Coronary Artery Spasm and Vasoconstriction
The Case for a Distinction

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It is now generally accepted that an episodic increase of the vasomotor tone of epicardial coronary arteries not only is the cause of variant angina but also may represent a pathogenetic component in other, more common, anginal syndromes.1,2 The terms “spasm” and “coronary constriction” are often used interchangeably when referring to increases in coronary vasomotor tone. This generalization may find some justification in the common clinical indication for coronary vasodilator therapy that nonspecifically reduces smooth muscle tone but is confusing when trying to identify the actual causes of vasoconstriction and to develop specific forms of treatment against it.

The degree of coronary constriction can vary. At one end of the spectrum of coronary constriction is the mild, physiological response to common constrictor stimuli normally observed in experimental animals and humans; at the other extreme is the severe, segmental constriction leading to total artery occlusion as typically observed in patients with variant angina. In between these two extremes are other forms of coronary constriction that do not cause total occlusion, which are observed in some patients with ischemic syndromes and in experimental conditions but cannot be considered physiological.

To set the stage for a better understanding and classification of these conditions, it may be useful to clearly differentiate at least the extreme forms of constriction that can result in segmental vessel occlusion. We suggest some basic criteria for distinguishing the mechanisms of coronary constriction according to the intensity of the stimuli and the response of the vessel wall.

Changing Concepts

The concept of coronary artery spasm proposed by Osler3 to explain the apparently spontaneous occurrence of some episodes of angina gradually fell into disrepute after both the dogmatic statement by Keefer and Resnik4 that the coronary arteries in patients with angina were so severely fibrosed and calcified that it was not possible for them to go into spasm and the classic studies of Blumgart et al.5,6 The pendulum swung to an extreme when Pickering7 stated that spasm was “a resort of the diagnostically destitute.” It began to swing in the opposite direction with the clinical reasoning of Prinzmetal et al.,8 who proposed that “increased tension at the site of an atherosclerotic plaque” was the likely cause of a “variant” form of spontaneous angina characterized by ST-segment elevation; however, at that time they did not dare use the term “spasm.” An occasional angiographic documentation of spasm was reported by Gensini et al.9 in 1962, but it was not until the early 1970s that the hypothesis of spasm was resurrected by MacAlpin et al.10 to explain the preserved exercise tolerance of patients with Prinzmetal’s angina. A “variant of the variant” was then described in some patients with this syndrome who had no detectable organic epicardial coronary artery stenoses.11 Objective demonstration of spasm in variant angina was first provided in isolated case reports12–14 and subsequently by systematic studies.15–19 Thus, it became “a proved hypothesis.”20

Consequences of the Revival of Coronary Artery Spasm

The proof that angina could be caused by a transitory reduction of coronary flow as well as by an excessive increase of myocardial demand, previously the only traditionally accepted cause,21 broke a conceptual barrier. In 1976, we presented our experience and proposed that many other nonvariant cases of angina at rest were caused by a transitory impairment of coronary blood supply rather than by increased demand. At the time, we proposed the term “primary” angina rather than “vasospastic” angina to emphasize not just coronary artery spasm as one of the possible causes but the more general concept of a transitory impairment of coronary flow.22 However, angina not caused by increased myocardial demand was still thought to be so rare that it was labeled “Pisa” angina, as McGregor recently recalled.23 In the years following, evidence rapidly accumulated that suggested that transitory impairment of coronary blood flow was quite commonly responsible for myo-
cardiac ischemia, and the possible pathogenetic role of increased coronary tone, either as a primary phenomenon or secondary to mural thrombosis, became widely accepted.\textsuperscript{1,2} The manufacturers of coronary vasodilator agents contributed to the increasingly widespread acceptance of this concept because the remarkable efficacy of these drugs in variant angina seemed a good reason for proposing their use in the other, much more common, ischemic syndromes. Thus, when considering pathogenetic mechanisms, the term “coronary spasm” is used to indicate any form of coronary vasoconstriction.\textsuperscript{24–26} This generalization appears incorrect, both because the literal sense of the word “spasm” implies an abnormal sudden, intense constriction and because the causes of occlusive segmental spasm are different from those of other forms of epicardial coronary artery constriction, as we argue below.

It would therefore seem reasonable to distinguish angiographic patterns and degrees of epicardial coronary artery constriction that could set the stage for the identification of the varied underlying mechanisms of coronary vasoconstriction and their association with ischemic syndromes.

**Different Degrees and Patterns of Coronary Vasoconstriction**

**“Physiological” Coronary Constriction and Spasm**

In response to vasoconstrictor stimuli, epicardial coronary arteries can undergo uniform, mild, diffuse constriction, occlusive segmental spasm, and also intermediate degrees of constriction. In animals, epicardial coronary arteries respond to a variety of common constrictor stimuli with a uniform reduction of diameter not exceeding 20–30%.\textsuperscript{27} Similarly, in patients who do not have variant angina, the reduction in epicardial coronary artery diameter in response to ergonovine is usually diffuse and quite mild, not exceeding 30%.\textsuperscript{28–30} This rather uniform and only mild-to-moderate degree of increased coronary vasomotor tone usually observed in both animal and human coronary arteries represents a constrictor response within the “physiological” range.

The very rare, severe degree of constriction, resulting in total vessel occlusion, that characterizes spasm as typically observed in variant angina can be easily distinguished angiographically from lesser forms of epicardial coronary constriction. Occlusive segmental spasm should be considered a separate entity because only when increased vasomotor tone causes occlusion of the vessel does blood flow become interrupted, with the possible consequences of potentially fatal arrhythmias and, if sufficiently prolonged, myocardial necrosis. Moreover, only complete vessel occlusion can cause distal blood stasis predisposing to the development or the extension of coronary thrombosis.

By angiographic criteria, it would seem reasonable to define as epicardial coronary artery spasm all forms of coronary artery constriction leading to angiographically defined total vessel occlusion or subtotal occlusion with only faint, delayed distal filling of contrast medium, whether observed in arterial segments with or without organic stenosis.

**Intermediate Forms of Coronary Constriction**

Between the physiological degree of constriction usually observed in normal coronary arteries in response to common constrictor stimuli and occlusive segmental spasm in patients with variant angina, intermediate forms of coronary constriction can be observed in both patients and experimental animal studies.

First, experimentally endothelium-denuded arteries\textsuperscript{31} and atherosclerotic coronary segments in patients\textsuperscript{30,32} can paradoxically develop constriction but without causing vessel closure in response to stimuli that normally cause vasodilatation. This paradoxical response to vasoactive stimuli may not necessarily have the same cause or clinical significance as occlusive spasm.

Second, during spontaneous or induced ischemic episodes, some patients with variant angina exhibit intense (>30% diameter reduction) diffuse constriction of all coronary artery branches rather than segmental occlusive spasm; a similar diffuse constriction is also occasionally observed in response to ergonovine, even in the absence of ischemic electrocardiographic changes, in patients who have no clinical features of variant angina.

The identification of an abnormal vasomotor response is straightforward when a normally dilator stimulus causes constriction but difficult to establish when the response to constrictor stimulus is just greater than normal, as the constrictor response is likely to be greater when the resting vasomotor tone is low than when it is high. Because the degree of resting vasomotor tone cannot be assessed, the vasomotor range has been estimated by some investigators as the difference between maximal dilatation and maximal constriction. This range was considered abnormally large when the coronary diameter after administration of nitrates was double that observed after ergonovine.\textsuperscript{33} Both the cause and the clinical significance of this generalized increase in coronary vasomotility are likely to differ from those of segmental occlusive spasm and should therefore be considered separately.

**Constrictor Stimuli and Constrictor Response**

In the attempt to separate occlusive spasm from other forms of coronary vasoconstriction, the question arises as to whether segmental occlusive spasm is caused by exceptionally strong local constrictor stimuli or by an abnormal, exaggerated local coronary artery response to common constrictor stimuli. The constrictor response of the coronary arteries should be considered in terms of the effect of constrictor stimuli on normal arteries and of the response of abnormal arteries to vasoactive stimuli (Figure 1).
First, in normal arteries, the effect of constrictor agents can be defined in pharmacological terms according to their potency and efficacy.* In Figure 1, potency is defined by the position of the dose-response curve with respect to concentration of the agonist. This term makes no statement about the maximal effect of the response. Efficacy is defined by

*The vasomotor response is more complex for the agonists that act on different components of the vessel wall, endothelium, smooth muscle, and nerve endings. The overall effect on the vessel lumen is the algebraic sum of the dilator or constrictor effect of each individual component, which is usually dose dependent. In these cases, the constrictor response can also be defined in terms of overall potency and efficacy.

the range of the response, irrespective of the dose, and therefore describes the maximal response.

In terms of constriction, a potent agonist will produce its effect at very low molar concentrations. However, the effect may well be slight and within the physiological range of constriction. Conversely, an efficacious constrictor produces a response that, when maximal, may be well beyond the physiological range for the vessel (see footnote).

