Clinical Review

Coronary Arterial Spasm

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Coronary arterial spasm has been postulated to be a cause of myocardial ischemia for over 100 years. It was not until the work of Prinzmetal et al in 1959, however, that major clinical attention and research began to be addressed to the role of vasospasm in the manifestations of ischemic heart disease.

It is now known that spasm may be clinically important in patients with significant underlying atherosclerotic coronary artery disease as well as in patients with anatomically normal or subcritically stenosed coronary vessels. Research has suggested that spasm may be associated with symptoms of stable resting and/or exertional angina pectoris and that it almost certainly plays a role in the pathogenesis of unstable angina pectoris and acute myocardial infarction. Symptomatic arrhythmias, including sinus bradycardia, heart block, and ventricular tachyarrhythmias, have been documented to complicate coronary vasospasm. Given the potential importance of coronary arterial spasm in so many different ischemic heart disease syndromes, the development of therapeutic agents that may prevent spasm has obvious clinical importance.

Much of the progress of modern medicine can be attributed to the rediscovery, re-exploration, and further development of old ideas and concepts. This is true for the subject of much recent excitement and work, coronary artery spasm, which was first postulated to be a mechanism for angina pectoris over 100 years ago.

This paper will first provide an historical overview of angina pectoris, particularly with regard to the concept of coronary vasospasm. The recent research into the role of coronary vasospasm in the broad spectrum of ischemic coronary artery disease will be discussed.

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Historical Perspective

Although symptoms compatible with myocardial ischemia were probably first described by Morgagni in a 42-year-old woman in 1761,[1] William Heberden is generally credited with describing the symptoms of ischemic heart disease and coining the term *angina pectoris* to describe them.[2] Although he did not recognize these symptoms as a disorder of the heart, he described provocation of angina by exertion and eating, nocturnal angina, progressive and unstable angina, angina of many hours' duration (probably representing what is known of today as myocardial infarction), and sudden death in patients with underlying angina.[2]

Pathologist Edward Jenner was the first individual to associate the symptoms of angina pectoris with pathologic abnormalities of the coronary arteries.[3] He did not publish the results of his work immediately, however, because he felt their publication might cause undue anxiety in a valued friend who had, at that time, developed the symptoms of angina. Citing Jenner's findings and those of subsequent patients, Parry in 1799 proposed a pathopysiologic mechanism for angina which resembles the current theory of supply and demand.[3] Ten years later, in 1809, Allan Burns more fully developed the theory of supply and demand.[4]

The recent excitement over coronary artery spasm would suggest that it is a relatively new concept. Like the idea of supply-demand inequality, however, the concept of coronary vasospasm has roots extending well back into medical history. In 1812, John Warren described the autopsy finding of dilated coronary arteries in a man with angina pectoris. Although he did not postulate spasm, he suggested that angina might occur independently of coronary artery ossification.[5] In 1876, Latham described the autopsy findings of three patients with angina pectoris.[6] Finding that two of the patients had normal or only minimally diseased coronary arteries, he suggested that coronary spasm, acting alone or in association with pathologic abnormalities of the coronary arteries, might be the cause of angina pectoris.[6]

Sir William Osler also noted the presence of normal coronaries in a dying man with a history of angina pectoris, and he concluded, in the Lumleian Lectures of 1910, that "angina pectoris may kill without signs of obvious disease in the heart or blood vessels." He too postulated spasm.[7]

Sir Thomas Lewis in 1931[8] further discussed the potential role of spasm, and Parkinson in 1931[9] suggested the superimposition of spasm upon fixed anatomic lesions.

