

# NONINVASIVE STRESS TESTING

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## Variant Angina: An Update and Review

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### Introduction

Variant angina (VA), also referred to as Prinzmetal's angina, is a distinct syndrome of ischemic chest pain classically occurring at rest and associated with transient ST segment elevation on the electrocardiogram (ECG).<sup>1,2</sup> Although its complex pathophysiology is poorly understood, it occurs as a result of coronary artery spasm and has traditionally been associated with a benign prognosis. Recent studies have helped to clarify the pathogenesis and to re-define the prognosis of VA. Because VA mandates specific therapy, its recognition and distinction from classic ischemic heart disease is critical for the interventionalist. This article provides an update and review of the pathophysiology, manifestations, diagnosis, treatment, and prognosis of VA.

### Historical Aspects

The protean manifestations of angina pectoris have long been appreciated. In 1772, Heberden noted a nonexertional form of angina, different from classic angina.<sup>2</sup> Latham postulated coronary artery spasm as a mechanism for angina pectoris in 1846, and in 1910, Osler, in his lectures on angina pectoris, referred to a variant of angina characterized by "the greater frequency in women, the milder character of the attacks,

and the hopeful outlook."<sup>3,4</sup> A form of angina "precipitated by contraction of the coronary arteries," as opposed to an increase in myocardial oxygen demand, and manifested by ECG changes suggestive of myocardial infarction, was described by Wilson and Johnston in 1941.<sup>5</sup> In a classic paper in 1959, Prinzmetal et al.<sup>1</sup> define VA as another type of angina pectoris, which unlike typical angina, comes on at rest or normal activity and is associated with transient ST segment elevation, not depression (Table 1). The concept of coronary artery spasm as the trigger of Prinzmetal's syndrome was furthered during the 1970s, when a number of investigators identified patients with VA and found that there was no relation between the degree of coronary stenosis or myocardial oxygen demand and the patients' chest pain.<sup>6-10</sup> Instead, a diminished myocardial blood supply presumably resulting from coronary artery spasm was more closely related to the onset of symptoms.

With the advent of coronary angiography and a provocative test to diagnose VA in the 1970s, investigators have had the opportunity to study the pathophysiology, treatment, and prognosis of this syndrome.

### Pathophysiology

VA results from focal coronary artery spasm, the exact etiology of which remains elusive.<sup>6-10</sup> A variety of factors, including the autonomic nervous system, altered coronary artery tone and reactivity, and endothelial dysfunction have been implicated. To what degree each of these factors contributes in a given patient is variable, and what determines that degree remains unknown.

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**Table 1.** Definition of Variant Angina

- |   |
|---|
| 1. Anginal syndrome, typically substernal chest pain, due to myocardial ischemia      |
| 2. Often occurs at rest and in the early morning                                      |
| 3. Transient ST segment elevation of the electrocardiogram during the episode of pain |

**Autonomic Nervous System.** The autonomic nervous system may contribute to the pathophysiology of VA in a number of ways. Yasue et al.<sup>11</sup> induced spasm in patients with VA with intracoronary acetylcholine injections and blocked it by pretreating with atropine, suggesting that excess parasympathetic activity may play a role in this entity. Endo et al.<sup>12</sup> had similar results using methacholine, an acetylcholine analogue. Clinical correlates can be found in patients with VA refractory to medical treatment whose pain has been successfully managed with surgical denervation of the heart followed by autotransplantation, and in the observation that ischemic episodes occur most commonly in the early morning when vagal tone is at its highest.<sup>13</sup> Alternatively, Lanza et al.,<sup>14</sup> after evaluating heart rate variability associated with episodes of spasm, recently concluded that changes in autonomic activity, in particular vagal withdrawal, not stimulation, may result in coronary artery spasm.