Second, in vessels reacting abnormally, the vasoconstrictor response should also be defined in terms of the sensitivity and reactivity of the vessel to constrictor stimuli as compared with normal vessels. The abnormal vessel might exhibit hypersensitivity, resulting in a degree of constriction similar to normal vessels but occurring in response to a lower dose of constrictor agent. It might exhibit hyperreactivity, resulting in a constriction greater than in normal vessels in response to the same dose of constrictor agent.

Thus, according to the above considerations, in arteries without significant subintimal plaques, occlusive epicardial coronary artery spasm could theoretically result from either extremely efficacious stimuli capable of inducing vessel occlusion, even in the absence of any abnormality of coronary arteries, or from an hyperreactivity of a segment of the artery that causes complete occlusion in response to stimuli that only produce constriction within the physiological range in adjacent coronary segments.

Vasoconstrictor Response of Normal Coronary Arteries

Constrictor substances have recently been identified that can cause severe myocardial ischemia at very low doses in the normal coronary circulation. Neuropeptide Y, a neurotransmitter abundantly present in adrenergic nerves and particularly around small coronary arteries and arterioles in animal hearts, induced severe myocardial ischemia in patients with angiographically normal coronary arteries, as well as a reduction of coronary flow in dogs; leukotriene D4 caused severe myocardial ischemia in sheep; fMLP, a chemotactic formyl peptide that probably acts by releasing leukotrienes from granulocytes and inflammatory cells, caused severe myocardial ischemia in rabbits; and endothelin, a peptide produced by endothelial cells, induced a dose-dependent massive coronary flow reduction and ischemia in dogs. All these substances, however, produce ischemia predominantly by small vessel coronary constriction. No significant change of epicardial coronary artery diameter was observed during maximal flow reduction and ischemia caused by neuropeptide Y and endothelin, and only a 30% reduction in epicardial coronary artery diameter was observed with fMLP.

These pharmacological studies indicate that although constrictor stimuli exist that are capable of inducing ischemia in a previously normal coronary circulation, they appear to exert their action predominantly on small vessels rather than on epicardial
Abnormal Response to Constrictor Stimuli

A typical example of hypersensitivity to constrictor stimuli is illustrated by observations in aortic strips taken from cholesterol-fed rabbits. The dose-response curve of these strips to low doses of ergonovine and serotonin was shifted to the left by three orders of magnitude (Figure 2), whereas maximal constriction as indicated by the absolute value reported in the text only increased by about 30%. These findings indicate the development of a remarkable hypersensitivity, but only very mild hyperreactivity, to these constrictor agents. Thus, this type of increased sensitivity to constrictor agents cannot cause occlusive spasm. Indeed, large doses of ergonovine failed to produce occlusive coronary artery spasm in similarly treated rabbits despite a severe reduction of the coronary artery lumen by cholesterol deposits. Patients with variant angina have also been found to have plasma cholesterol values similar to those who have the common syndrome of chronic stable angina, and variant angina has not been reported in patients with familial hypercholesterolemia.

A typical example of hyperreactivity is provided by patients with variant angina. The localized hyperresponsiveness of the spastic segment was clearly documented by intracoronary injection of increasing doses of ergonovine (Figure 3). This study showed that reduction of luminal diameter at the level of the spastic segment was severalfold greater than that in adjacent branches or controls. A segmental increase of coronary constrictor response is also consistent with further observations in patients with variant angina and coronary stenosing plaques (Figure 4) and in miniature swine 3 months after endothelial denudation. This local coronary hyperreactivity...
has also been documented during spontaneous coronary artery spasm in patients with variant angina and no critical coronary stenoses.48

It has not yet been clearly established whether the segmental coronary spasm, observed in patients with variant angina and the miniature swine model, is the result of local hyperreactivity alone or of a combination of local hyperreactivity and hypersensitivity. However, available data both from patients (Figure 3) and the miniature swine model indicate that a local coronary hyperreactivity is the most prevalent phenomenon as the doses of constrictor agents that cause spasm are not distinctly lower than those that cause constriction in nonstenotic vessels.

Spasm at Site of Organic Stenoses

Theoretically stimuli that are not efficacious enough to cause occlusive spasm in normal arteries might become so in arteries with subintimal plaques, which may magnify the reduction of the lumen caused by such a mild degree of smooth muscle shortening that result in only a small lumen reduction in normal coronary segments.49

However, if the extent of luminal narrowing tends to be magnified geometrically by subintimal plaques, it tends to be reduced by medial smooth muscle atrophy and increased wall stiffness. In patients who did not have variant angina, the constriction observed in stenotic coronary artery segments after ergonovine was in general much less than that predicted on the basis of the geometric theory45 (Figure 4). This finding suggests that stiffness or smooth muscle atrophy at the site of the stenosing plaque exerts a dominant negative effect on the degree of lumen reduction. This conclusion is supported by results of studies by Crea et al50 and Nordlander and Orinius51, which showed that ergonovine induced ischemia in only a very few patients with chronic stable exertional angina; moreover, ischemia developed only in patients with the most severe stenoses and positive exercise tests at very low work loads and was never associated with ST-segment elevation, which suggests that ergonovine failed to cause complete vessel occlusion. These results are also consistent with the findings of Bertrand et al, who detected spasm after ergonovine in only 4% of patients with chronic effort angina and 6% with old myocardial infarction (Figure 5).

The possibility cannot be excluded that occasionally plaques that occupy a substantial part of the lumen without causing increased rigidity of the wall could lead to local occlusion in response to constrictor stimuli that uniformly constrict all branches of epicardial coronary arteries within the physiological range. However, this event must be extremely rare in stable coronary patients as elevation of the ST segment during ambulatory electrocardiographic monitoring is not observed in patients with chronic effort angina and multiple, severe stenoses even in the absence of collateral vessels.

Therefore, in the vast majority of atherosclerotic coronary arteries, the development of occlusive spasm at the site of the stenosing plaque seems to require a degree of smooth muscle contraction that is much greater than that which produces only a moderate constriction of adjacent coronary segments to overcome the rigidity of the plaque itself, and hence, such a response is likely to be the result of a local hyperreactivity.

Occlusive Spasm and Segmental Coronary Hyperreactivity

According to the above considerations, it would seem reasonable to assume that a local coronary artery hyperreactivity to even normal constrictor stimuli represents the obligatory substrate of occlusive spasm. Local hyperreactivity would also be the basis of nonocclusive spasm, manifesting as segmental constriction reducing local diameter by at least 50% in arteries without significant stenosis or reducing the caliber of a stenosis clearly in excess of what could be predicted by the geometric theory.45–48 These forms of nonocclusive but segmental constriction indicate the potential for the development of occlusive spasm in response to a stronger stimulation.

Causes of Segmental Epicardial Coronary Artery Hyperreactivity

The causes of segmental hyperreactivity responsible for occlusive coronary artery spasm are still unknown. At present, they can only be investigated in patients with persistent hyperreactivity (i.e. the typical case of that human model of the disease represented by variant angina) and in the miniature swine model. In patients with variant angina, the exagger-
ated local response can be elicited by a variety of constrictor stimuli acting on different receptors and can either vary markedly in time or persist practically unchanged for weeks, months, or years. In these patients, the cause of the local hyperreactivity certainly cannot be attributed simply to the presence of atherosclerotic plaques or cholesterol deposits, which are extremely common, as this explanation would not be compatible with the rarity of the syndrome of variant angina or the negative results of ergonovine challenge in patients with chronic stable angina. It is now firmly established that endothelial cells produce vasodilator substances and in deendothelialized vessels, stimuli that normally result in dilation can become constricting. So far, the altered response of atherosclerotic arteries has not been specifically considered in terms of changes in sensitivity and reactivity to constrictor stimuli. On the one hand, endothelial denudation and massive platelet deposition in previously normal carotid arteries caused only a 30% diameter reduction on the other hand, a paradoxical constrictor response and the geometric magnification of constriction within this range, at the site of stenosing plaques, does not appear sufficient to result in occlusive spasm in the absence of variant angina or acute coronary syndromes, probably because of the low compliance of the plaque as argued above.

Thus, abnormalities of coronary vasomotor response, related simply to the presence of atherosclerotic plaques, are by themselves likely to play only a modulatory rather than a major role in impairing coronary blood flow. This conclusion is also consistent with the observation that raised atherosclerotic plaques are quite common by middle age. Postmortem studies show that raised fibrous plaques occupy 15–20% of the surface of epicardial coronary arteries, with a similar percentage of the wall surface occupied by fatty streaks, in individuals aged 40–44 years who had died accidentally or of nonischemic natural causes.

In the model of segmental coronary hyperreactivity in miniature swine, spasm can be elicited by either histamine or serotonin. In some patients with variant angina, coronary artery spasm can be induced by handgrip, with a delay of about 30 seconds, and cold pressor test, with a delay of about 1 minute, suggesting a neutral trigger. In the same patients, spasm can be caused by a variety of drugs acting on different receptors such as ergonovine, histamine, dopamine, acetylcholine, and intracoronary injection of noradrenaline and serotonin (A. Maseri, G. Davies, D. Hackett, and J. C. Kaski, unpublished observations). Finally, spasm can also be caused by just increasing the arterial blood pH to 7.65–7.70. As spasm has also been observed in human transplanted hearts and explanted perfused hearts in the miniature swine model, a primary neural origin seems unlikely. Conversely, the multiplicity of possible triggers and possible persistence of local hyperreactivity for months and years in some patients without macroscopic progression of the gross atherosclerotic lesion would seem more compatible with a postreceptor alteration of signal transduction in local smooth muscle cells rather than an alteration of the local endothelial lining or an unusual response of resident cells in the wall of the spastic segment.

Segmental Hyperreactivity of Epicardial Coronary Arteries in Acute Ischemic Syndromes

Although segmental coronary artery spasm and local coronary hyperreactivity is best recognized in the clinical syndrome of variant angina, a local hyperreactivity to ergonovine has also been detected in other more common ischemic syndromes. In an angiographic study of 1,089 patients by Bertrand et al, ergonovine induced occlusive spasm in only 2% of patients with “atypical chest pain,” 4% with chronic stable exertional angina, and 6% of those with old myocardial infarction but in as many as 36% of patients with rest angina and in 20% of those with recent infarction (Figure 5). Although the pathophysiological implications of a positive ergonovine test are not clear, the results of this study indicate that a local coronary hyperreactivity to ergonovine, similar to that encountered in variant angina, seems to be quite rare in patients with stable angina, old infarction, and atypical chest pain but may be rather frequent in the acute coronary syndromes of myocardial infarction and angina at rest. Thus, the variability of ischemic threshold so frequently observed in patients with chronic stable angina is not related to the presence of a segmental coronary artery hyperreactivity, similar to that commonly observed in variant angina. This conclusion is in keeping with the markedly different response of patients with chronic stable angina to ergonovine, hyperventilation, and cold pressor tests. In contrast, the presence of an exaggerated segmental response to constrictor stimuli capable of leading to vessel occlusion similar to that observed in variant angina seems more frequent in unstable angina and recent myocardial infarction. The possible occurrence of intense, persisting smooth muscle constriction in these acute coronary syndromes would be consistent with the postmortem report of contraction bands found in the smooth muscle surrounding plaques in patients who died with acute infarction or unstable angina. However, the differences in clinical presentation suggest that the nature of the coronary lesion responsible for the hyperreactivity to ergonovine in acute coronary syndromes and in variant angina with a chronic course may not be the same.

The possible existence of smooth muscle hyperreactivity in acute coronary syndromes, whatever its cause, is intriguing and seems worth exploring. As most recently recanalized infarct-related stenoses show the potential to dilate, often considerably, after administration of intracoronary nitrates, the degree of constriction produced by thromboxane A2, serotonin, and thrombin at the site of intraplaque or mural thrombosis would be greatly influenced by local hyperreactivity. The coincidental presence of a local
coronary hyperreactivity may be a crucial factor in the transition from platelet-fibrin mural thrombus to occlusion by a red thrombus and may be one of the factors that account for the rarity with which acute coronary occlusion occurs during the life of an individual with severe diffuse coronary atherosclerosis.73

Conclusion

In the search for the causes of the increased coronary vasomotor tone of epicardial coronary arteries, responsible for or contributing to myocardial ischemic syndromes, it seems conceptually important to consider occlusive coronary artery spasm as a distinct entity, different from milder forms of coronary artery constriction observed in response to a variety of constrictor stimuli, both in normal and abnormal coronary arteries. It is only occlusive spasm that causes complete interruption of coronary flow and may hence contribute to the development of occlusive coronary thrombosis by fissuring a plaque and by leading to distal blood stasis. On the basis of data available so far, we argue that the development of segmental occlusive spasm is caused by a local hyperreactivity of the arterial vessel wall in response to a variety of stimuli acting on different receptors rather than by a dysfunction of the autonomic nervous system as previously proposed.16,74,75

An understanding of the causes of segmental coronary hyperreactivity to constrictor stimuli may have wide implications because segmental hyperreactivity could be a frequent component of unstable angina and acute myocardial infarction.

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