Animal experiments and observations in humans raised the possibility that reflex coronary vasoconstriction might play a role in the precipitation of angina in situations such as gastric distension, smoking, and cooling of the hands.[10-14] Reflex coronary spasm was postulated to be a factor in determining the extent of myocardial necrosis following infarction.[15]

Despite the excitement of those authors about the possible role of spasm, the idea waned and lay relatively dormant until it was taken up again by Prinzmetal in 1959.[16] The reason for this hiatus is likely that mentioned by Parkinson; it was an idea incapable, at that time, of anatomic verification, which would have to await the development and application of coronary angiographic techniques. In addition, in the 1930s to 1950s, detailed pathologic studies, including those of Blumgart et al,[17] Saphir et al,[18] Yater et al,[19] and Zoll,[10] firmly established the relationship between severe fixed atherosclerotic disease of the coronary arteries and the syndromes of angina pectoris and myocardial infarction.

The concept that fixed lesions of the coronary arterial tree were responsible for the symptoms of angina pectoris was strengthened by hemodynamic studies demonstrating a significant relationship between increases in the factors governing myocardial oxygen consumption and the onset of ischemic symptoms. The major factors governing myocardial oxygen consumption were known to include heart rate, contractility, and wall tension.[20-22] Estimates of myocardial work and, therefore, of myocardial oxygen consumption could be made using heart rate and ventricular or aortic systolic pressure. Increases in factors governing myocardial oxygen consumption were found to precede attacks of angina in humans.[23-24] In patients with typical exertional chest pain, the rate-pressure product (the product of heart rate and systolic blood pressure) was found to be nearly constant for any patient at the onset of angina.[24]

Although a number of authors had described isolated patients in whom the onset of angina pectoris bore no clear relationship to presumed increases in cardiac work,[25] Prinzmetal et al in 1959 were the first investigators to call attention to a variant form

of angina pectoris.[16] Classic Heberden's angina had been characterized by pain provoked by increases in cardiac work, and electrocardiogram (ECG) during pain generally showed ST segment depression.[16] In contrast, Prinzmetal's variant angina was characterized by pain occurring at rest or during ordinary activity, not brought on by exertion, and associated with transient ST segment elevation.[16] Prinzmetal and co-workers summarized the results from 23 of their own patients and from 12 similar patients previously reported in the literature.[16,25] In each of the three patients coming to autopsy, there was marked narrowing of a large coronary artery supplying the area of the heart responsible for ST segment elevation during pain. The arteries, however, although narrowed, were still patent, and the authors concluded: "Temporary increased tonus of a large narrowed coronary artery is suggested as the cause of attacks of pain in the variant form of angina."[16]

In 1969, Gorlin documented by radioactive tracer techniques a decrease in myocardial blood flow during angina pectoris in patients with severe diffuse disease of the left anterior descending coronary artery. Since the decrease in blood flow occurred despite an increase in heart rate and blood pressure, Gorlin postulated coronary vasoconstriction.[26]

Gianelly and associates in 1968 were the first to report the association of variant angina pectoris with insignificant coronary artery disease.[27] Their patient, a 49-year-old woman with nocturnal chest pain, accompanied by ST segment elevation in the inferior leads, was documented to have only mild atherosclerotic narrowing of the right coronary artery at subsequent autopsy evaluation.

The idea of spasm was reawakened by the reports of Prinzmetal and Gianelly, but it still lacked angiographic proof. Although Mason Sones first performed selective coronary arteriography in 1958,[28] spasm was not demonstrated angiographically until 1972, when Dhurandhar demonstrated spasm of the proximal right coronary artery during a spontaneous episode of chest pain.[29] His patient was a 52-year-old man with a six-week history of nonexertional chest pain associated with ST segment elevation in leads II, III, aVF, V_5, and V_6. Ventricular ectopic activity, including ventricular tachycardia, had occurred during pain. Repeated coronary arteriography after sublingual nitroglycerin and isosorbide dinitrate demonstrated disappearance of the spasm, with only slight residual irregularities of the right coronary artery. In 1973, Oliva and co-workers demonstrated recurrent, reversible spasm to be the cause of ischemic symptoms and of ECG changes of ST segment elevation and complete heart block in a 46-year-old woman with angiographically normal coronary arteries between attacks of spasm.[30] Subsequently, many reports have documented coronary spasm occurring during spontaneous pain or during attacks of pain provoked by such agents as ergonovine maleate.[29-51]