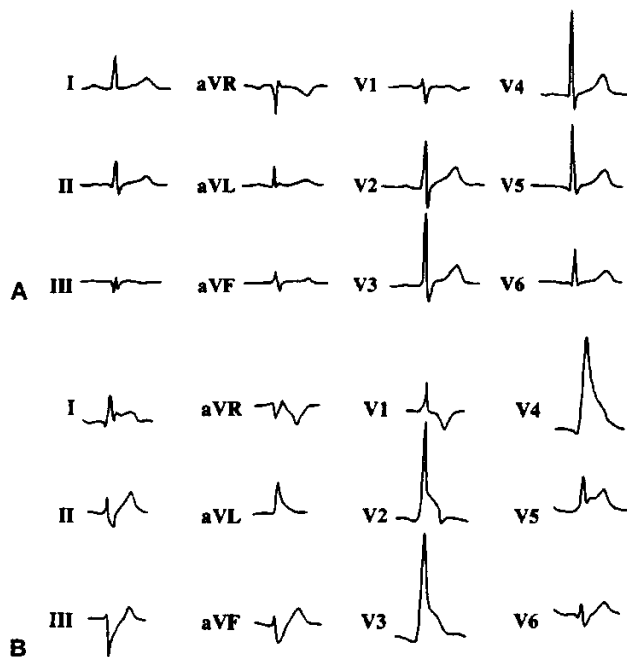
Others have shown that coronary artery spasm can be provoked by enhanced alpha adrenergic activity and prevented by alpha adrenergic blockers.<sup>15-17</sup> Chierchia et al.,<sup>18</sup> however, questioned the link between alpha adrenergic activity and coronary spasm. These investigators used an increase in heart rate as a marker for increased sympathetic activity in patients with coronary spasm. They found no correlation between heart rate and several hundred episodes of spasm. Nor did they find a decrease in frequency of ischemic attacks with phentolamine, an alpha adrenergic blocker, compared to placebo.<sup>18</sup> These discrepancies, and the fact that VA is known to occur in transplanted denervated hearts, imply that other factors besides the autonomic nervous system must contribute to coronary artery spasm.<sup>19</sup>

**Altered Coronary Artery Tone and Reactivity.** A heightened coronary artery tone with localized hypersensitivity, unrelated to endothelial dysfunction from atherosclerotic lesions, may be responsible for spasm in some patients with VA. For example, ergonovine, a stimulator of coronary artery spasm, not only de-

creases lumen diameter at the spastic site of a coronary artery, but also leads to a greater than normal vasoconstrictor response throughout the entire coronary artery, suggesting a diffusely heightened tone.<sup>20</sup> Kaski et al.<sup>21</sup> have shown that during spontaneous spasm in patients with VA, not only does focal and exaggerated vasoconstriction occur at the spastic site, but also to a lesser degree, throughout the entire coronary artery tree. In addition, Kuga et al.<sup>22</sup> demonstrated that basal coronary artery tone is elevated at spastic sites and nonspastic sites in some patients with VA, and Hoshio et al.<sup>23</sup> have shown that basal coronary artery tone at nonspastic sites is greater in patients with VA than in those without it.

Why some patients have a generalized increased coronary tone is controversial. Changes in the levels of circulating vasoactive substances may contribute to the heightened tone. Levels of endothelin, a known potent vasoconstrictor, and of histamine and serotonin are elevated in some patients with VA.<sup>24-27</sup> Alternatively, a deficiency in nitric oxide (endothelium derived relaxation factor) bioactivity, resulting in impaired coronary vasodilation may contribute.<sup>28</sup> Finally, variable changes in the intracellular mechanisms responsible for coronary vasoconstriction may explain the diffuse increase in tone; drugs that decrease intracellular calcium, such as calcium channel blockers, and drugs that increase intracellular cyclic guanylate monophosphate (GMP) concentrations, such as nitrates, can prevent coronary artery spasm, which supports this theory.<sup>29</sup>

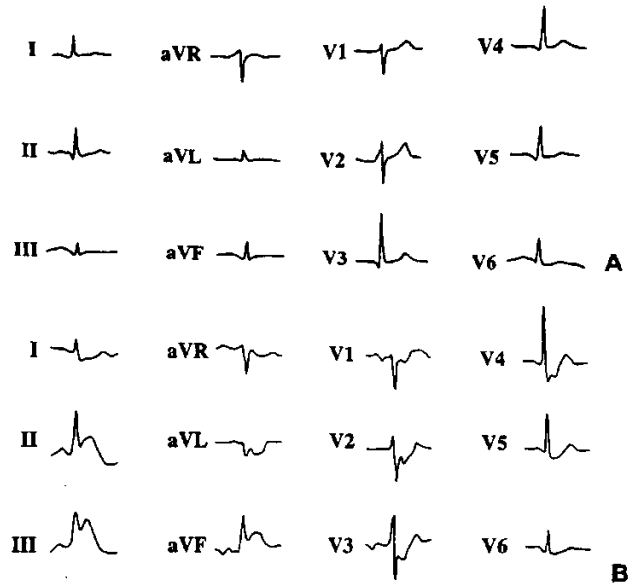
Various mediators may precipitate the local hyperreactivity in patients with increased basal tone. We have evaluated a patient with probable VA and aminophylline-induced coronary artery spasm. The patient was a 51-year-old man with an extensive tobacco history who presented with 2 months of recurrent chest pain, recently awakening him from sleep. An exercise test was unremarkable. Angiography initially demonstrated a 70% stenosis of the left anterior descending artery (LAD). An angioplasty was planned, and follow-up angiography 1 week later showed only a 40% stenosis of the LAD. In retrospect, the initial 70% stenosis was felt to be secondary to spasm. A myocardial perfusion study was performed to evaluate persistent chest pain. It revealed normal myocardial perfusion, however, with administration of aminophylline to reverse the effect of Persantine, the patient developed ischemic chest pain and 5-mm anterior ST segment elevation (Fig. 1A and B). The patient's chest



