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LOUIS F. BISHOP LECTURE

Role of Coronary Artery Spasm in Symptomatic and Silent Myocardial Ischemia

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The revival of the concept of coronary spasm has stimulated research into coronary artery disease. Observations in patients with variant angina have substantially contributed to the appreciation of painless myocardial ischemia. However, the presence or absence of pain during ischemic episodes is not related to the cause of ischemia, because painless ischemia can be observed in variant angina (caused by spasm), in effort-induced angina (caused by increased myocardial demand) and in myocardial infarction (caused by thrombosis).

Continuous monitoring initially of patients with variant angina and subsequently of patients with unstable and stable angina proved that often painful and painless ischemic episodes are caused by a transient impairment of regional coronary blood flow rather than by an excessive increase of myocardial demand. The transient impairment of coronary flow appears to be caused by dynamic stenosis of epicardial coronary arteries. This most often occurs at the site of atherosclerotic plaques encroaching on the lumen to a variable extent.

Dynamic stenosis can be caused by 1) "physiologic" increase of coronary tone, as in stable angina, 2) spasm, as in variant angina, and 3) thrombosis, usually in combination with "physiologic" changes in tone or with spasm, or both, as in unstable angina. The mechanisms of spasm, as typically observed in variant angina, are different from those of "physiologic" increase of tone; they appear to be related to a local alteration that makes a segment of coronary artery hyperreactive to a variety of constrictor stimuli causing only minor degrees of constriction in other coronary arteries. The nature of this abnormality, which may remain stable for months and years, is yet unknown.

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I am greatly honored by the privilege to give the 1986 Bishop Lecture following such a formidable list of distinguished predecessors. I am proud of having been assigned this topic and I will do my best to cover it without bias, separating facts from extrapolations, very much in the spirit of the late Louis Bishop.

About 10 years ago, the word spasm used to elicit a certain smile and I remember being accused now and then of having a leaning toward spasm. Then it became a "proven hypothesis" (1). Now in the 1980s the pendulum is swinging too far in the opposite direction and the term spasm is often used too liberally to describe any form of constriction of epicardial coronary artery. This generalization is not justified and I will try to prove it.

In my opinion the major effect of the revival of the concept of coronary spasm (2) was the stimulus to begin to look at coronary artery disease as a much more varied and dynamic process than the static and rather stale picture we were presented with in medical school. The diagram from my 1983 article in Lancet (3) summarizes fairly well our views on the varied causes and on the possible clinical manifestations of myocardial ischemia (Fig. 1). In the first part of my presentation I shall concentrate on the lower part of the diagram of Figure 1 dealing with the clinical manifestations of acute myocardial ischemia.

Painless Myocardial Ischemia

It appears now fairly well established that acute transient myocardial ischemia can manifest clinically with angina or only with signs of acute left ventricular failure or arrhythmias or remain totally silent.

Documentation of Painless Myocardial Ischemia

Variant angina. The study of variant angina (4) played an important role in our appreciation of painless ischemia. In variant angina silent myocardial ischemia was first described by Guazzi and coworkers (5,6) in Milan in their

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JACC Vol. 9, No. 2
February 1987:249–62

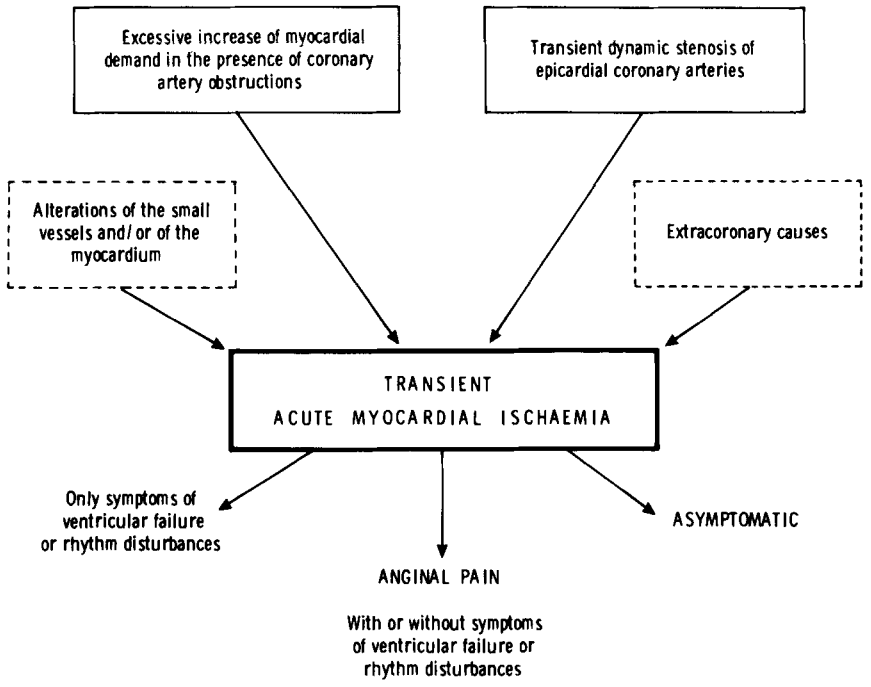
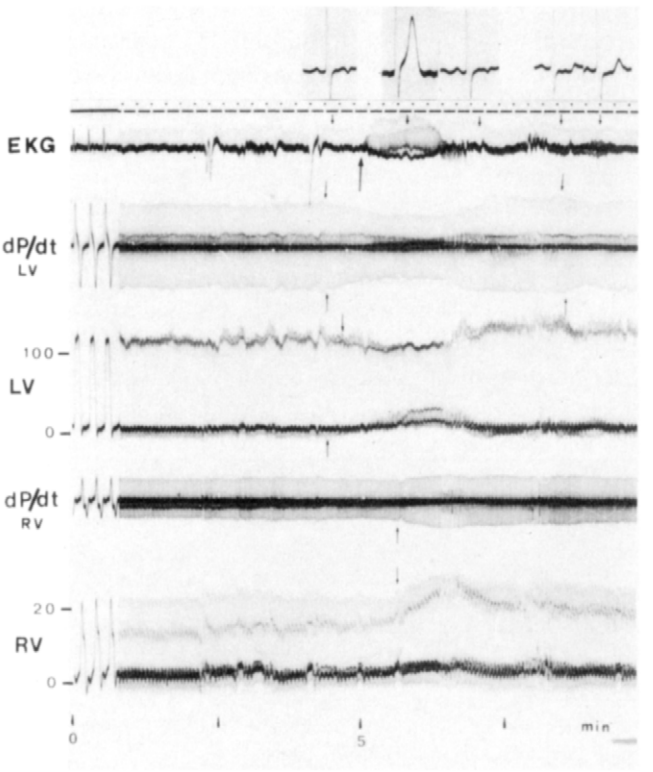


Figure 1. Possible pathogenetic mechanisms and clinical manifestations of myocardial ischemia. Dynamic stenosis is often caused by vasoconstriction or intravascular plugging by blood constituents, or both, and can involve relatively normal as well as severely atherosclerotic segments. These mechanisms cause ischemia by reducing flow or by transiently impairing its appropriate increase. Extracoronary causes are typically represented by severe aortic stenosis. Changes in the small vessels or the myocardium, or both, are typically represented by syndrome X. Pain is the most commonly recognized symptom because it brings the patient to seek medical attention. The mechanisms that produce pain in some ischemic attacks but not in others are unknown. (Reprinted with permission from Maseri A [3].)

articles of 1970 and 1971 in the *British Heart Journal*, which I consider to be milestones. In the early 1970s, during our studies based on hemodynamic monitoring in the coronary care unit, we demonstrated that totally silent ST elevation was associated with severe impairment of left ventricular function. A typical recording taken in 1975 (7) illustrates the sequence of events during two spontaneous ischemic episodes (Fig. 2). It is readily apparent that an obvious impairment of relaxation and constrictor peak left ventricular maximal rate of rise in pressure (dP/dt) and an increase of all diastolic pressures clearly precede the onset of ST segment changes. This sequence is remarkably similar to that observed in dogs after sudden coronary occlusion (8), and now it can be seen reproduced in humans during coronary balloon angioplasty.

In these hemodynamic studies we confirmed and expanded the observations by Guazzi et al. (5,6) that pain usually appears only minutes after the onset of ST elevation. Subsequently, we documented (9) that silent anterior ST elevation lasting 8 minutes was associated with a transient massive anterior wall thallium-201 defect (Fig. 3). During those years we also observed (10,11) that about 70% of more than 7,000 episodes of ST elevation recorded in the coronary care unit were painless and that ventricular tachycardia during these episodes was nearly as common in prolonged episodes of silent ischemia as in painful ischemia with ST elevation. In a double crossover trial (12), our group demonstrated that verapamil reduced the number of painful and painless ischemic episodes by the same amount (that is, by about 80%). In another similar study (13), we showed similar results with intravenous isosorbide dinitrate (Fig. 4).

Figure 2. Low speed playback of a continuous recording in the coronary care unit of lead V_3 of the electrocardiogram (EKG) and left (LV) and right (RV) ventricular pressure tracings during two ischemic episodes not accompanied by pain observed in a patient with variant angina. Reduction in left ventricular contractility (dP/dt) clearly precedes the onset of ST segment elevation. Another episode characterized by ST segment depression and positive T waves can be noted on the right side, also preceded and accompanied by a drop of dP/dt. (Reprinted with permission from Maseri A et al. [7].)



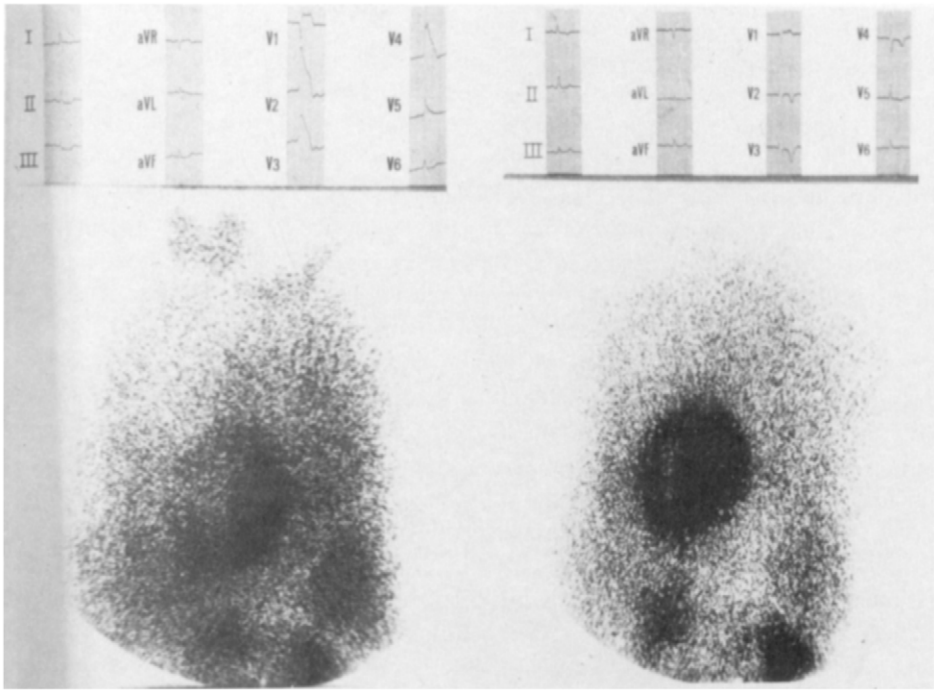
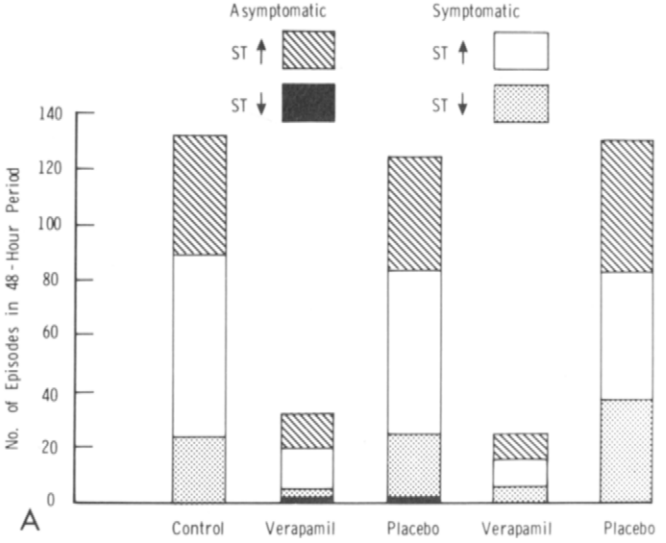
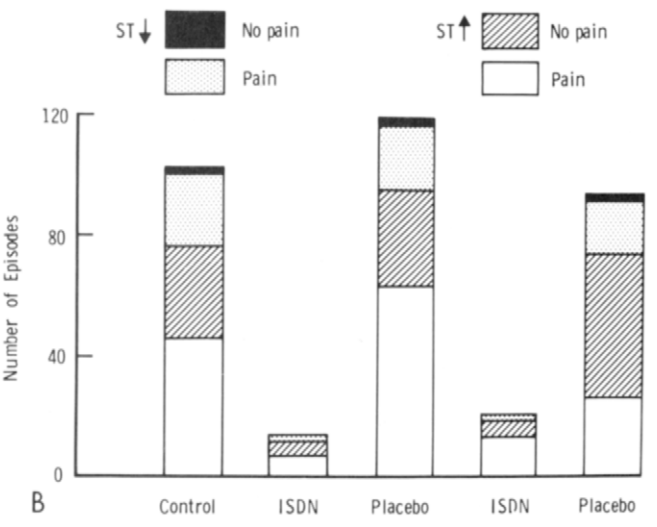


Figure 3. Thallium scintigraphy in the left anterior oblique view during a painless episode of ST segment elevation lasting 8 minutes (**left**) showing a massive anteroseptal defect not visible in the redistribution image (**right**). (Reprinted with permission from Maseri A et al. [9].)

Stable angina. However, silent ischemic ST segment shifts are not a feature solely of variant angina. A high frequency of episodes of asymptomatic ST depression during Holter monitoring in patients with stable angina had been previously reported (14,15). We also made similar observations in patients with chronic stable angina. In a study based on ambulatory electrocardiographic monitoring for several days of 30 patients with chronic stable angina (16), our group observed that of 877 episodes of ST segment depression of 1 to 2 mm, 83% were painless; of 624 episodes of depression of 2 to 3 mm, 71% were painless; and of 381 episodes of depression of 3 mm or more, 63% were painless. In the same study we showed that asymptomatic episodes

Figure 4. A, The total number of episodes in 12 patients with vasospastic angina in each 48 hour period of the trial. C = run-in period; A_1, A_2 = verapamil periods; B_1, B_2 = placebo periods. Control and placebo periods show similar number and type of ischemic episodes, whereas during treatment with verapamil there is a conspicuous reduction in frequency of all types of episodes, both painful and painless. (Reprinted with permission from Parodi O et al. [12].) **B,** Pooled results in 12 patients with vasospastic angina. The reduction in the number of the ischemic episodes during treatment with intravenous isosorbide dinitrate (ISDN) is similar both for episodes with ST elevation (ST ↑) and for those with ST depression (ST ↓), either with or without pain. (Reprinted with permission from Distante A et al. [13].)





JACC Vol. 9, No. 2
February 1987:249–62

of ST depression were associated with severe regional defects of rubidium-82 uptake in positron tomographic scans. Therefore, we decided to investigate the effects of therapy on painless ischemic ST segment depression in stable angina. Thus, we documented (17) that successful bypass surgery abolished both painful and painless episodes during Holter monitoring in 25 patients. In another study (18) which was single blind, double crossover, and placebo-controlled, we found that atenolol reduced painful and painless episodes by 69 and 61%, respectively, in 10 patients during Holter monitoring. The results of these two studies indicate that the effects of successful therapy on painful and painless episodes are similar to those we had previously observed in variant angina, although variant angina was treated with nitrates and calcium antagonists and chronic stable angina with bypass surgery and beta-receptor blockers.

Therefore, on the basis of all these lines of evidence, we became convinced that a totally silent transient ischemic ST segment shift in patients with ischemic heart disease does indicate severe ischemia and we turned our attention to the identification of possible differences between episodes of painful and painless ischemia.

Mechanism of Cardiac Ischemic Pain

Duration and severity of ischemia. In a study performed in patients with variant or rest angina (19), we observed that: 1) episodes shorter than 3 minutes were always painless; 2) episodes associated with an increase of left ventricular diastolic pressure of less than 7 mm Hg were also always painless; and 3) longer and more severe episodes could be either painful or painless. Thus, longer duration and greater severity of ischemia appear to be necessary but not sufficient conditions to explain the presence of pain.

Role of acute ventricular dilation. Finally, we set out to investigate whether a different magnitude or rate of ventricular dilation could account for the presence or absence of pain. In a recent study (20), we continuously monitored left ventricular volume during episodes of spontaneous or ergonovine-induced ischemia with and without pain. We used a single, nonimaging precordial nuclear probe which detects beat by beat changes in left ventricular volume (after labeling of the blood pool by technetium-99m pyrophosphates) as long as the geometry between the probe and the ventricle is constant (21). The results of this study show that the increase of left ventricular end-systolic and end-diastolic volumes is large during ischemic episodes, either spontaneous or induced by ergonovine, and both painful or painless, so that it is impossible to predict the presence or absence of pain from either the magnitude or the rate of ventricular dilation.

Activation of painful stimuli during ischemia. These findings should not be totally surprising if we consider that more than 20% of myocardial infarctions appear to be unaccompanied by symptoms recognizable by the patient or by the observing physician (22). In a recent review of the subject (23) we arrived at the following conclusions: 1) Short episodes may be painless because the stimulus is inadequate or because pain usually appears quite late after the onset of ischemia, or both. 2) However, severe, prolonged ischemia (causing massive thallium perfusion defects, a large increase of left ventricular end-diastolic pressure and volume, or even infarction) should represent an adequate painful stimulus. 3) Hence, central transmission or perception, or both, of potentially painful stimuli is likely to play a major role in determining the presence or absence of cardiac pain, particularly in patients who have both painful and painless episodes of apparently similar severity. (Subsequently, we occasionally observed that in some patients the onset of pain may precede the onset of detectable ST segment changes. The reasons for this difference remain thus far unexplained.)

In a series of studies on experimental myocardial ischemia Malliani and coworkers (24,25) postulated a partially restricted activation of potentially painful stimuli. However, it seems difficult to extrapolate this hypothesis to patients having apparently similar electrocardiographic severity and spatial distribution of ischemia during painful and painless episodes.

An important role of the perception of pain is supported by two recent studies, the first by Droste and Roskamm (26), in patients with totally painless ischemia, and the second from our institution (27) in patients with predominantly painless ischemia (more than 95% painless episodes during Holter monitoring). Both studies indicate that patients with painless ischemia have on average a reduced perception of painful stimuli. However, both studies show overlap in sensitivity and tolerance to painful stimuli between some patients with painful and some with painless ischemia (Fig. 5). Thus, a generalized reduction of the sensitivity to painful stimulation cannot explain all cases of painless myocardial ischemia. Plasma concentrations of met-enkephalin and beta-endorphin levels at rest or during painful stimulation also fail to account for these differences (27).

Spectrum of Patients

Some patients may have only painless ischemic episodes and, therefore, are totally asymptomatic and come to medical attention by chance. They should not be confused with patients who, although having coronary atherosclerotic obstructions, *do not have any episodes of ischemia* either 1) because the obstructions are not critical or are compensated by collateral vessels, or 2) because they have no tendency to develop transient impairment of coronary flow. A minority of patients have only painful ischemic episodes. The large majority of patients have both painless and painful episodes in variable proportion. The proportion of painful and painless episodes can vary greatly even in the same

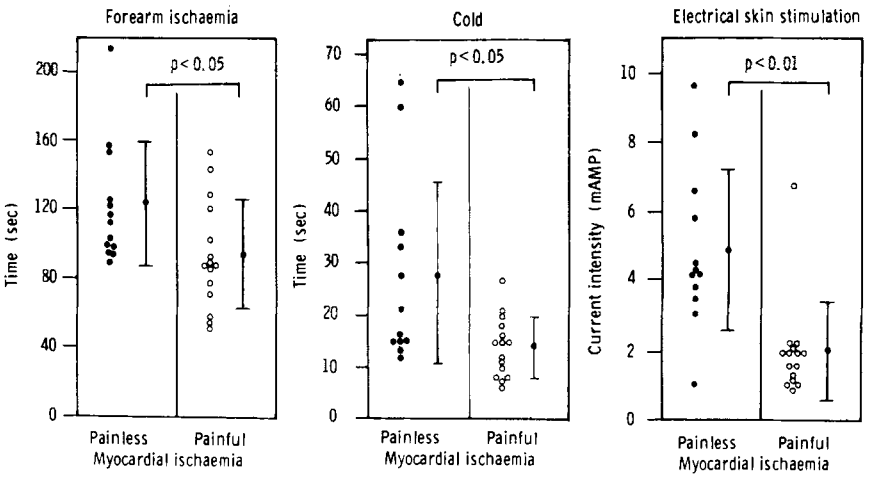


Figure 5. Values of threshold time to pain induced by forearm ischemia during tourniquet test (**left**) and cold pressor test (**middle**) and by electrical skin stimulation (**right**) in patients with predominantly painless myocardial ischemia and in patients with painful ischemia during exercise stress testing and Holter monitoring. (Reprinted with permission from Glazier JJ et al. [27].)

patient, depending not only on the duration of the episodes but also on a variable transmission or perception of painful stimuli. Usually, but not always, the patients with frequent painful ischemic episodes also have frequent painless episodes; conversely, those with rare painful episodes also have rare painless episodes. The prevalence of individuals with silent ischemic-like ST segment changes in the population appears to be low when the criteria for positivity are strict (15).

Practical Questions

Two important questions remain to be answered:

1. *Does the pathogenetic mechanism of ischemia contribute in any way to determining the presence or absence of pain?* There is no evidence whatsoever to suggest that the mechanisms of ischemia can influence the presence or absence of pain. Painless ischemia can be caused by thrombosis as in acute myocardial infarction, by spasm as in variant angina and by excessive increase of demand as in chronic stable angina.

2. *What is the prognostic significance of painless ischemia?* It appears reasonable to assume that, for a comparable severity and duration of ischemia, the prognostic significance of painless episodes should be similar to that of painful episodes because it is actually ischemia that causes both necrosis and arrhythmias. The available information seems to support this assumption (22,28–30). Hence, prognosis depends on the causes of ischemia and on the general setting in which it occurs. The presence of pain has potentially useful and potentially dangerous effects: 1) On the one hand, pain alerts patients to stop activities and to seek medical attention; on the other, it causes anxiety, increases sympathetic tone and heart work and may favor the onset of arrhythmias. 2) Conversely, in the absence of pain, patients are not alerted to stop activities and to seek medical attention.

Therefore, if I am asked today how I deal with silent ischemia in my clinical practice, I would say that I do not consider it reasonable to go out looking for it, except in individuals suspected to be at very high risk of coronary artery disease. However, when I come across it by chance, I am inclined to manage patients with unequivocally documented silent ischemia in the same way as those with painful ischemia.

Varied Causes of Acute Myocardial Ischemia

In addition to epicardial coronary artery involvement, transient acute myocardial ischemia can be brought about by a variety of other causes: extracoronary causes (such as aortic stenosis) and small coronary vessel disease. I believe that the latter disease does exist; it seems to be benign, but we do not know enough about it. The extent of our knowledge about small vessel coronary disease is concisely summarized by the term proposed by some authors: syndrome X (31,32). Therefore I will concentrate on the two causes of ischemia that by far appear to be the most frequent and of greatest prognostic importance: excessive increase of myocardial demand in the presence of fixed stenosis, or sudden impairment of coronary blood flow caused by *transient* impairment of flow through epicardial coronary arteries.

Passive Changes in Caliber of Epicardial Coronary Arteries

Passive changes in caliber of epicardial coronary arteries can occur (33) and have been demonstrated in elegant experiments in animals (34–36). However, in these studies the production of the critical stenosis by a ligature magnifies passive changes, as shown by a study in our laboratory (37) (Fig. 6). From a pathogenetic point of view the role of passive changes should be important only when they are secondary to changes in prestenotic distending pressure (aortic). In fact, reduction in poststenotic pressure (resulting

JACC Vol. 9, No. 2
February 1987:249–62

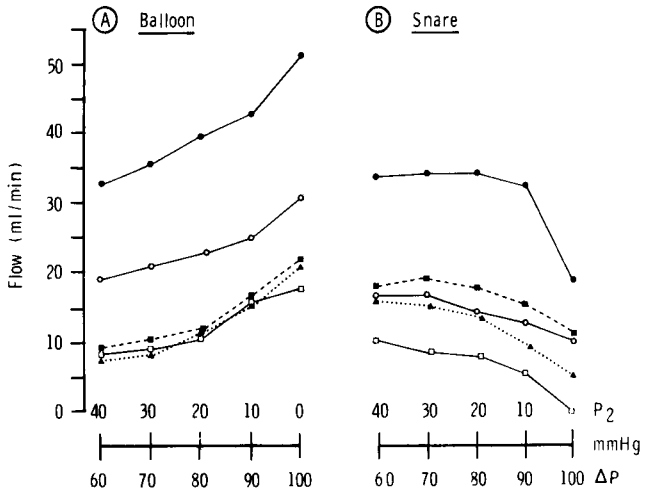


Figure 6. Influence of type of stenosis on coronary flow in response to decreasing outflow pressure in five dog carotid arteries. **A,** Intravascular balloon stenosis: when outflow pressure (P_2) is lowered and thereby pressure difference across the stenosis (ΔP) is increased, flow increases as well. **B,** Circumferential snare stenosis: when P_2 is lowered, flow decreases. A marked decrease occurs only when P_2 is lower than 30 mm Hg. Each line of symbols in **A** and **B** represents the same vessel with internal stenosis in **A** and external stenosis in **B**. (Reprinted with permission from von Arnim T et al. [37].)

from arteriolar vasodilation) should not affect flow because compliant stenoses should act as Starling resistors (38). Conversely, a reduction in aortic pressure can also cause ischemia independently from passive reduction in the coronary lumen *when coronary flow reserve is minimal,* so that coronary flow depends on perfusion pressure. I will limit my discussion to the causes of active dynamic stenoses of epicardial coronary arteries which, together with increased myocardial oxygen demand, often coexist in variable combination or concur to cause ischemia in the same patient.

Varied Causes of Active Dynamic Stenosis

The possible causes of active dynamic stenosis are the following: 1) "Physiologic" response of coronary smooth muscle to constrictor stimuli in the presence of a subintimal plaque in a pliable segment of artery; 2) hyperresponse to ordinary constrictor stimuli or abnormal stimuli resulting in total or subtotal occlusion of a segment of coronary artery; 3) intravascular plugging by platelets and thrombus; 4) combination of causes 3 + 1 *or* 3 + 2 *or* 2 + 3.

Intravascular plugging by platelet aggregates and thrombosis probably plays a major role in severe unstable angina resistant to medical therapy (39–41), most likely in combination with increased vasomotor tone or with spasm. Spasm is typically recognized in variant angina (4), which is a rare syndrome. A "physiologic" increase of coronary smooth muscle tone is likely to play the major role in determining the variability of exercise tolerance and episodes of spontaneous ischemia in patients with chronic stable angina.

"Physiologic" Coronary Vasoconstriction

Control of normal coronary tone. A number of features distinguish spasm from "physiologic." ("Physiologic" coronary constriction is in quotes to allow contemplation of the possibility that vasomotor changes of this magnitude could be caused by pathologic mechanisms.) coronary constriction. "Physiologic" coronary constriction represents a normal response, because vasoconstrictor stimuli produce a rather predictable and uniform but small reduction of caliber in all epicardial coronary arteries. The magnitude of the constriction depends on vascular basal tone, reactivity and compliance. The mechanisms that control normal coronary tone are poorly understood. Complex neuromodulation by corelease of transmitters (42) appears to be integrated with endothelial control (43). Neuropeptides are probably also involved in this regulatory process. A recent study by our group (44) showed that a calcitonin gene-related peptide, naturally present in cardiac nerves, is a very powerful dilator of epicardial human coronary arteries in vivo. The effect of "physiologic" smooth muscle constriction, which usually reduces the normal diameter by 10 to 20%, may be magnified by the presence of a subintimal plaque when the arterial wall is pliable (45).

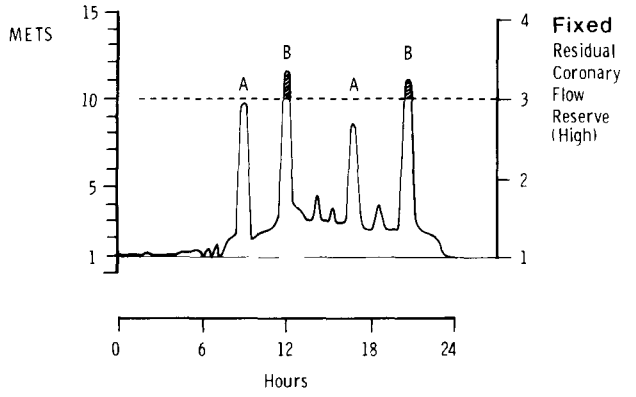
Physiologic constriction versus spasm. A major distinctive feature between physiologic coronary constriction and spasm is demonstrated by a classic study (46) on unselected patients with chronic stable angina. During handgrip the caliber of both normal and stenotic segments is reduced on average by about 10% and transtenotic resistance increased by about 40%. Conversely, after nitroglycerin both normal and stenotic segments dilate about 20% and transtenotic resistance decreases by about 20%. Thus, on the average, transtenotic resistance appears to vary by as much as 60%; obviously in some patients it may vary more, in others less. This behavior, observed in a group of unselected patients, is indicative of a common type of response, hence "physiologic," quite at variance with the rarity of coronary artery spasm at least of the kind seen in variant angina. Subsequent studies (47) indicate that eccentric but not concentric lesions can vary their caliber because they are more pliable. Postmortem studies (48) indicate that about 75% of stenoses are eccentric and pliable.

Heart rate and blood pressure during ischemic episodes. Changes of transtenotic resistance of the magnitude calculated by Brown et al. (46) can well account for important variations of the ischemic threshold. They may well explain the observations made during ambulatory monitoring in patients with chronic stable angina. A number of other studies (14–16,49) indicate that most ischemic episodes recorded during ordinary daily life are not preceded

by an increase of heart rate. Chierchia et al. (50) confirmed these findings by beat by beat computer analysis of Holter ambulatory electrocardiographic tapes showing that on other occasions large increases in heart rate were not associated with ST depression. Moreover, our computer analysis of tapes obtained at Northwick Park Hospital by Chierchia et al. (51) during ambulatory monitoring of blood pressure, indicated that the majority of ischemic episodes were not preceded by an increase in heart rate-blood pressure product greater than those tolerated at other times of the day without any signs of ischemia. How can these findings be explained?

Role of fixed coronary flow reserve. It is apparent that these observations are rather difficult to reconcile with the traditional view that the impairment of coronary flow reserve caused by coronary occlusion is fixed (the result of the balance between severity of a critical stenosis and development of collateral vessels). This traditional concept is illustrated in the scheme presented in Figure 7: residual coronary flow reserve is reduced moderately so that myocardial perfusion can increase, for example, up to three times the level at rest but no more. This fixed impairment of coronary flow allows the patient to increase his total body oxygen consumption about 10 times (10 multiples of basal metabolic oxygen consumption [METs]) without developing ischemia, but ischemia will develop for efforts greater than 10 METs. Obviously this scheme is an approximation because a variable cardiac adaptation to exercise may allow the patient to perform slightly more or slightly less than 10 METs without developing ischemia (up to about 12 or down to only 8) for the same degree of limitation of coronary flow reserve. In any case, a fixed reduction of coronary flow reserve can explain only rather moderate variations of the ischemic threshold (± 1 or 2 METs).

Figure 7. Fixed coronary flow reserve. Schematic illustration of the relation between physical activity (during the 24 hours) expressed in multiples of basal metabolic oxygen consumption (METs) and increase in coronary flow reserve. When myocardial metabolic demand increases, coronary flow can normally increase at least up to four to six times the value at rest to match the increased demand of flow by the myocardium so that no ischemia occurs. The presence of fixed coronary artery obstructions, not adequately compensated by collateral vessels, may reduce coronary flow reserve. In this schematic diagram it is reduced to three times the values at rest. The patient can exercise up to about 10 METs (**dashed line**) without having ischemia (A); however, if he exercises above about 10 METs he will consistently develop ischemia (B). (Modified with permission from Maseri A et al. [52].)



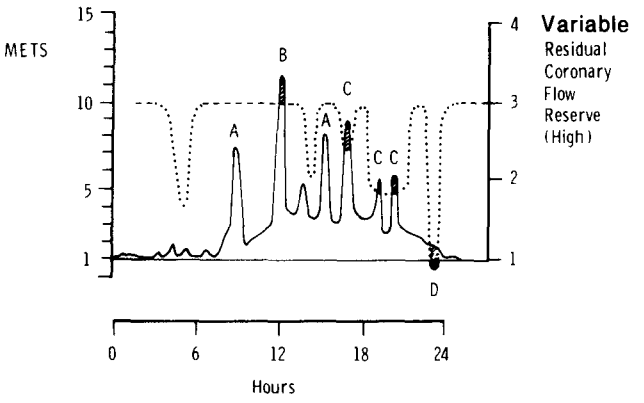


Figure 8. Variable coronary flow reserve. Residual coronary flow reserve may have an upper limit that is indeed fixed, but can decrease transiently because of the presence of mechanisms that transiently interfere with coronary blood flow. Thus, the residual coronary flow reserve can vary throughout the day. Under these conditions, if the patient exercises beyond the maximal residual coronary flow reserve he will always develop ischemia (B). However, he may also develop ischemia on other occasions after smaller degrees of exercise, when residual coronary flow reserve is reduced by these functional factors (C). Occasionally, coronary flow reserve can decrease so that rest flow is impaired and ischemia occurs at rest (D). At other times of the day, this patient can exercise below the level of his maximal residual coronary flow reserve without experiencing ischemia (A). (Modified with permission from Maseri A et al. [52].)

Variability of residual coronary flow reserve in stable angina. The very wide variability of the ischemic threshold often observed during ambulatory monitoring in many patients with chronic stable angina appears more compatible with the modification of the traditional scheme of fixed residual coronary flow reserve illustrated in Figure 8. In this scheme residual coronary flow reserve is reduced to three times the level at rest but it is not fixed during the 24 hours as it is modulated by changes in resistance at the site of the flow-limiting stenoses. Thus, occasionally flow may be dramatically reduced to produce ischemia at rest, or coronary flow reserve may be only moderately reduced so that ischemia develops only in coincidence with moderate efforts, well tolerated on other occasions. Also, in this diagram efforts greater than about 10 METs are never tolerated but lesser efforts may or may not cause ischemia depending on the simultaneous behavior of coronary flow reserve. This is a schematic representation of a kind of mixed angina (52) in which ischemia can be caused both by transient changes in transtenotic resistance and by increased demand or by

their combination. Changes in coronary vasomotor tone at the site of pliable stenoses are thought to contribute to the variability of ischemic threshold in patients with chronic stable angina (53–55). The causes of mixed angina in patients in unstable condition are more complex (56).

Changes in vasomotor tone versus spasm. We were able to document a number of features that suggest that the changes of vasomotor tone responsible for this wide variability of residual coronary flow reserve in chronic stable angina are different from spasm, at least in the form that is most commonly seen in variant angina. Crea et al. (57) showed that patients with chronic stable angina may have a positive ergonovine test but never with ST elevation or coronary occlusion. They also showed (58) that these patients often have a positive cold pressor test but never a positive hyperventilation test; Chierchia et al. (59) showed that such patients have predominantly diurnal ischemic episodes as opposed to patients with variant angina. More recent studies (60,61) in patients with total occlusion of a major branch as the only detectable coronary lesion suggest that change of resistance at the site of small vessels may influence the ischemic threshold during effort. This possibility is supported by results obtained in dogs (62).

Coronary Artery Spasm

Besides these observations and the rarity of variant angina, a final conclusive indication that spasm, as typically seen in variant angina, is totally different from the "physiologic" changes in coronary vasomotor tone seen in normal subjects and in those with chronic stable angina is provided by the results of a series of studies on the pathogenetic mechanisms of spasm that we have performed during the last few years in patients with variant angina. In our review (63), spasm was defined as: "Inappropriate active constriction of a segment of coronary artery resulting in total or subtotal occlusion in response to stimuli which cause only minimal constriction in individuals who do not have the symptoms of variant angina." It is best recognized in "variant" angina, but it is possible that some other forms of spasm may play a role in other ischemic coronary syndromes.

Transitional forms of coronary spasm. In our initial studies we were impressed by transitional forms, between typical variant angina with ST elevation and spontaneous angina with ST depression. We have shown (64) that in variant angina spasm can involve apparently normal vessels or severely stenotic arteries resulting in ST elevation or depression with a similar location and morphology whether occurring spontaneously or induced by ergonovine. In subsequent studies (65,66) based on monitoring of left ventricular pressure and of coronary sinus oxygen saturation by a fiberoptic catheter in the coronary care unit, we observed that a reduction of oxygen saturation in the coronary sinus (Fig. 9) was the first detectable change not only in patients with variant angina but also in those with rest angina. We also observed in a series of thallium-201 studies (67,68) that most cases of rest angina with ST depression were associated with a regional decrease of thallium uptake suggesting that they were caused by a reduced coronary perfusion rather than by increased demand. We observed a wide variety of clinical presentations with transition forms between the most typical features of variant angina and those of rest angina. Finally, we (69) documented possible progression to infarction in the region supplied by the artery undergoing spasm, as subsequently found also by others (70–72). Therefore, in a report (11) based on the observation of 138 patients, we proposed that variant angina was an aspect of a continuous spectrum of vasospastic myocardial ischemia. Similar conclusions were reached by other groups in large series of patients (73,74).

Possible mechanisms of spasm in variant angina. Although we have noted and emphasized both the variable clinical and angiographic features of coronary spasm in variant angina and in transitional forms and the sudden reduction of coronary blood supply as the most frequent cause of spontaneous myocardial ischemia at rest, we chose to

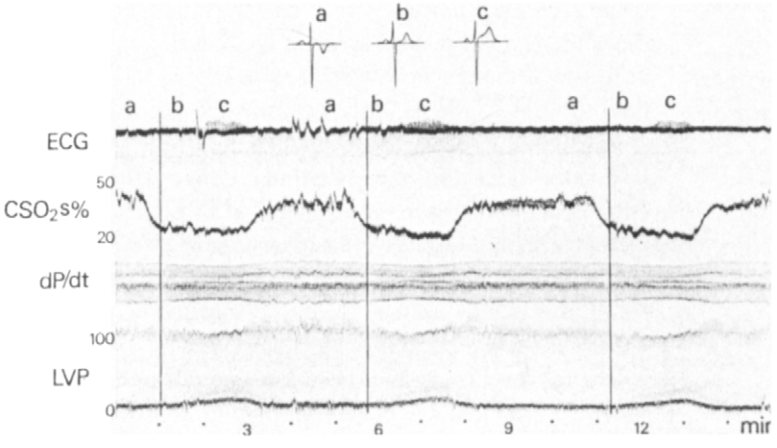


Figure 9. Low speed playback (paper speed 0.3 mm/s) of electrocardiogram (ECG), coronary sinus O_2 saturation (CSO_2s), left ventricular pressure (LVP) and maximal rate of rise in pressure (dP/dt) during three successive asymptomatic episodes recorded in a patient over a period of about 15 minutes. At the **top** are electrocardiographic patterns (lead V_2) in rest conditions (a), at the onset (b) and at the peak (c) of the ischemic episode. **Vertical lines** correspond to the onset of the ST-T changes. A sharp drop of CSO_2s consistently precedes the onset of the electrocardiographic and hemodynamic changes. The same pattern continued uninterrupted for a total of 26 episodes, after which all the variables remained stable without any intervention until the next episode which occurred about 1 hour later. (Modified with permission from Chierchia S, et al. [65].)

investigate the mechanisms of spasm only in patients with the most typical clinical form of variant angina.

About 10 years ago we proposed (9) the following working hypothesis on the pathogenetic mechanisms of spasm in variant angina: "The usual recurrence of ST segment changes in the same leads and of spasm in the same artery suggest the presence of two causes: 1) A local factor that makes the vessel hypersensitive to constrictor stimuli to a variable extent in different phases of the disease. 2) A series of triggering mechanisms that cause spasm and may be different in different patients and even in the same patient at different times."

Aware of the difficulty to identify the local alteration we initially tried to assess the role of triggering factors by attempting to prevent the development of spasm by a number of specific drugs, but we had a series of negative results. We were unable to document any beneficial effect of low dose aspirin (75), prostacyclin (76) or phentolamine (77) and we could not prevent the spasm with ketanserin, a serotonin inhibitor (78). These negative results results are consistent with other findings (79–81).

Although the reasons for negative results can be multiple, this series of negative results is also compatible with a dominant role of a nonspecific local hypersensitivity to a variety of constrictor stimuli. Indeed some reports (82–84) indicate that a variety of constrictor agents can induce spasm in patients with variant angina.

Spasm as a localized abnormality. A recently completed systematic study in our institution (85) appears to support this possibility rather strongly. Of 40 patients with active typical variant angina studied during the last 5 years, 28 were submitted to a series of provocative tests within 3 weeks while in an active phase of the disease. In all, spontaneous or induced spasm was demonstrated at angiography. The provocative tests included: ergonovine, hyperventilation, exercise testing, cold pressor, handgrip, histamine (15 patients), and vasopressin (Pitressin) (8 patients). All tests were performed in the noninvasive laboratory during continuous 12 lead electrocardiographic recording. Several patients had a positive response to more than one type of constrictor stimulus known to act on different receptors. Ergonovine administered in doses of 25, 50, 100, 200 and 300 μg at 5 minute intervals, was, by far, the most powerful spasmogenic stimulus, producing a positive response in 27 of the 28 patients. Other tests with perhaps the exception of hyperventilation and histamine, more often produced a positive response when the response to ergonovine was positive at a low dose (Table 1). (Recently Crea et al. [88] showed that in patients with variant angina spasm can also be produced by intravenous dopamine.)

Because ergonovine was by far the most powerful spasmogenic stimulus in vivo, contrary to findings in isolated human coronary arteries (86), we thought it legitimate to investigate whether this drug acted directly on the coronary arteries or indirectly by triggering coronary constrictor stimuli originating in other parts of the body. Hackett et al. (87) in our institution resolved this doubt by showing that the intracoronary injection of ergonovine caused spasm in all six patients with variant angina tested and in none of the nine control patients. The dose at which intracoronary ergonovine was effective (20.7 μg on the average) corresponded to about 10% of the effective intravenous dose. The time lag between the intracoronary injection and spasm was 60 to 180 seconds.

Computerized analysis of the high resolution angiograms by an automatic edge detection program allowed us to construct dose-response curves. The preliminary results of this analysis indicate that only spastic segments hyperreact to ergonovine (89,90) but not the proximal segments of the same branches or the other branches, which behave like the

Table 1. Results of a Series of Provocative Tests in 28 Patients With Active Variant Angina

	Ergonovine iv Dose (μg)		
	100	200	300
Patients with a positive response to ergonovine	18	6	3
Patients with a positive response to the other provocative tests			
Hyperventilation	8 of 18	2 of 6	2 of 3
Histamine	4 of 9	1 of 2	2 of 3
Exercise	4 of 18	4 of 6	—
Cold pressor	3 of 18	—	—
Handgrip	2 of 18	—	—
Vasopressin (Pitressin)	1 of 5	1 of 3	—

Data are taken with permission from Kaski JC et al. (85); those for Pitressin are unpublished. Eighteen patients had a positive response at an ergonovine dose of 100 μg, 6 at a dose of 200 μg and 3 at a dose of 300 μg. Below each column is indicated the number of patients with a positive response to the other provocative tests. One of the 28 patients had a negative response to ergonovine and to all other tests. iv = intravenous.

JACC Vol. 9, No. 2
February 1987:249–62

arteries of control patients and show only 10 to 20% reduction of diameter (a physiologic response) similar to that observed in control subjects after intravenous injection of ergonovine. The effective dose that causes 50% of the maximum constriction (ED_{50}) of the spastic segment and of the other branches was not significantly different. Thus, total occlusion of a coronary artery segment appears to result from a local hyperresponse to the same dose of ergonovine that causes only physiologic constriction in other branches or in other patients. This behavior is quite different from that in hypercholesterolemic animal models in which the dose response to constrictor agents is markedly shifted to the left (91).

Therefore, in this interesting human model of disease that is variant angina in its most typical form: 1) Spasm can be caused by a variety of constrictor stimuli acting on different receptors. This is compatible with a local alteration of a segment of the arterial wall that makes it hyperreactive to a variety of constrictor stimuli. 2) The documented persistence of spasm (in the absence of therapy) for 6 to 48 months in 10 of the 28 patients suggests that the local segmental alteration is often chronic and stable.

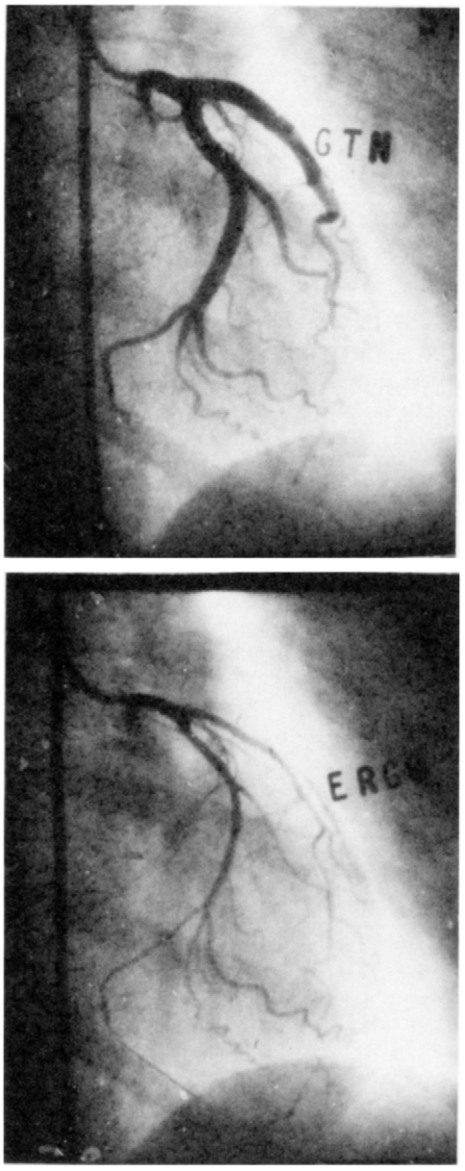
Nature of the local alteration in spastic segments. The alteration responsible for the local arterial hyperreactivity to constrictor stimuli must be quite uncommon because the syndrome is rare. In our studies we could not detect differences in reactivity when the spasm occurred at the site of an obstructive plaque or in an angiographically normal artery. Therefore the presence of a subintimal plaque encroaching critically on the lumen (4) is clearly not a necessary element for the occurrence of spasm in variant angina, as already suggested by Freedman et al. (92). Indeed, although the geometric effect of a plaque can modulate transstenotic flow resistance during generalized "physiologic" changes of coronary smooth muscle tone (44), it does not lead to coronary occlusion during intravenous ergonovine challenge in patients with stable angina (93) even when stenoses are multiple and very severe (45).

Having established that in typical variant angina coronary occlusion is not the result of a diffuse coronary constriction that only occludes the segment site of a critical plaque (4,44), the *local* chronic abnormality responsible for the hyperreactivity may be in the smooth muscle, in the cellular components of the adventitia, in the intima or in the perivascular neural plexus.

Postmortem studies of segments of a coronary artery site of spasm are few. One report (94) describes a fibromuscular dysplasia that might be primary or secondary, but the majority of reports fail to reveal special features of the wall which in some studies (95–98), had a variable degree of atheromatosis and in others was histologically normal (99,100). However, it is difficult to draw firm conclusions from postmortem studies not performed with the specific aim of identifying the possible presence of unknown local alterations. An increase in periarterial mast cells was reported in a patient with variant angina (101); however, the significance of this finding is difficult to assess because mast cells are present in variable amounts in coronary arteries of patients dying from ischemic heart disease (102).

The recent surge of interest in the role of endothelium in controlling vascular smooth muscle tone (103) raises the possibility that a local endothelial alteration may be re-

Figure 10. Left coronary angiogram in a patient with a history of atypical chest pain (no radiation, duration 20 to 40 minutes, either spontaneous or brought on by emotion or effort) not reproduced by exercise stress test or ergonovine test (ERGO), which also failed to produce ischemic electrocardiographic changes. The change in arterial diameter between the ergonovine and postnitroglycerin (GTN) angiograms is generalized and in several segments exceeds 100% (which implies a 400% change in lumen). It is conceivable that a similar constriction could produce ischemia during increased myocardial demand.



sponsible for the hyperactivity of coronary artery segments. However, this possibility must be considered rather cautiously. The role of the endothelium-derived relaxing factor in coronary arteries in humans appears different from that observed in animals (104,105). Indeed, in human coronary artery rings with intact endothelium, acetylcholine consistently causes constriction (86). Also, in patients acetylcholine has a constrictor effect in most coronary segments (106,107). Hence, this type of reaction is obviously far too common to be considered among the causes of spasm in variant angina, although it could be a mechanism of "physiologic" changes of vasomotor tone. Ulceration of plaques and a particular phase of plaque development (108) also appear unlikely causes of the local susceptibility to spasm because they seem to be too frequent and the hyperreactivity can persist unchanged for months and years.

Finally, the observation of spasm in transplanted hearts (109) suggests that spasm may occur independently from the control of the central autonomic nervous system. However, alterations of the local periarterial nervous plexus cannot be ruled out because the occasional cyclic pattern of spasm recurring at regular intervals of a few minutes, already observed by Prinzmetal et al. (4) and of which we have presented examples (65,69) (Fig. 9), suggests a possible alteration of the local feedback mechanism that controls local smooth muscle tone.

Intriguing questions. 1) Occasionally in patients with or without a typical history of variant angina an intense diffuse constriction of all coronary branches can be seen during the ergonovine test and even spontaneously (64,110). This may be associated with ST elevation or ST depression with chest pain or without electrocardiographic changes or even without any apparent sign or symptom of ischemia (Fig. 10). Is the mechanism responsible for these nonsegmental forms of spasm different?

2) Spasm has been postulated in allergic reactions (111,112); is it possible that stimuli exist that are so powerful as to cause total coronary occlusion in the absence of local hyperreactivity to constrictor stimuli?

3) Spasm has been reported after chronic nitrate exposure (113); was it induced by the exposure or was it evidenced during withdrawal in patients who happened to have vasospasm? Spasm refractory to nitrates has been reported (114,115); is it possible that under some circumstances spastic segments or some forms of spasm may not be responsive to nitrates or other vasodilator drugs, as is the case of catheter-induced spasm in brachial arteries and veins? If this is the case, is this lack of response caused by the persistence of the stimulus or by some particular form of contraction such as the formation of "latch" bridges (116)? Two studies (117,118) documented the persistence of spasm at postmortem in four patients with variant angina who died during an attack; can these findings be explained by some form of rigor of smooth muscle (119)?

General Implications

Quiescent phase of coronary artery disease. The revival of the concept of coronary spasm has stimulated research and thought that is expanding our understanding of coronary disease. As a first approximation we can assume that in the absence of mechanisms causing transient impairment of regional coronary flow, even in the presence of atherosclerotic obstructions, coronary disease is in a quiescent phase (120). When coronary disease is in a quiescent phase, the only possible cause of ischemia is an excessive increase of myocardial demand beyond the ischemic threshold set by the balance between obstructions and collaterals.

Active phase of coronary artery disease. Dynamic coronary stenoses are responsible for active phases of coronary disease in which ischemia also occurs independently of excessive increase of myocardial demand. During active phases the disease may be stable, with the picture of chronic stable angina and variable effort tolerance, or may be unstable with organic stenoses progressing rapidly or suddenly because of thrombotic deposition (39).

Local coronary artery hypersensitivity early in coronary thrombosis. The concept of a local vascular abnormality that can cause coronary segments to become occluded in response to constrictor stimuli that produce only a modest constriction in other branches might be extrapolated. If we reexamine now the varied causes of active dynamic stenoses we could entertain the possibility that mural or intraintimal white thrombus formation may be associated with only moderate constriction or with occlusive spasm depending on the local reactivity of the smooth muscle. If this hypothesis is valid, then a local hyperreactivity of the coronary smooth muscle might play a role in some cases in the very early phase of coronary artery occlusion; subsequently, when the arterial segment is totally occluded a red thrombus is likely to form, especially in diseased arteries, and can maintain a total occlusion even when a spasm is relieved. The 20% incidence of positive ergonovine tests in patients with recent infarction observed by Bertrand et al. (121) would lend support to the hypothesis that a local coronary artery hyperreactivity is frequent in acute myocardial infarction.

The rarity of acute persistent coronary occlusion in the life of patients with even severe coronary atherosclerosis compared with the frequent finding of plaque fissures in patients dying of noncardiac causes and with the frequency of transient spasm in variant angina suggests either a rare mechanism or the simultaneous occurrence at the same site of more than one pathologic event (122). A combination of local alterations (plaque fissure, increased susceptibility to constrictor stimuli or vice versa) together with displacement of the local thrombotic/thrombolytic equilibrium toward thrombosis may be required to initiate occlusion and clot formation unless large plaques become ulcerated or unless irreversible spasm occurs for mechanisms yet unknown (123).

JACC Vol. 9, No. 2
February 1987:249–62

Conclusions

In my presentation I have shown how occasional observations may prompt systematic studies and how the results of studies can modify our thinking and suggest new hypotheses that in turn have to be tested. At this stage the hypotheses clearly extend beyond the supporting evidence provided by available data. However, because we see nature in the light of the questions we ask, we ought to be curious and keep asking questions with an inquisitive mind. Some may be the right questions.

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