The 14-year hiatus between the development of selective coronary arteriography and the first arteriographic demonstrations of spasm is probably explained by several factors. The patients were often premedicated with sedatives, tranquilizers, and/or atropine prior to catheterization, and those medications might have prevented spasm.[44] Nitroglycerin, an agent now known to reverse or prevent spasm, was often given routinely prior to coronary angiography. If pain occurred during catheterization, nitroglycerin was administered and contrast studies delayed until the patient became painfree. Contrast dye itself is a vasodilator and could have interfered with the recognition of spasm.[44-52] Finally, catheter induced spasm, usually occurring at or near the tip of the catheter, had been recognized.[44-52] Catheter induced spasm, however, was not associated with pain or ECG changes, perhaps causing the potential role for spontaneous spasm to be overlooked.

Clinical Presentation

Since those first angiographic documentations of spasm, there have been multiple reports of patients with variant angina.* In most reports, variant angina has been defined by chest pain of ischemic quality, which is usually unrelated to exertion, occurs at rest, and is associated with ST-T wave changes of ischemia, usually transient ST segment elevation.**

Both men and women may present with variant

*Refs. 30-36,38-40,42-45,48,50,51,53-65
**Refs. 30,37,39-41,43,48,54,56,66

angina.* The large patient series, which include a large percentage of patients with variant angina in association with fixed coronary artery disease, exhibit high prevalence of men.[40,44,54,62] There is a wide range of patient ages. Variant angina in association with coronary artery disease generally is a disease of middle-aged or older individuals, as is the typical exertional angina pectoris of Heberden.[14,62] Some patients, including those with angiographically normal coronary arteries, have a history or electrocardiographic evidence of old myocardial infarction.** Angina pectoris may have been present for days to years.[34,38,40,44,58] The ischemic pain of variant angina is generally typical of classic Heberden's angina in terms of quality, location, and radiation.[16,25,29,34,42,64] In contrast to classical angina, however, it occurs predominantly at rest or during minimal exertion and is frequently nocturnal.† It may be precipitated as well by exertion in some patients, including occasional patients with normal or nearly normal coronary arteries.†† In a series of 138 patients with transient, reversible ST segment elevation by Maseri et al, 80 patients had rest angina alone, and 58 had a combination of rest and exertion related angina.[40] Precipitation of variant angina has also been reported with ingestion of alcohol[67] or iced water,[68] smoking,[69] gag reflex,[65] hyperventilation,[65] and, in munitions workers, withdrawal from chronic exposure to nitrates.[47] Pain is often cyclic in pattern, occurring at the same time each day,[16,25,34,43,66] often in the early morning.[16,32,34] Many patients have more than one attack per day.[40,66]

Selzer and co-workers compared 27 patients with variant angina pectoris and normal or near normal coronary arteries with 20 patients having variant angina pectoris in association with obstructive coronary artery disease.[62] Patients with relatively normal arteries generally had a long history of nonexertional angina, without effort related angina or prior myocardial infarction. In contrast, 75 percent of the patients with coronary artery disease had a history of exertional angina preceding the onset of rest angina. The association of more extensive coronary artery disease with classical exertional angina pectoris, in addition to rest angina, was also noted by Maseri et al.[40]

The electrocardiographic ischemic changes may occur without symptoms.[30,39-41,57,58,65] In two studies, 68 to 89 percent of episodes of ST segment elevation occurred without pain.[40,65] If pain does occur, it generally follows the onset of ECG changes by 30 seconds to several minutes.[31,38-40,61]

Syncope may occur as a result of asystole, bradyarrhythmias, and ventricular tachycardia and fibrillation.[34,56,64,70]

Electrocardiographic Changes

The electrocardiographic hallmark of variant angina is reversible ST segment elevation, with the electrocardiographic changes reverting to baseline between attacks.* The magnitude of ST segment elevation may be marked. The ST segment generally remains elevated for 20 to 380 seconds and is usually followed by deep T wave inversions.[39] ST elevation may occur in virtually any lead facing the left ventricle.[39,40,63] In a given patient, recurrent episodes of pain are generally associated with changes in the same, rather than different, leads, suggesting that a local hypersensitivity of one coronary vessel causes recurrent spasm.[38] Involvement of more than one vessel, however, has been reported in occasional patients.[13,46,70] ST segment depression may also be a manifestation of spasm.** It has been shown that different degrees of spasm in a single patient may be associated with ST segment elevation or ST segment depression.[36,39,40,41] ST segment elevation is generally associated with severe, including occlusive, spasm, probably producing transmural myocardial ischemia.[36] ST segment depression has been associated with lesser degrees of spasm, presumably resulting in subendocardial ischemia.[36] In occasional patients, only T wave changes are seen with some episodes. If the control T waves are inverted, they may pseudonormalize, usually prior to ST segment elevation.[40] The QRS complex is often affected. The R wave may become taller and broader or may even disappear.[16,60]

As mentioned before, continuous electrocar-

*Refs. 34,35,37,40,44,48,57,66
**Refs. 35,37,40,42,44,46,48,57,60,62
†Refs. 16,25,30,32,34,35,41,56,66
††Refs. 33,34,38,39,42,44,56,63

*Refs. 16,27,30,32,34,38,39,40-44,48,54,56,58,59,61,62,64-66
**Refs. 32,36,39,41,42,44,49

diographic monitoring has revealed that many, perhaps a majority, of episodes of ST segment elevation are asymptomatic.[34,39,40,57,58,65] Nevertheless, asymptomatic episodes may be accompanied by the same hemodynamic alterations and arrhythmias seen with symptomatic episodes.[39,58]

Exercise Testing

Results of exercise tests are variable.[16,25,56] They are often negative in terms of precipitation of pain and/or ECG changes.[64,66] Exercising and/or pacing may, however, be associated with pain and ST segment elevation or ST segment depression, either in the leads showing ST segment changes with spontaneous angina or in different leads.* Positive exercise tests with pain and ST segment elevation have even been reported in patients with angiographically normal coronary arteries.[33,34] The changes may be produced by exercise induced spasm or, in the case of patients with underlying atherosclerotic disease, by myocardial oxygen supply-demand inequality.

Hemodynamics

In contrast to classic Heberden's angina, which is precipitated by an increase in myocardial oxygen demands, variant angina appears to be precipitated by a primary decrease in myocardial oxygen supply. No increase in the hemodynamic determinants of myocardial oxygen consumption are noted prior to spontaneous episodes of variant angina.[38-41,57-59,66] Certain hemodynamic changes, however, commonly precede and/or accompany the episode of chest pain or ST segment changes.[34,39,40,57-59] Impairment of left ventricular function is common, as evidenced, for example, by increases in end-diastolic pressure and decreases in systolic pressure, peak rate of pressure development, and ejection fraction. Severe hypotension that is refractory to medical therapy and electromechanical dissociation have been reported in association with spasm.[46] The rate of diastolic relaxation may also decrease and the heart may become less compliant.[59] No qualitative differences in the hemodynamic changes have been noted in symptomatic as opposed to asymptomatic episodes.[58] The magnitude of the changes, however, has been correlated with the magnitude of the ECG abnormalities.[58] As ST segment elevation wanes, systolic arterial pressure often increases considerably and the heart rate may also increase.[38,40,58,66]

Nuclear Imaging

Nuclear imaging with thallium 201 during spontaneous or provoked spasm generally demonstrates a large transmural deficit of tracer uptake in the heart wall corresponding to the angiographic localization of spasm and to the electrocardiographic leads showing ST segment elevation.[33,38,40,41,70] Regional defects are generally seen during episodes of ST segment elevation,[38,40] whereas episodes associated with ST segment depression may be accompanied by a more diffuse decrease in thallium uptake.[40] Large perfusion defects may develop during exercise in patients with variant angina who have normal or only subcritically stenosed coronary arteries.[33]

