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REVIEW

Current advances in the understanding of coronary vasospasm

Ming-Jui Hung

Ming-Jui Hung, Cardiology Section, Department of Medicine, Chang Gung Memorial Hospital at Keelung, Chang Gung University College of Medicine, Keelung 20401, Taiwan, China
Author contributions: Hung MJ solely contributed to this paper.
Correspondence to: Ming-Jui Hung, MD, PhD, Cardiology Section, Department of Medicine, Chang Gung Memorial Hospital at Keelung, Chang Gung University College of Medicine, 222 Maijin Road, Keelung 20401, Taiwan, China. miran888@ms61.hinet.net
Telephone: +886-2-24313131-3168 Fax: +886-2-24335342
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Abstract

Recent years have witnessed progress in our understanding of coronary vasospasm (CVS). It is evident that this is not only an East Asian but also a global disease associated with significant symptoms and possible lethal sequelae for afflicted individuals. A correct diagnosis depends on the understanding of pathogenesis and symptomatology of CVS. With the correct diagnosis, we can manage CVS patients effectively and promptly, providing optimal patient safety. Advances in our understanding of interactions between inflammation, endothelium, and smooth muscle cells have led to substantial progress in understanding the pathogenesis of symptoms in CVS and have provided some insights into the basic etiology of this disorder in some patient subpopulations. We look forward to a time when therapy will address pathophysiology and perhaps, even the primary etiology.

Key words: Coronary vasospasm; Endothelial nitric oxide synthase; Inflammation; Nitric oxide; Rho-kinase

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INTRODUCTION

Coronary vasospasm (CVS) with transient ST-segment elevation can occur in diseased coronary arteries as Prinzmetal's variant angina[1]; it may also occur in angiographically normal coronary arteries as so-called 'variant of the variant' angina[2]. Subsequently, many investigators found that most CVS are associated with ST-segment depression rather than ST-segment elevation on electrocardiography (ECG)[3-5]. Therefore, variant angina is only one aspect of the spectrum of coronary vasospastic myocardial ischemia[6]. CVS plays an important role in the pathogenesis not only of variant angina, but also of ischemic heart disease, including effort angina, unstable angina, acute myocardial infarction, and sudden death[7-11]. Therefore, angina caused by CVS is now usually called 'coronary vasospastic angina'. The name 'variant angina' is less often used and is usually denoted as angina with transient ST-segment elevation.

CASE PRESENTATION

A 67-year-old man was admitted at midnight (0:30 am) to the emergency department due to sudden onset ischemic chest pain associated with cold sweating and palpitation. He was a heavy smoker who had experienced several of these episodes during the past 15 years in which most episodes occurred in the early morning hours. The baseline ECG (Figure 1A) showed no evidence of

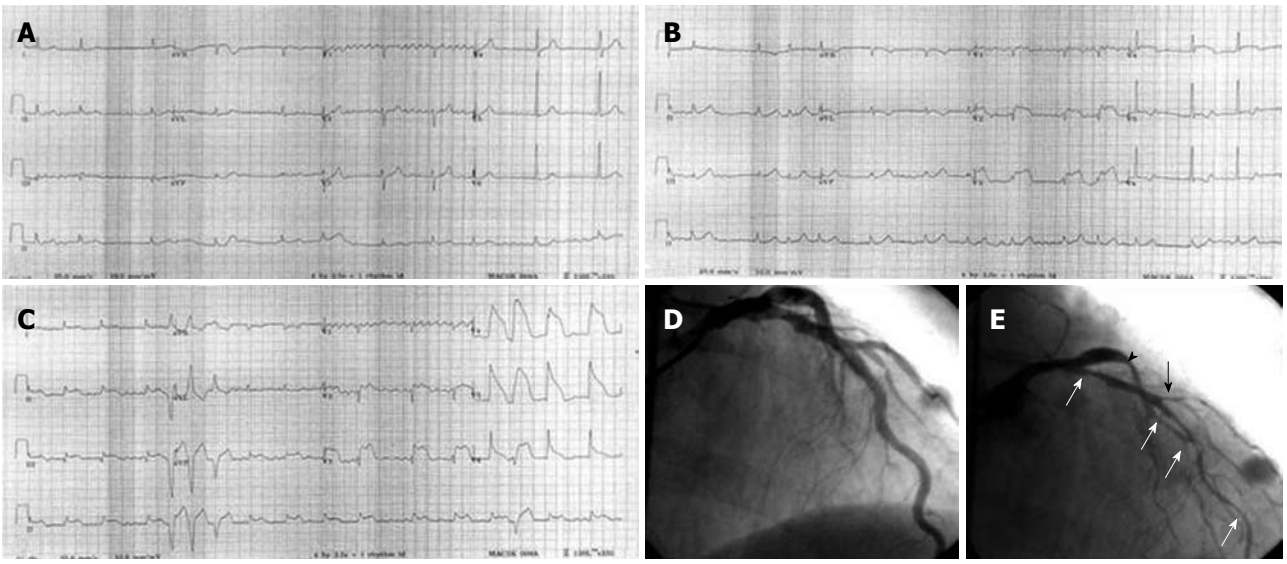

Figure 1 Baseline electrocardiography (ECG) of a patient with variant angina. A: The ECG showed no evidence of myocardial ischemia on admission to the emergency department; B: A few hours later, the follow-up ECG, due to chest pain, showed ST-segment elevation in the V_{2-4} leads. C: During the following days, serial ECGs due to chest pain showed dynamic ST-segment elevation in the anterior and inferior leads. D: The patient's ECG was normal when he was not having chest pain. Baseline coronary angiography showed no evidence of significant fixed coronary artery stenosis; E: Diffuse spasm in the proximal to distal portion (white arrows) and diagonal branch (black arrow) of the left anterior descending artery and in the proximal portion of the left circumflex artery (arrowhead) were noted following intracoronary methylergonovine administration.

myocardial ischemia on admission to the emergency department. A few hours later, the follow-up ECG due to recurrent chest pain (Figure 1B) showed ST-segment elevation in the V_{2-4} leads. In the following days, serial ECGs due to chest pain showed dynamic ST-segment elevation (Figure 1C) in the anterolateral and inferior leads associated with multiform premature ventricular contractions. Cardiac troponin I was normal in two successive tests 6 h apart. The high-sensitivity C-reactive protein was also normal (0.65 mg/L). Baseline coronary angiography during admission showed no evidence of significant fixed coronary artery stenosis (Figure 1D). Diffuse spasm in the proximal to distal portion (white arrows) and diagonal branch (black arrow) of the left anterior descending artery and in the proximal portion of the left circumflex artery (arrowhead) were noted following intracoronary methylergonovine administration (Figure 1E). The diagnosis of coronary vasospastic angina was made. The patient responded well to two long-acting calcium antagonists (nifedipine and verapamil) and nicorandil. He had an uneventful follow-up period of 2 years.

DIAGNOSIS OF CVS: MOST CVS ARE ASSOCIATED WITH ST-SEGMENT DEPRESSION

The diagnosis of CVS is not necessarily easy. In contrast to stable effort angina, which is reproducibly induced by exercise testing, CVS is usually not induced by exercise, particularly in the afternoon; it occurs usually at rest, particularly from midnight to early morning. The attack is transient, often lasts only a few minutes, and is unpredictable. Thus, ambulatory monitoring of ECG is important to detect the attack. However, even during ambulatory ECG monitoring, an attack may not be apparent, especially when attacks are infrequent. Furthermore, most CVS are associated with ST-segment depression rather than ST-segment elevation, which may not attract the cardiologists' attention[12]. Therefore, provocation tests for CVS were developed to make a diagnosis of CVS-related ischemic heart disease. An important issue is the indication of provocation testing performed. The pharmacologic provocation testing of CVS is recommended in patients with recurrent episodes of apparent ischemic chest pain at rest who have normal or mildly abnormal coronary angiograms, with no clinical observations substantiating the diagnosis of variant angina, i.e. ST-segment elevation during pain[13].

Several provocative tests for CVS are available. Of these, the ergonovine and acetylcholine tests are most commonly used. Ergonovine is an ergot alkaloid that stimulates both α-adrenergic and serotonergic receptors, and intracoronary administration of doses ranging from 10-80 μg in total are most commonly used. Intracoronary nitroglycerin 50-200 μg is administered subsequently if the luminal diameter is decreased more than 70% after intracoronary ergonovine, in association with clinical symptoms and/or electrocardiographic changes[14]. There is no standard definition for a positive intracoronary provocation test. Yasue *et al*[15] defined CVS as an abnormal contraction of an epicardial coronary artery resulting in myocardial ischemia. With this definition, there are no limits to the degree of lumen reduction required to diagnose CVS, since ischemia must accompany

the changes in vessel size. The American College of Cardiology/American Heart Association guidelines for coronary angiography suggest that CVS is present when a reduction in lumen diameter of > 50% occurs during a provocative test[13]. In early 1990, coronary provocation testing using methylergonovine was developed[16]. The intracoronary route of administration of methylergonovine for provocation of CVS is safe, sensitive, and specific. This route is preferable in hypertensive patients and affords the opportunity to evaluate the left and right coronary circulations separately. Auch-Schwelk *et al*[17] reported that the contractions to ergonovine are not dependent on nitric oxide release, but are synergistically augmented by thromboxane. However, methylergonovine causes similar effects on vascular smooth muscle, but contractions are inhibited by the release of nitric oxide from the endothelium.

Intracoronary acetylcholine administration in doses of 10-100 μg is also used for CVS provocation[18]. The duration of the action of acetylcholine is very short and the induced CVS usually disappears spontaneously within 2-3 min, without the need for intracoronary nitroglycerin administration. Sinus node and conduction system inhibition is a major side effect of the acetylcholine test in which temporary pacing is needed, especially when intracoronary acetylcholine is administered into the right coronary artery. Acetylcholine provocation is also commonly used to assess coronary endothelial function as it stimulates the release of endothelium-derived nitric oxide with subsequent vasorelaxation of the vascular smooth muscle cells. However, with increasing doses of acetylcholine application, the vasoconstrictor effect on the vascular smooth cells may override the endothelial effect and a vasoconstrictor response may result. Thus, in the normal setting, there is an endothelium-induced coronary vasodilation in response to acetylcholine stimulation, while in the presence of a dysfunctional endothelium the vasoconstrictor effects of acetylcholine prevail and cause a vasoconstriction. Overall, it may be difficult to differentiate between coronary endothelial dysfunction and a CVS, unless the vasoconstrictor response is distinct or > 50% of the vessel diameter. The vasomotion can result in as much as a < 50% change in vessel diameter in patients without CVS[19]. This can also be applied for the cold pressor test.

CVS can also be induced by hyperventilation, which causes respiratory alkalosis[20]. Its sensitivity is 65% and the specificity is 100%. It may be safe when CVS is induced by hyperventilation. Nonetheless, it may be dangerous to use this method to induce multivessel CVS. Histamine, epinephrine, dopamine, dobutamine, serotonin, exercise in the morning, and the cold pressor test all induce CVS with a lower sensitivity than ergonovine or acetylcholine[21].

Angiographically normal coronary arteries occur in 25% of patients with acute coronary syndrome[4,5,10]. The CVS can be induced in 50%-60% of these patients[5,10]. Since variant angina is a presentation of transient ST-elevation acute coronary syndrome, the diagnosis and initial management procedures must adhere to the guidelines proposed by the American Heart Association in 2005[22]. Initial general therapies for acute coronary syndrome include immediate oxygen therapy, continuous cardiac monitoring, establishment of intravenous access, and medications of aspirin, nitroglycerin, and/or morphine. Morphine is indicated only for refractory chest pain after nitroglycerin use. If a normalized ST-segment is noted after the above general therapies, a diagnosis of variant angina is most likely and reperfusion therapy is unnecessary. If ST-segment elevation persists, then reperfusion therapies are necessary, according to the facilities available in the emergency room.

The importance of the differential diagnosis between persistence and transience of elevated ST-segments lies in the follow-up ECG and patient monitoring. The next diagnostic step for transient ST-segment elevation is coronary angiography, as this is the only certain method to distinguish between patients who have severe fixed multivessel disease or only angiographically normal or near-normal coronary arteries. This differential diagnosis is important because the treatment strategies proposed for variant angina with severe, fixed multivessel disease (e.g. aspirin, clopidogrel, nitrates, angiotensin-converting enzyme inhibitor, and/or percutaneous coronary intervention) or only angiographically normal or near-normal coronary arteries (e.g. calcium antagonists and/or nitrates) are different. Because there are some patients with CVS who are refractory to the conventional medications and who may suffer from life-threatening arrhythmias[10] or sudden death[23], and because percutaneous coronary intervention is not the correct management for CVS[24], it is important for every emergency room, ward doctor, and cardiologist to be alert to the presence of CVS, a type of dynamic coronary artery stenosis, which may be silent and lethal.

In 1991, Dote *et al*[25] first reported 5 cases of multivessel CVS and transient myocardial stunning. Thereafter, the term transient left ventricular apical ballooning or Takotsubo cardiomyopathy was used to describe transient myocardial stunning by many investigators. After recent investigations, Takotsubo cardiomyopathy is recognized as a form of myocardial stunning following a stressful event that is presumably induced by intense CVS[26,27], microvascular dysfunction[28,29], or a marked catecholamine response[30,31]. Clinically, Takotsubo cardiomyopathy is characterized by (1) acute onset (usually following a stressful or emotional event, especially in older women); (2) variable severity of clinical (mainly, dyspnea and chest pain) and electrocardiographic manifestations of acute myocardial ischemia (typically involving territories larger than a single coronary branch); (3) mild cardiac enzyme elevation; (4) absence of obstructive, fixed coronary lesions on early angiographic images; (5) apical, anteroapical, and inferoapical hypo- or dyskinesia, with preserved basal-segment contractility, producing an ampulla-like systolic deformity of the left ventricular sil-

houette; (6) spontaneous resolution of all features in 1-4 wk, including normalized left ventricular function; and (7) a generally favorable late prognosis and rare recurrence rate. There are some different features between Takotsubo cardiomyopathy and CVS: (1) more postmenopausal female patients have Takotsubo cardiomyopathy; (2) older patients have Takotsubo cardiomyopathy; and (3) more daytime attacks of Takotsubo cardiomyopathy. Recent prospective studies suggest that the incidence of Takotsubo cardiomyopathy in acute coronary syndromes is 0%-2% on early coronary angiography[32]. Another study in an Italian population revealed that 12% of female patients with suspected anterior acute myocardial infarction had Takotsubo cardiomyopathy[33]. Although it is important to differentiate CVS from Takotsubo cardiomyopathy, there are some overlaps of these 2 entities. In a recent case series study of Takotsubo cardiomyopathy, the author described an experimental reproduction of transient apical ballooning in the catheterization laboratory during acetylcholine testing[34]. The author suggested that coronary vasospastic angina is caused by localized, long-term neurohormonal dysfunction of one coronary artery, making patients susceptible to localized spastic episodes under transient influences of physiologic stimuli, such as emotions. On the other hand, onset of Takotsubo cardiomyopathy appears to represent the superimposition of transient diffuse endothelial dysfunction (probably lasting a finite period) and of an adrenergic surge episode. Persistent apical ballooning after the early stages appears to represent residual, secondary myocardial stunning. As a newly recognized disorder, much remains unknown about Takotsubo cardiomyopathy, especially its etiology. Many aspects are also puzzling. Nevertheless, delayed (5-30 d) acetylcholine testing accompanied by echocardiographic monitoring should be routinely pursued to identify the mechanism of Takotsubo cardiomyopathy, to better characterize individual prognoses, and to tailor treatments[34].

NEW UNDERSTANDING OF THE MECHANISMS OF CVS

Autonomic system dysfunction

In the 1980s, researchers demonstrated that autonomic nervous system dysfunction was one of the possible mechanisms involved in the development of CVS[18,35]. Pathologic findings of degeneration and fibrotic changes in the perivascular nerves of vasospastic coronary arteries support the hypothesis of autonomic nervous system dysfunction in CVS[36].

Endothelial dysfunction, oxidative stress, and genetic susceptibility

In the 1990s, deficiency of nitric oxide activity due to endothelial dysfunction and oxidative stress were identified as other possible mechanisms for CVS[37-40]. Plasma levels of vitamin E and another antioxidant were also found to be low in patients with CVS[40,41]. Subsequently, Japanese investigators showed that polymorphisms of Glu298Asp in exon 7 and T-786C in the 5'-flanking region of the endothelial nitric oxide synthase (eNOS) gene and paraoxonase gene Gln192Arg (Q192R) polymorphism were significantly associated with CVS[42-44]. Paraoxonase I gene has an antioxidant effect and CVS occurs more often in cigarette smokers[45]. Of CVS, endothelial function is impaired both in coronary and brachial arteries and is improved by vitamin C infusion in smokers[46]. Cigarette smoke extract suppresses the acetylcholine-induced endothelium dependent vasorelaxation and the suppression is prevented by antioxidants in isolated arteries[47,48]. Thus, cigarette smoking degrades nitric oxide through oxygen radicals. These findings suggest that decreased nitric oxide activity in CVS patients is partly due to increased nitric oxide degradation by oxygen radicals. However, eNOS polymorphisms are found in only one-third of CVS patients and therefore, other genes or factors may also be involved in the pathogenesis of CVS. Murase *et al*[49] showed that while genetic risk and gene environment in both genders were involved with CVS, eNOS gene polymorphism was associated with CVS only in women[50]. Type A personality, severe anxiety, and panic disorders were factors associated with CVS, even without significant obstructive coronary artery disease. Although the oxidized form of low-density lipoprotein impairs production of nitric oxide due to down-regulation of eNOS and the oxidative inactivation of nitric oxide by oxygen free radicals[51,52], hypercholesterolemia is not a risk factor for CVS[45,53]. Nakagawa *et al*[12] found that CVS preferentially occurs at branch points and nonplaque sites, whereas the atherosclerotic lesion is predominantly localized at the nonbranch points of the curved proximal segments. This indicates that CVS may be a manifestation of coronary artery disease distinctly different from coronary atherosclerosis which is associated with hypercholesterolemia.

Smooth muscle hypercontraction

The classical pathway of vascular smooth muscle contraction through which stimuli induce myosin light chain phosphorylation is an increase of the intracellular Ca^{2+} concentration. However, Ca^{2+}-independent regulation also occurs through the inhibition of myosin light chain phosphatase, and the level of myosin light chain phosphorylation is determined by a balance between myosin light chain phosphorylation by myosin light chain kinase and dephosphorylation by myosin light chain phosphatase[54]. Some investigators found that small GTPase RhoA and its downstream effector, ROCK/Rho-kinase, inhibit myosin light chain phosphatase resulting in accentuation of myosin light chain phosphorylation and Ca^{2+} sensitization in response to vasoconstrictor stimuli[55]. In the late 1990s, researchers showed that RhoA/ROCK activity was enhanced in rat arteries with hypertension and vasospasm[56,57]. Shimokawa *et al*[58] and Kandabashi *et al*[59] developed swine models of CVS and showed that ROCK activity is enhanced in coronary ar-

tery smooth muscle after wrapping the coronary artery with interleukin-1 beads. They subsequently showed that the ROCK inhibitor, fasudil, relieved CVS in humans[60]. Thus, enhanced vascular smooth muscle contraction through the Rho/ROCK pathway plays an important role in the development of CVS. Recent studies show that decreased endothelial nitric oxide activity increases RhoA/ROCK activity in coronary arteries[61,62]. Fluvastatin, which blocks the RhoA/ROCK pathway was also found to suppress CVS[63]. These findings connect the activity of RhoA/ROCK to endothelial nitric oxide and are in agreement with the clinical observations that spastic arteries are supersensitive to both vasoconstrictor agonists and nitrates[64].

Inflammation

In 1978, Lewis *et al*[65] first reported a case of variant angina and localized pericarditis. They postulated that there was a link between inflammation and CVS. In the mid and late 2000s, we and others showed that chronic inflammation was associated with CVS, as evidenced by elevated peripheral blood monocyte counts, high-sensitivity C-reactive protein, interleukin-6, and adhesion molecules[66-75]. Cigarette smoking, a major risk factor for CVS, is associated with low-grade inflammation[76]. An interaction between smoking and high-sensitivity C-reactive protein was recently reported by our group[77]. Based on several studies, inflammation exists in patients with CVS. However, the mechanism remains elusive.

Magnesium deficiency, insulin resistance, and K_{ATP} channel dysfunction

In the 1980s to 1990s, magnesium deficiency was also considered as a possible factor contributing to the genesis of CVS[78,79]. Furthermore, it has been reported that infusion of magnesium reduced coronary spasm attacks in patients with CVS[80,81]. The plausible mechanism might be the calcium channel blocking effect of magnesium ions at the level of vascular smooth muscle cells. Extracellular magnesium inhibits capacitative calcium ion entry in vascular smooth muscle cells[82]. Magnesium-induced coronary dilatation may also be mediated *via* intracellular cyclic adenosine 3',5'-monophosphate. Previous studies have shown that adenosine 3',5'-monophosphate elevations contribute to coronary dilatation[83]. Magnesium infusion may cause an increase in adenosine 3',5'-monophosphate within coronary smooth muscle cells, leading to the dilatation of coronary arteries[84]. In 1995, Shinozaki *et al*[85] found that insulin resistance associated with compensatory hyperinsulinemia is an independent factor for CVS. They postulated that hyperinsulinemia causes vascular endothelial dysfunction and CVS, and subsequently amplifies atherosclerotic lesion formation. However, CVS does not always precede obstructive atherosclerotic coronary artery disease. The mechanisms between insulin resistance and CVS have not been definitely defined. In 2006, Kakkar *et al*[86] found that spontaneous CVS occurs in K_{ATP} mutant mice, which arises from a smooth muscle-extrinsic process. They postulated that endothelial dysfunction with loss of K_{ATP} channels and decreased nitric oxide production and/or bioavailability promotes smooth muscle hypercontractility. Another possibility includes the sympathetic neurons, where opening of presynaptic K_{ATP} 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 CVS.

Summary

CVS provoked by ergonovine results in altered vascular muscle function rather than a disturbance in endothelial nitric oxide release[17]. This is in line with clinical studies demonstrating endothelial dysfunction in many patients without evidence of CVS. Dysfunctional endothelium could play an additional role in the pathogenesis of CVS, because contractions due to the endogenous ligand serotonin are markedly augmented after inhibition of nitric oxide synthase[17]. The interactions between the autonomic nervous system, inflammation, nitric oxide availability, eNOS regulation, Rho/ROCK activity of vascular smooth muscle cells, and K_{ATP} channels in smooth muscle cells provide some insights towards the basic etiology of this disorder in some subpopulations.

MANAGEMENT

In the event of an acute CVS attack, chest pain can usually be relieved by sublingual nitroglycerin. With occasional refractory CVS, intravenous or intracoronary administration of nitroglycerin may be necessary. Since the durations of action for nitroglycerin and nitrates are short, i.e. 1 h or less, the long-acting calcium antagonists are necessary to prevent recurrence. The effect of the calcium antagonists is often dramatic. Of particular importance, the calcium antagonist should be given before going to bed at night as CVS attacks usually occur from midnight into the early morning. It may require 2 calcium antagonists (dihydropyridine and non-dihydropyridine) to relieve CVS-related angina. Calcium antagonists should not be withdrawn even if symptomatic attacks occur rarely because of long-term spasticity-related silent myocardial ischemia[45,87] and sudden death from life-threatening cardiac arrhythmias[10]. Long-acting nitrates are also useful, but their potency is reduced by their tolerance. Combinations of different classes of calcium antagonists with nitrates may be necessary for patients with refractory CVS. β-blockers are not effective in suppressing CVS-related chest pain, especially in patients with angiographically normal or near-normal coronary arteries[88]. Recent clinical research shows that magnesium[81], statins[63], antioxidants[39,40], and the Rho-kinase inhibitor fasudil[60] are also beneficial for the treatment of CVS. In addition to the use of effective anti-CVS medications, CVS inducers must be avoided. These inducers include cigarette smoking, catecholamines,

Table 1 Therapeutic strategies for CVS

Quit smoking	Obligatory
Long-acting Calcium antagonists	Use before going to bed at night
Long-acting Nitrates	Decreased potency by tolerance
Magnesium	Evidence by intravenous infusion
RhoA/ROCK inhibitor	Fasudil
Statins	Evidence by fluvastatin
Coronary bypass graft	Controversial
Implantable cardioverter defibrillator	For life-threatening ventricular arrhythmias

CVS: Coronary vasospasm.

muscarinic agonists, ergot alkaloids, prostaglandins, alcohol, emotional stress, and propranolol[21].

The role of coronary intervention in patients with refractory CVS and organic stenosis is limited[89]. In CVS patients who did not respond to conventional treatments, internal mammary artery revascularization with angiographically normal coronary arteries was reported[90]. An implantable cardioverter defibrillator with aggressive medical therapy for CVS was reported to be effective in patients who had a previous syncopal event, documented ventricular tachycardia, or surviving out of hospital cardiac arrest[91-93] (Table 1).

PROGNOSIS

The natural history of CVS-related ischemic heart disease is generally good as long as patients avoid cigarette smoking and have good compliance with adequate calcium antagonists therapy[45,94-98]. Cardiac events are likely to occur during the first 3-6 mo. Patients without a stenosis of 70% or more have a 94% 1-year MI-free survival rate, while patients with multivessel atherosclerotic coronary artery disease and variant angina only have a 83% 1-year MI-free survival rate[94]. A recurrent angina rate of 11% was noted in patients with CVS without significant fixed coronary artery disease during a 4-year follow-up period[45]. Nonfatal acute myocardial infarction is a possible complication of variant angina with a incidence of 5%-10%[94,99]. Seventy-five percent of nonfatal myocardial infarction occurs during the first 3 mo[94]. The extent and severity of underlying fixed obstructive coronary artery disease is the prognostic factor which predicts survival within 3-6 mo after the diagnosis of CVS[94]. Significant arrhythmic events during or following attacks of variant angina occur in 20%-50% of patients, among a large series of mostly untreated patients[90]. The risk of sudden death for patients with coronary vasospastic angina is approximately 2% and is most common in patients with multivessel CVS and prior significant arrhythmias during angina occurrence[99]. From another point of view, Wakabayashi *et al*[100] tested consecutive Japanese patients for CVS 10-20 d after acute myocardial infarction treated by percutaneous coronary intervention. They found that provoked CVS occurs in 70% of infarct-related arteries and about 50% of noninfarct-related arteries. Provoked CVS was an independent predictor of adverse outcome.

CONCLUSION

Advances in our understanding of interactions between inflammation, the vascular endothelium, and smooth muscle cells have led to substantial progress in our understanding of CVS-pathogenesis and symptomatology, and have provided some insights towards the basic etiology of this disorder in some patient subpopulations. The absence of significant obstructive coronary artery disease should not lead the physician to conclude that the patient does not have ischemic heart disease. Since most patients with CVS present with ST-segment depression rather than ST-segment elevation, a high index of suspicion for CVS-related ischemic chest pain is important, because the treatment of choice varies accordingly. Many young cardiologists are now much interested in coronary intervention and, therefore, are not familiar with CVS-related angina. Since CVS may be complicated by lethal cardiac arrhythmias, sudden death, and incorrect management, it is very important for every physician to be alert to the presence of CVS, which is a dynamic type of coronary artery stenosis[101,102]. With the correct diagnosis, we can manage CVS patients effectively and promptly, providing for optimal patient safety.

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