**Figure 1.** Electrocardiograms done at (A) baseline and (B) during spasm of a 51-year-old man with probable variant angina and aminophylline induced coronary artery spasm.

pain and ECG changes resolved promptly with nitroglycerin administration. The patient's symptoms have subsequently been controlled with a calcium channel blocker. To our knowledge, aminophylline has not been previously reported as a cause of coronary artery spasm.

Topol and Fortuin<sup>30</sup> reported on a patient with carcinoid heart disease and coronary spasm, felt secondary to elaboration of vasoactive amines, in particular histamine, by the carcinoid tumor. We recently evaluated a 64-year-old man with a 2-year history of chest pain at rest. Exercise stress testing had revealed ST segment elevation in the inferior leads and angiography showed only a 30% stenosis in the LAD. Ultimately, the patient was admitted with an episode of chest pain as well as nausea, vomiting, diarrhea, abdominal pain, flushing, and wheezing. An echocardiogram demonstrated normal valvular and left ventricular function. An abdominal computed tomographic (CT) scan revealed multiple hepatic lesions of unclear etiology. He had recurrent episodes of chest pain resulting in transient 4-mm ST segment elevation in the inferior leads of the ECG (Fig. 2A and B); the last episode resulted in ventricular tachycardia progressing



**Figure 2.** Electrocardiograms done at (A) baseline and (B) during spasm of a 64-year-old man with carcinoid tumor of the distal ileum with hepatic metastases.

to electrical-mechanical dissociation and ultimately death. Autopsy revealed a carcinoid tumor in the distal ileum with hepatic metastases. The heart was normal without significant atherosclerosis or valvular involvement by the carcinoid tumor. We concluded that the patient had VA exacerbated by the vasoactive amines produced by his carcinoid.

Kanazawa et al.<sup>31</sup> demonstrated vasospasm in patients with VA that was triggered by serotonin and ergonovine, but not by acetylcholine, further suggesting a hypersensitivity specific to certain agents. However, Kaski et al.<sup>32</sup> have shown that the same patient with VA can have spasm induced by a variety of vasoconstrictive stimuli implying a nonspecific hyperreactivity. In addition, the failure of specific receptor antagonists, such as alpha adrenergic blockers, thromboxane A<sub>2</sub> blockade, and serotonin receptor blockers to consistently inhibit coronary artery spasm, further implies a nonspecific stimulus triggering constriction of coronary artery smooth muscle.<sup>26,33-35</sup>

Unfortunately, not all investigators have found an increased basal coronary tone in patients with VA. For example, Hackett et al.<sup>36</sup> found no difference in the basal coronary artery tone of spastic coronary segments as compared to nonspastic segments in six patients with VA, and another group<sup>37</sup> demonstrated no

difference in the basal coronary artery tone of non-spastic segments in 13 patients with VA as compared to 41 patients without coronary spasm. This discrepancy may be related to differences in patient selection, use of nitrates, and disease activity.<sup>38</sup> For example, Ozaki et al.<sup>38</sup> have shown that the increase in coronary tone at spastic segments is not constant, but varies with disease activity in patients with VA.

**Endothelial Dysfunction.** Dysfunction of the autonomic nervous system and altered coronary artery tone with focal hyperreactivity are present in some patients with VA; endothelial dysfunction, however, appears to be the underlying and most important pathophysiological mechanism for coronary artery spasm in the majority of patients with VA. MacAlpin<sup>39</sup> initially hypothesized that coronary artery spasm in patients with VA resulted from endothelial dysfunction leading to an exaggeration of the normal vasoconstriction that can occur at the site of an atherosclerotic lesion. This "geometric theory" proposes that the degree of lumen obstruction secondary to spasm is related to and can be predicted by the severity of intimal encroachment by an atherosclerotic lesion. Recent investigation using intravascular ultrasound, a more sensitive means of detecting atherosclerotic coronary changes, provides further support for the association between atherosclerotic coronary artery disease (CAD) and focal spasm. Yamagishi et al.<sup>40</sup> detected a significantly thicker intimal leading edge and increased sonolucent area with intravascular ultrasound, suggestive of atherosclerosis, at 15 sites of spasm compared to 7 control sites in patients with normal or near normal coronary angiography.

Freedman et al.<sup>41</sup> tested MacAlpin's hypothesis by performing angiography in patients with positive ergonovine tests and coronary artery atherosclerosis. They found that the degree of spasm was greater than would be predicted by the geometric theory alone. Furthermore, although some series demonstrate CAD in up to 90% of patients with spasm, patients with VA can have spasm at sites without angiographically apparent atherosclerotic disease. Other series reveal that as many as 40% of North American, and over 60% of Japanese patients with VA have coronary angiograms with no stenosis > 70%.<sup>42-47</sup>

**Role of Nitric Oxide in Endothelial Dysfunction.** More likely, endothelial dysfunction, which may or may not be related to atherosclerosis, results in decreased production of, or impaired response to, endogenous vasodilators, particularly nitric oxide. For

example, intracoronary acetylcholine results in nitric oxide mediated vasodilation in normal coronary arteries, however, in patients with VA, acetylcholine causes vasoconstriction, possibly due to decreased nitric oxide release secondary to dysfunctional endothelium.<sup>48</sup>

In a compelling study, Kugiyama et al.<sup>49</sup> found that infusion of an inhibitor of nitric oxide synthase into coronary arteries of control patients resulted in vasoconstriction, but had no effect in patients with VA. This implies a basal secretion of nitric oxide occurs to maintain basal tone and suggests a deficiency in nitric oxide activity in spastic arteries. They also showed that spastic arteries are hyperresponsive to nitroglycerin. This, they suggest, results because nitroglycerin is converted to nitric oxide and the spastic artery is deficient in endogenous nitric oxide. Another group found that although levels of serotonin across the coronary bed in patients with VA increase, there is no corresponding increase in serotonin mediated nitric oxide release, again implicating nitric oxide deficiency in the pathogenesis of spasm.<sup>50</sup> Another group of investigators have recently found decreased levels of vitamin E in patients with active VA as compared to groups with inactive VA, CAD, or no CAD.<sup>51</sup> They argue that the antioxidant deficiency allows oxidative modification of low density lipoprotein (LDL), impairing endothelial dependant vasorelaxation, presumably by affecting nitric oxide levels or activity.

In an attempt to find genetic factors associated with abnormal nitric oxide activity, Yoshimura et al.<sup>48</sup> identified a variant in the coding region of the endothelial nitric oxide synthase gene that occurred in a significantly greater proportion of patients with VA. The authors hypothesize that this variant results in decreased nitric oxide production in these patients and is associated with their development of VA.

It should be noted that not all investigators believe nitric oxide release is decreased in patients with VA. Egashira et al.<sup>52</sup> found that an arginine analogue, and an inhibitor of nitric oxide synthesis, delivered via intracoronary infusion, resulted in a greater decrease in basal lumen diameter at the spastic site of the artery, than at nonspastic sites. The authors conclude that the arginine analogue must be blocking the vasodilatory effects of a basal level of nitric oxide at the spastic site.

Furthermore, not all patients with atherosclerosis develop coronary artery spasm, although atherosclerosis does impair endothelial nitric oxide release. Therefore, a deficiency in other endogenous vasodilators,

such as prostacyclin, probably contributes to spasm in some patients. This relative lack of vasodilators may result in platelet aggregation and the release of potent vasoconstrictors, such as thromboxane A<sub>2</sub>, serotonin, and adenosine diphosphate, culminating in coronary artery spasm.<sup>53</sup> Because studies using aspirin to inhibit thromboxane A<sub>2</sub> production by platelets or using specific serotonin blocking agents in patients with VA have not shown a significant effect on the number of ischemic episodes in patients with VA, it's important to note that spasm related to endothelial dysfunction probably results from a tipping of the normal balance between vasoconstrictor and vasodilatory stimuli, rather than from an increase or decrease in a single vasoactive substance.<sup>33,54</sup>

There does not appear to be a unifying pathophysiology for coronary spasm in all patients with VA. Most likely, endothelial dysfunction, often but not always in the presence of atherosclerosis, leads to abnormal nitric oxide activity and an imbalance in the normal milieu of vasoactive substances culminating in focal coronary artery spasm.

### Clinical Manifestations

The clinical features of VA are outlined in Table 2 and discussed in this section. VA is most commonly seen in patients between the ages of 35 and 50.<sup>55</sup> Women are affected more than men.<sup>55</sup> The prevalence of VA in patients with ischemic heart disease varies between 2% and 14% depending on the population studied.<sup>47,56</sup> Risk factors typically do not include classic coronary risk factors except for tobacco use; associations between VA and stress, alcohol use and withdrawal, certain chemotherapeutic agents, a family history of migraine, a history of Raynaud's Syndrome,

pericarditis, and primary mitral valve prolapse have also been noted.<sup>57-64</sup> Spasm can also occur after coronary artery bypass surgery and angioplasty.<sup>65-68</sup>

Patients with VA complain of episodes of typical angina pectoris, characterized as substernal pressure that radiates to the jaw and left arm. It most commonly occurs at rest between midnight and 8 AM, although as many as 50% of patients also have angina with exertion or excitement.<sup>69</sup> The circadian nature of the pain is usually constant in a given patient, however, the frequency and severity of episodes can be quite variable and often related to emotional stress.<sup>70</sup> Exercise capacity is generally preserved, but aspirin use can reduce it by provoking spasm.<sup>71</sup> The chest pain generally responds to sublingual nitroglycerin, and if this is not the case, the diagnosis should be questioned. Furthermore, a history of being awakened from sleep by the chest pain should trigger the consideration of VA.

The routine ECG in a patient with VA is typically normal.<sup>2</sup> Electrocardiographic manifestations during an episode of chest pain include transient ST segment elevation in the distribution of a specific coronary artery and reciprocal ST segment changes. Commonly an increase in R-wave amplitude is also evident.<sup>2,72</sup> Patients who do have baseline abnormal ECGs, can have pseudonormalization of their ECG during episodes. At times of ischemia, conduction disturbances can occur, manifested as a variety of arrhythmias, especially ventricular.<sup>2,73-76</sup> Electrocardiographic changes and arrhythmia occur most often in the early morning.<sup>77</sup>

Exercise testing in patients with VA can provoke a variety of responses. In a large study of patients with VA who underwent exercise treadmill testing, 44% of patients had no ST segment changes, 30% had ST segment elevation, and 26% had ST segment depression.<sup>78</sup> The ST segment changes did not correlate with degree of CAD, however, patients with frequent attacks of VA were more likely to have ST segment elevation. In another report, ST segment elevation during the recovery phase of exercise treadmill testing proved to be another manifestation of VA.<sup>79</sup> Interestingly, in a comparison of treadmill testing with cycle ergometer exercise as stressors for inducing ST changes in patients with known VA, ST segment elevation and depression were provoked significantly more often by treadmill testing.<sup>80</sup> The authors hypothesize that the difference may be related to a variable neurohumoral response depending on the type of stressor. One may infer that treadmill testing may be more valuable than cycle ergometer exercise in this population.

**Table 2.** Features of Variant Angina

1. Middle-aged subjects; women more frequently than men
2. Ergonovine-induced angina-like chest pain, often at the same time in the early morning
3. Associated with tobacco use, but no other "classic" cardiac risk factors
4. Can occur in "normal" coronaries or at angiographic sites of atherosclerosis
5. Pain responds to nitroglycerin and calcium antagonists
6. Complications are common in the first 3 months after diagnosis

## Diagnosis

The diagnosis of VA is generally made by obtaining a classic history and by noting transient ST segment elevation during episodes of chest pain at rest. An empiric trial of a calcium antagonist, if successful, further supports the diagnosis. If the symptoms are relatively frequent and predictable, ambulatory ECG monitoring can be a helpful diagnostic tool. We personally have seen a patient diagnosed by ST elevation, complete heart block and then ventricular fibrillation (which autoconverted) during an episode of VA recorded by such monitoring.

However, because not all cases are classic and because VA can masquerade as typical unstable angina, a number of provocative tests can be performed to confirm the diagnosis.<sup>81</sup> In the past, ergonovine maleate, an ergot alkaloid that stimulates alpha adrenergic and serotonergic receptors, was used to elicit coronary artery spasm in patients with VA.<sup>82,83</sup> Subsequent studies have defined a sensitivity for this test in the mid-90% range and a specificity in the high 90% range.<sup>84,85</sup> An inverse relation between the dose of ergonovine necessary to provoke spasm and the frequency of spontaneous attacks has been noted.<sup>86</sup> Moreover, in those patients with one or more daily attacks of VA, ergonovine has a sensitivity of 100%, while in those with less than one daily attack it is only 77%.<sup>87</sup> Side effects of ergonovine include nausea and hypertension, and complications are rare, occurring in only .03% in one study of over 3,000 patients.<sup>86</sup> However, refractory spasm, myocardial infarction, and death have been reported from ergonovine infusion.<sup>88</sup> Ergonovine infusion may be especially dangerous in the early postinfarction period and in patients on beta blockers.<sup>89</sup> Provocation of coronary spasm must be done in a controlled setting with appropriate resuscitative equipment and personnel available. Because of the inherent risks, only patients with otherwise normal coronary arteries should undergo ergonovine provocation, and doses should be gradually escalated.

More recently, intracoronary acetylcholine injection has been suggested to be over 90% sensitive and specific at diagnosing VA.<sup>11</sup> Because of the potential complications with ergonovine and because it has the added advantage of being given into individual coronary arteries, acetylcholine infusion is replacing ergonovine. Other methods for provoking attacks include methacholine infusion, histamine infusion, and cold pressor testing, but because of low sensitivities,

low specificities, or adverse side effects, none of these are used frequently.<sup>12,25,90</sup>

The use of hyperventilation to provoke VA, first used in combination with Tris-buffer by Yasue et al.,<sup>91</sup> and then alone by Mortensen et al.<sup>92,93</sup> in 1983, recently was shown to have a sensitivity of 62% and specificity of 100%. Nakao et al.<sup>94</sup> recommend hyperventilation as a noninvasive test for detecting VA, that, if positive, can eliminate the need for acetylcholine or ergonovine infusion. When used in conjunction with echocardiography to detect wall-motion abnormalities occurring with hyperventilation-induced spasm, the sensitivity of hyperventilation can be increased to 84%.<sup>95</sup> Another noninvasive method of diagnosing VA involves using echocardiography to measure the dilation response of the left main coronary artery to nitroglycerin. Morita et al.,<sup>96</sup> using this technique, found increased coronary tone in the morning in patients with vasospastic angina, leading to an increased dilatory response to nitroglycerin and a sensitivity of 80% and specificity of 94%.

## Treatment

**Medical Therapy.** Acute attacks of VA are promptly relieved by nitroglycerin, presumably via its coronary vasodilating effects, however, calcium channel blockers appear to provide the most effective long-term management. Pepine et al.<sup>97</sup> found that diltiazem decreased angina frequency and nitroglycerin consumption compared to placebo in patients with VA. Schroeder et al.<sup>98,99</sup> and Rosenthal et al.<sup>100</sup> found that diltiazem reduces new cardiovascular events by 92%, overall anginal frequency by 94%, and significantly decreases consumption of nitroglycerin. This same group then demonstrated that long-term therapy with diltiazem (over a 44-week period) decreased frequency of anginal attacks up to 80% versus placebo.<sup>101</sup>

A number of studies have demonstrated the efficacy of nifedipine at decreasing anginal attacks and arrhythmia in the short- and long-term treatment of VA.<sup>102-106</sup> For example, Antman et al.<sup>104</sup> treated 127 patients with symptoms refractory to nitrate and beta blocker therapy with nifedipine and found that > 60% had complete control of anginal attacks and > 80% had at least a 50% reduction. Furthermore, a single dose of nifedipine can prevent angiographic expression of ergonovine provoked coronary arterial spasm.<sup>107</sup> Withdrawal of nifedipine treatment in these

patients often results in a recurrence of symptoms.<sup>98,102</sup> Verapamil, and more recently felodipine, have also been shown to be effective at preventing the frequency of angina and myocardial ischemia, respectively, in patients with coronary artery spasm.<sup>108-112</sup> In a review of over 250 patients with VA treated in Japan with calcium channel blockers, nifedipine, diltiazem, and verapamil were effective in 94%, 90.8%, and 85.7% of patients, respectively.<sup>113</sup> Long-acting nitrates have been used successfully to treat VA, however, in a trial comparing the efficacy of nifedipine with isosorbide dinitrate, Ginsburg et al.<sup>114</sup> found that although both agents prevented attacks, nifedipine appeared more effective and was preferred by most patients.

In patients whose VA is refractory to calcium channel blockers, the addition of a long-acting nitrate is often effective. Alternatively, alpha adrenergic blockers and serotonergic antagonists have been used successfully in this setting.<sup>115,116</sup> Of note, high dose aspirin, by impairing coronary artery dilatation as a result of inhibition of prostaglandin synthesis, can worsen VA.<sup>117</sup>

The use of beta blockers in VA is somewhat controversial because of a limited number of small studies with disparate results.<sup>118,119</sup> Yasue et al.<sup>118</sup> noted that propranolol aggravated angina attacks in 13 patients with VA. Robertson et al.<sup>120</sup> found that propranolol, compared with placebo, prolonged angina attacks in six patients with VA. However, Gauzzi et al.<sup>119</sup> documented that propranolol decreased symptoms in patients with VA on a short-term and long-term basis.

Most likely these disparate results can be explained by differences in the patient populations studied. In those with VA and normal coronary angiograms, beta blockers can potentially aggravate spasm by blocking the vasodilatory beta adrenergic receptors, thereby allowing unopposed alpha adrenergic stimulation. While in patients with VA and associated CAD, beta blockers can potentially decrease the frequency of exertional angina related to flow-limiting stenoses. Therefore, the distinction between these two populations of patients with VA will impact on the decision regarding beta blocker use.

**Interventional Therapy.** Percutaneous transluminal coronary angioplasty has been used effectively for patients with CAD associated with VA. Corcos et al.<sup>121</sup> successfully performed angioplasty in 19 of 21 patients with CAD and VA; but recurrences of VA (in 11 of the 19 patients within 4 months) and restenosis

were frequent complications in this study and others.<sup>67,121-123</sup> Stents have been used in conjunction with angioplasty in patients with atherosclerotic lesions and refractory VA.<sup>124-126</sup> One group reported successful treatment of VA resistant to medical therapy by stenting the vasospastic segment despite no evidence of atherosclerotic disease.<sup>127</sup>

**Surgical Therapy.** Coronary artery bypass grafting can be an effective intervention in patients with active VA refractory to medical management. It has been used successfully in patients without significant atherosclerotic disease, but it can be detrimental in these patients and is, therefore, generally reserved for those who also have significant obstructive lesions.<sup>128-130</sup> Mark et al.<sup>56</sup> followed 48 patients with VA who underwent bypass surgery for 5 years and documented a 94% survival rate.

Cardiac denervation (plexectomy) has been proposed as a viable treatment option; when combined with coronary artery bypass grafting the probability of recurrent VA is significantly lowered compared with coronary artery bypass grafting alone.<sup>131,132</sup> More radical surgical intervention for refractory cases, like denervation with autotransplantation (surgical removal followed by immediate reimplantation), may relieve symptoms, but can be complicated by persistent spasm.<sup>13,133</sup> Surgical therapy for VA should be a last resort as experience is limited and pharmacological management is the most effective form of treatment.

## Prognosis

The traditional belief that VA has a benign prognosis may only apply to patients without CAD who receive appropriate treatment; a recent study shows that even this group has a greater morbidity than initially appreciated.<sup>134</sup> Because of the complex pathophysiology and the variable degree of CAD in patients who present with VA, the prognosis changes depending on the subgroup analyzed (Table 3).

Walling et al.<sup>135</sup> followed 217 patients with VA for a mean of 65 months and found a 99% survival rate at 1 year and 94% at 5 years in those without coronary artery stenoses > 70%. In an earlier report on this same cohort, Waters et al.<sup>136</sup> noted that survival without myocardial infarction was 93% in those without CAD if they were treated with a calcium channel blocker, whereas it was only 77% in those treated with perhexiline maleate or nitrates. Yasue et al.<sup>46</sup> followed

**Table 3.** Prognostic Subgroups of Patients with Variant Angina

	5-year MI-free Survival
1. Patients with endothelial dysfunction and no significant coronary artery disease	> 80%
2. Patients with early single vessel atherosclerosis	> 70%
3. Patients with multiple fixed atherosclerotic lesions	> 50%

245 patients for an average of 80.5 months. The high 5-year survival rate of 97% reflected the fact that only 16% of patients had multivessel CAD. ST segment elevation during an attack, lack of use of calcium channel blockers, abnormal left ventricular function, smoking, and alcohol intake all correlated with a decreased survival. Two other smaller studies document similarly high survival rates and survival rates without myocardial infarction in patients with VA and no CAD, especially when treated with calcium channel blockers.<sup>137,138</sup>