Angiographic Findings

Spasm may be visualized during a spontaneous episode of chest pain, during pain provoked by exercise, or during an episode of angina pectoris provoked by pharmacologic agents such as ergonovine maleate.[29-51] Angiographically documented spasm may involve normal or near normal coronary arteries or arteries with advanced underlying atherosclerotic disease.* In the latter cases, which appear to make up the majority of patients reported in the literature, the spasm tends to occur in the vicinity of the fixed disease, suggesting that intimal disease may, in some way, change the vasomotor responsiveness of the underlying media.[35,39,42] Relative to the organic stenosis, the spasm

*Refs. 33-35,39,40,42,44,63

*Refs. 30-34, 38-40, 42-46, 48

may extend proximally, distally, or both.[40] Spasm may involve the left main, left anterior descending, circumflex, or right coronary arteries,[37,42,44,46] and there may be involvement of more than one vessel.[33,46] Spasm may also occur in the proximal or distal portion of the major coronary arteries.[34] The coronary artery site of spasm corresponds to the electrocardiographic localization of ST segment changes.[32,33,66] Although highly localized spasm may ocur, a long segment of a vessel is generally involved.[37,39] Spasm may be of variable intensity.[30,36,39,40] Nonocclusive spasm, with delayed filling and runoff may be observed.[40] Commonly, complete occlusion of the vessel, with no distal filling, is noted during spasm.[39,40] ST segment elevation is generally associated with more advanced degrees of spasm than is ST depression.[40] Retrograde visualization of the vessel distal to occlusive spasm is unusual, suggesting infrequent collateralization.[44] This finding contrasts with the greater frequency of collateral vessels in patients with fixed occlusions secondary to significant organic coronary artery disease. Left ventriculograms performed during spasm demonstrate contraction abnormalities and decreases in ejection fraction.[35,39] Marked lactate production may be noted during pain.[44]

Exertion Induced Coronary Artery Spasm

Spasm was first suspected and documented in patients with resting angina pectoris. As previously mentioned, however, patients with the variant form of angina pectoris, including those with normal resting coronary angiograms, may have positive exercise tests in terms of ST segment changes and production of pain.* Waters, Specchia, and their co-workers have demonstrated exercise induced coronary spasm and large zones of hypoperfusion, documented with thallium 201 imaging, in spasm patients with and without significant underlying coronary artery disease.[33,63] The zones of hypoperfusion correspond both to the electrocardiographic site of ST segment elevation and to the site of previously documented spontaneous coronary spasm during catheterization. The occurrence of vasospasm during physical exertion blurs somewhat the distinction between vasospastic variant angina and the classic exertional angina of Heberden. The two different pathophysiologic mechanisms, spasm and myocardial oxygen supply-demand inequality, may each be responsible for production of ischemic symptoms at different times in the same patient.[49] It is obvious that spasm plays a role in the precipitation of ischemic symptoms in some patients with chronic stable angina and fixed coronary artery disease, but the magnitude of its role, both in individual patients and in the coronary artery disease population in general, remains to be determined.

Possible Role of Spasm in Unstable Angina Pectoris

Although it is not proven, spasm may be an important factor in the development of unstable angina. A potential role for spasm is suggested by the following facts. First, a certain percentage of patients with classic symptoms of unstable angina, up to 19 percent in one series, are found to have normal coronary arteries.[71,72] Second, there appears to be no significant difference in the extent of coronary artery disease or in the presence or absence of collaterals in patients with unstable versus stable angina.[73,74] Third, occasional patients with unstable angina have lower double or triple products (heart rate × mean systolic arterial pressure, or heart rate × mean systolic arterial pressure × ejection time) at the onset of angina than they do during pain-free rest,[75] raising the question of a primary decrease in myocardial oxygen supply as a cause for the ischemia.

