Acute Myocardial Infarction

For many years, coronary thrombosis was considered the sole and immediate cause of myocardial infarction. This conclusion was understandably reached because of the high prevalence of coronary thrombi in fatal acute infarction when death occurred more than six hours after the onset of symptoms. It was assumed that the thrombus was present at the moment of infarction and initiated the event. In fact, however, the pathologist is hindered in his attempts to understand the initiation of infarction because myocardial necrosis cannot be detected by conventional hematoxylin-eosin stain and light microscopy until six or more hours have elapsed. Electron microscopy and dehydrogenase stains allow earlier detection of infarction, but nevertheless, it is not possible to confidently diagnose acute infarction during the critical early hours. Consequently, the presence and prevalence of coronary thrombosis at the time infarction begins is unknown.

When the onset of chest pain, rather than the presence of necrosis, is used to signal the time of infarction, a thrombus is rarely found when death occurs within an hour or two. In two patients who died suddenly after the occurrence of chest pain and in one instance ST-segment elevation as well, a ruptured plaque with platelet aggregates adhering to subintimal collagen was present, but no occlusive thrombus had formed by the time of death. This suggests that some factor other than thrombosis caused the acute plaque changes and, pari passu, myocardial infarction.

Recent clinical observations have established that a coronary thrombus is often present as early as two to six hours after the onset of an infarction and that the thrombus can be lysed by intracoronary streptokinase. However, this does not preclude the possibility that spasm and or plaque rupture did not occur earlier and lead to occlusion of the vessel and, subsequently, thrombosis. Failure to detect spasm in many of these patients may be due to a number of reasons: 1) spasm has not been systematically sought by the intracoronary injection of nitroglycerin before streptokinase administration; 2) spasm may be refractory even to intracoronary nitroglycerin; 3) intracoronary nitroglycerin is given as a bolus injection over 30 seconds while intracoronary streptokinase is given as a continuous infusion over 30 to 90 minutes; 4) intracoronary nitroglycerin is injected into the coronary ostium while intracoronary streptokinase is often injected through a small catheter in close proximity to the thrombus or the thrombus is penetrated with a guidewire to allow more exposure of the thrombus to the drug. These studies help to fill the void created by the dearth of pathologic information regarding the presence of coronary thrombi during the first few hours of infarction, but they do not help elucidate the initiation of the infarction process.

Activity at the Time of Infarction

Most acute myocardial infarctions occur at rest or during low levels of physical activity. A similar level of activity exists at the onset of ischemia in patients with Prinzmetal's angina and those with unstable rest angina. