to standard antianginal medications. In addition to these combinations of antianginal medications, magnesium[32,33], antioxidants[49], and statins[50] suppress coronary artery spasm.

Because ischemic episodes show circadian variation in patients with variant angina, antianginal drugs should be given to cover the period with ischemic episodes in accordance with the circadian

variation[4–6]. The suppression of both symptomatic and asymptomatic ischemic episodes is important, because asymptomatic episodes occur frequency in patients with variant angina. Therefore, careful evaluation with ambulatory electrocardiographic monitoring is essential to confirm the effects of antianginal drugs in each patient and to avoid inadequate medical treatment.

The prognosis of patients with variant angina is favorable, if early complications can be overcome[43,45]. Kishida et al.[43] have reported that the cumulative cardiac event rates at 1, 3, 5, and 10 years of observation were 16%, 16%, 17%, and 19%, respectively. Cardiac events, including coronary artery bypass graft surgery, nonfatal acute myocardial infarction, and cardiac death, occur at an early stage of variant angina; in 76% of patients who have had a cardiac event, the event occurred within 1 month of the onset of angina pectoris. Ito et al.[51] have reported that survival rates without cardiovascular death at 5 and 10 years were 97% and 93%, respectively, for patients with vasospastic angina registered before 1990 and were 98% and 94% respectively, for patients registered after 1990. Furthermore, survival rates of patients with significant coronary artery stenosis were lower than those of patients without stenosis before and after 1990.

Attacks of variant angina can be suppressed with antianginal drugs in most patients. However, in some patients, coronary artery spasm cannot be suppressed even with a combination of medications[6]. In a Japanese study of the role of coronary spasm in ischemic heart disease[52], intractable vasospastic angina was defined as angina that cannot be controlled even with the administration of 2 types of coronary vasodilators. This study found that vasospastic angina was present in 921 of 2,251 (40.9%) patients with angina pectoris and was intractable in 126 of these patients (13.7%). The patients with intractable vasospastic angina were younger at the time of onset and were more likely to be tobacco smokers and to be normotensive than the patients with treatable vasospastic angina[8,52]. For patients with intractable coronary artery spasm, treatment with a combination of different classes of calcium channel blockers and nitrates or nicorandil or both is necessary and should be continued. In addition to these medications, magnesium[32,33], antioxidants[49], and statins[50] suppress coronary artery spasm.

Patients with multivessel coronary artery spasm often have lethal arrhythmias[6,45]. The development of the automated external defibrillator has allowed some patients to survive ventricular tachycardia or fibrillation and to receive a diagnosis of vasospastic angina. The implantation of cardioverter defibrillator in patients who survive ventricular tachycardia or fibrillation due to coronary artery spasm is controversial[8]. Further research into the mechanisms of coronary artery spasm and the development of prophylactic medications to suppress intractable coronary artery spasm are required.

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