Role of Spasm in Myocardial Infarction

A role for spasm in certain patients with myocardial infarction appears clear. Myocardial infarctions have been reported in patients with variant angina, including patients with angiographically normal coronary arteries.* In some patients,

*Refs. 33-35,39,40,42,44,63

*Refs. 16,37,40,42-44,72,73

spasm has been documented prior to or following myocardial infarction.[37,42,44] The ECG localization of myocardial infarction has corresponded to the site of ECG changes with prior variant angina and to the site of spasm demonstrated angiographically.[16,37,40,42,44] Perhaps spasm might explain the cases of those patients with transmural myocardial infarction documented by electrocardiographic and enzymatic changes who are subsequently found to have no apparent or subcritical fixed coronary artery disease. In patients with significant underlying coronary artery disease, spasm could precipitate or potentiate myocardial infarction. Based on changes in the angiographic appearance of the coronary arteries following intracoronary injection of nitroglycerin, Oliva and Breckinridge demonstrated spasm superimposed upon atherosclerotic coronary artery disease in 6 of 15 patients angiogrammed within 12 hours of onset of myocardial infarction.[76] In all patients, the spasm occurred at the site of fixed disease. It was not possible to ascertain, however, whether the spasm was responsible for the myocardial infarction or was a consequence of it.

Thrombi have frequently been visualized angiographically during the early stage of acute myocardial infarction.[77] Angiographic studies,[77] pathologic evaluation,[78,79] and studies involving incorporation of fibrinogen I 125^{80} into coronary thrombi, however, suggest that a sudden organic change in caliber of a coronary artery, due to thrombus or to plaque hemorrhage, does not occur in all patients with acute myocardial infarction. This again raises the possibility of a primary decrease in myocardial oxygen supply as a precipitant of infarction.

Arrhythmias Associated with Coronary Vasospasm

Arrhythmias, including those responsible for sudden death, are also important complications of coronary artery spasm. In contrast to classical exertional angina in which significant arrhythmias are rare, arrhythmias are common during variant angina.[16,39,40] They occur in approximately 50 percent of patients.[16,39,48] They are seen during asymptomatic as well as during symptomatic episodes.[40] Ventricular ectopic activity, including ventricular tachycardia and ventricular fibrillation, is frequent* and may be more common in patients with spasm of the left anterior descending coronary artery.[62] Complete heart block, usually in the setting of inferior wall ST segment elevation, is also common,** as is first-degree atrioventricular block and second-degree heart block of the Wenckebach type.[30,44,66] The arrhythmias are more common after resolution of the ST segment elevation, at the time of T wave inversion, suggesting reperfusion arrhythmias.[39] Bradyarrhythmias may require pacemaker therapy.[27,34,37,64] Sudden death has been reported in patients with variant angina and is likely secondary to a bradyarrhythmia or tachyarrhythmia.[16,40]

Diagnosis of Coronary Spasm

The possibility of coronary vasospasm should be suspected in patients presenting with the variant form of angina pectoris—that is, angina occurring predominantly at rest—in association with ST segment changes. While ST segment elevation is more typical of variant angina, ST segment depression may also occur.† Both ST segment depression and ST segment elevation may be observed in the same patient during different episodes of spasm.[32,36,39,40] The diagnosis can be proven only by catheterization-documented coronary spasm occurring spontaneously or secondary to pharmacologic provocation. Spontaneous or induced spasm is generally associated with ECG changes if the vessel is appreciably narrowed. It has been estimated or demonstrated that 1 to 3 percent of patients undergoing catheterization may have spasm at the time of study, including both catheter induced and spontaneous spasm.[44,52,56] The prevalence of catheterization-documented spasm will depend, as does the clinical diagnosis of spasm, on how hard it is searched for. If spasm is considered possible and documentation felt to be necessary, no premedication should be given, vasodilators should not be given

*Refs. 16,27,29,37,39,40,43,46,48,56,61,62,64,66
**Refs. 27,30,40,46,56,62,64,66
†Refs. 16,27,34,36,38,39,41,58,59

prior to dye injection into the coronaries, the coronary arteries should be injected during pain, and nitroglycerin should be given subsequently to look for any improvement in apparent vessel stenosis.[44] Spasm is documented by a localized or segmental decrease in the vessel diameter, which disappears or improves after subsidence of pain and/or ECG changes.* This improvement may occur spontaneously or may follow the administration of nitroglycerin.** Efforts should be made to exclude catheter induced spasm.[52] Nonselective coronary injections may occasionally be necessary.

Since spontaneous pain is a chance occurrence in the catheterization laboratory, provocative agents such as methacholine or ergonovine maleate may be injected intravenously to induce spasm.† Ergonovine causes direct coronary vasoconstriction.[35,37,82] While ergonovine produces a generalized decrease in the caliber of all of the coronary arteries in almost all patients, the precipitation of a localized or a segmental spasm appears highly sensitive and specific for the diagnosis of variant angina.[31,35,37,42,46] A few false positive studies and false negative studies occur.[31,37,42,46,51] In general, provocative agents have been safe, since spasm and the resultant pain and ECG changes usually are rapidly reversed by sublingual or intravenous nitroglycerin.[31,35,37,42,50] Serious complications, especially arrhythmias, may occur, however, and five cases of ergonovine induced coronary vasospasm, refractory to sublingual nitroglycerin and resulting in cardiac arrest with three patient deaths, have been reported.[46] The two survivors were treated acutely with intracoronary nitroglycerin. The possibility of producing severe spasm that necessitates intracoronary injection of a vasodilator should temper enthusiasm for provocative testing as a bedside technique. It should preferentially be performed in the catheterization laboratory.

The role of provocative testing in the evaluation of atypical chest pain, including that suspected to represent spasm, remains to be clarified. One group has suggested that ergonovine testing does not permit greater accuracy in diagnosing the presence or absence of spasm than do clinical data alone, especially the ST segment response to spontaneous pain.[51] The test may be useful in patients with a history compatible with variant angina but in whom episodes of ischemic pain have not been observed.[51,53] In view of the potential adverse effects, which appear to be more common in patients with variant angina,[46,51,53] the decision to perform provocative testing should be carefully considered in each patient. Personnel and equipment for resuscitation should be immediately available.

Treatment of Angina

Rational treatment of angina should be based on an understanding of the mechanism of ischemia in each patient. If angina results from an increase in myocardial oxygen demands, the work of the heart can be decreased by use of nitrates and/or propranolol. A fixed lesion that results in symptoms refractory to medical therapy can be bypassed if the distal vessel is adequate—the basis for treatment of classical Heberden's angina. It stands to reason that variant angina, which results from a different mechanism—that of a primary decrease in myocardial oxygen supply—might require different or additional therapy designed to prevent vasospasm.[83] Sublingual or intravenous nitroglycerin is generally effective in terminating acute attacks of variant angina* and is beneficial in decreasing the frequency of attacks in most patients.[16,30,32,34,35,65] Most likely it acts by its direct vasodilatory effects on the extramural coronary arteries. Results with propranolol have been variable.** Some patients have manifested a worsening of symptoms.[45,48,64,65] Blockade of beta 2 coronary receptors may leave unopposed alpha induced vasoconstriction. Phentolamine may cause reversal of spasm.[32] Variable results have been reported with atropine and phenoxybenzamine.† Vasodilators such as nitroprusside and nylidrin have been effective in isolated cases[16,43,61] and may be synergistic with nitroglycerin in prevention of spasm.[61] The differing responses of patients to

*Refs. 14,30,31,33,34,36-40,42-45,48,63,76
**Refs. 31,33-37,39,42-44,48,63,76
†Refs. 31,36,37,40,42,48,53,63,81

*Refs. 16,30,34-39,42-45,56,59,63,66
**Refs. 43,48,56,57,61,64,65,70,81
†Refs. 32,38,43,56,61,70,81

therapy may be related to differing stimuli for vasoconstriction.[38]

There is a new class of agents that appear very promising in the treatment of variant angina—calcium antagonists, which cause relaxation of smooth muscle cells, including those of the coronary arteries, by inhibiting the slow inward current of calcium.[83] They include nifedipine, verapamil, perhexiline maleate, and diltiazem; all have been reported to favorably influence the frequency of symptoms of variant angina.* Nifedipine has been shown to prevent the induction of spasm by ergonovine in patients with previously inducible variant angina.[50] A patient unresponsive to nitroglycerin or verapamil alone may respond to the combination of both agents.[61] It is possible that differing modes of action of the two agents may allow an additive vasodilatory effect. The results of very long term treatment with calcium antagonists and their effect on the natural course of variant angina are unknown. In a mean 47-week follow-up, however, verapamil was effective in decreasing the number of ischemic episodes in patients with fixed coronary artery disease in whom the clinical and/or angiographic findings were compatible with spasm.[41] Nifedipine, in a nonrandomized, nonblind study of 127 patients with symptomatic episodes of myocardial ischemia associated with electrocardiographic and/or angiographic evidence of coronary spasm, was efficacious over a mean study period of six months in eliminating or markedly reducing the frequency of anginal attacks in the vast majority of patients.[48] Nifedipine also appeared to be as efficacious in patients with underlying coronary artery disease as in those without apparent fixed coronary narrowing. Although not without side effects, the drug appeared to be well tolerated.[48] In contrast, high incidence of adverse effects was noted with long-term perhexiline maleate.[84] In addition to their direct coronary vasodilatory effects, which may increase oxygen supply, the calcium antagonists may also act favorably in patients with classic angina by decreasing metabolic demands. They decrease peripheral arteriolar resistance by causing smooth muscle relaxation, and they decrease myocardial contractility.[35,40,44,69,85]

Some patients have responded favorably to coronary artery bypass grafting. Others, however, have reported a high failure rate, death rate, and myocardial infarction rate following bypass surgery.[44,66] There is a high rate of graft closure, probably related to the presence of competing flow through the native vessel when spasm is not present.[83] Some patients have recurrence of typical angina pectoris pain and ST segment elevation despite patency of the bypass graft, suggesting that spasm may be able to occur more distally in the native vessel or at the site of anastomosis.[29,56]

The natural history of variant angina remains to be defined. Myocardial infarction and sudden death may occur[54,86] and perhaps more commonly in those patients with significant underlying atherosclerotic coronary artery disease.[54] Spontaneous disappearance of variant angina has been reported, and remarkable variations in frequency of episodes over time, with remissions and exacerbations, have been observed.[16,65,70,86] Such variations in clinical course may make it difficult to assess the efficacy of drug therapy in any single patient.

Conclusion

Spasm may be responsible for anginal symptoms in patients with atherosclerotically narrowed coronary arteries as well as in those with anatomically normal or subcritically stenosed vessels. It may produce a picture of stable resting and/or exertional angina and may perhaps be important in the pathogenesis of unstable angina pectoris and acute myocardial infarction. Symptomatic bradyarrhythmias and ventricular tachyarrhythmias and sudden death may complicate spasm. In many patients with atherosclerotically diseased coronary vessels, the mechanisms of both spasm and supply-demand inequality may play important roles in the production of ischemia.

The discovery of coronary vasospasm is one of the most important results of cardiovascular research in this century. It may help to explain phenomena previously not understood, including, for example, the occurrence of myocardial infarction in patients with anatomically normal or only mildly obstructed coronary arteries. In addition, it opens a whole new realm of potential therapeutic interventions in the medical treatment of sympto-

*Refs. 41,43,48,50,55,56,61,70,84

matic coronary disease. Since spasm may be an important cause of ischemia in so many different ischemic heart disease syndromes, a great number of patients may benefit from the development and clinical application of therapeutic agents that cause coronary dilatation either directly or through alterations in neurogenic stimulation of the coronary arteries.

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