Most studies on the natural course of coronary artery spasm in patients with normal or nearly normal coronary arteries are based on medium-term follow-up in small populations. The French series cited above is particularly notable since 277 successive patients were followed for a median of 7.5 years (range 1–198 months).<sup>134</sup> There were 206 men and 71 women whose mean age was  $54 \pm 9$  years. They all had a coronary angiogram revealing no stenosis > 50%. Spasm was confirmed during the coronary angiogram in 157 (57%) patients by a positive provocation test following the angiogram in 113 (41%) patients, and by an ECG that showed ST elevation in 7 (2.5%) patients. The majority of patients, 264 (95.3%), were treated with calcium channel blockers. At the end of this study 35 (12.6%) patients were lost to follow-up, 20 (7.2%) patients died including 10 (3.6%) from cardiac causes, and 18 (6.5%) patients had a myocardial infarction, 11 of whose repeat coronary angiogram now demonstrated a significant stenosis. In addition, 109 (39%) patients had persistent angina, in 52 of whom the severity (more than one episode per month) warranted repeat coronary angiogram (with significant stenosis in 19 cases). Only one third (95 patients) of the group were asymptomatic. Multivariate analyses showed that the only predictors of major coronary events were systemic hypertension or the finding of minor parietal irregularities on the initial coronary angiogram. In this

most complete series, despite treatment with calcium channel blockers, persistent or recurrent episodes of angina were frequently observed, whereas complications such as myocardial infarction or death were rare.

A number of investigators have identified a subgroup of patients who have a markedly worse prognosis, especially early in the course of their disease. This subgroup primarily consists of patients with VA and significant CAD. Twenty of the 22 myocardial infarctions and 8 of the 14 deaths in the study by Waters et al.<sup>136</sup> occurred in the first 3 months. The strongest predictor of survival was CAD; indeed, the survival at 5 years was 77% in those with multivessel disease compared to 94% in those without significant CAD. Left ventricular function was also noted to be a predictor of prognosis, probably because of its strong correlation with CAD.

Mark et al.<sup>56</sup> reviewed the course of 109 consecutive VA patients who underwent coronary angiography over an 11-year period. Eighty-six percent of the nonfatal myocardial infarctions occurred within 1 month of coronary angiography and the risk of death was greatest during the first 3–6 months of follow-up. Moreover, 93% of nonfatal myocardial infarctions and 83% of deaths during the follow-up occurred in patients with significant CAD. Maseri et al.<sup>139</sup> and Severi et al.<sup>140</sup> noted a similar pattern, with 87% of nonfatal myocardial infarctions occurring within 1 month of hospitalization in the former study, and 91% occurring during the first 3 months of follow-up in the later study. In the study by Severi et al.,<sup>140</sup> a similarly high percentage of coronary events occurred in patients with concomitant CAD.

Presumably this increased morbidity and mortality reflects the fact that disease activity is greatest when these patients present to the hospital and the additive effects of the presence of CAD and VA. In fact, Mark et al.<sup>56</sup> noted that the morbidity and mortality of patients with VA and CAD was significantly worse than that of patients with CAD alone.

Summarizing the prognosis in various subgroups of patients with VA is made easier by the fact that most Japanese patients with VA have a lower prevalence of CAD compared to Caucasian VA patients. For example, in a pooled analysis of several predominantly Caucasian studies and Japanese studies, one group found that Caucasian VA patients have a much higher rate of prior myocardial infarction (24% vs 7%,  $P < 0.0001$ ) and a greater prevalence of CAD (66% vs 41%,  $P < 0.0001$ ) than Japanese patients.<sup>141</sup> The myocardial in-



farct-free survival at 3-year follow-up in this pooled analysis was 75% in the Caucasian studies and 91% in the Japanese studies ( $P < 0.0001$ ), while overall 3-year survival rates were 89% in the Caucasian studies as compared to 97% in the Japanese studies.<sup>141</sup> This analysis helps to give a point estimate of rates of death and myocardial infarction for different categories of patients diagnosed with VA.

Therefore, the mortality of patients with VA and no CAD, treated with calcium channel blockers, is low, although the morbidity, according to the French study, can be quite high. Patients with atherosclerotic coronary disease and VA have a significantly worse prognosis and demand careful medical attention.<sup>134</sup>

### Conclusion

VA has a characteristic presentation consisting of typical ischemic chest pain at rest, usually in the early morning, with transient ST segment elevation on the ECG. The clinical manifestations are a result of coronary artery spasm, but the pathophysiology of the spasm often is unclear. Treatment with long-acting calcium channel blockers is recommended and is associated with a lower mortality in those without concomitant CAD. Because the interventional cardiologist continually evaluates patients with chest pain syndromes and because the management and prognosis of patients with VA differ significantly from patients with classic CAD, it is important for the interventional cardiologist to remain knowledgeable about VA.

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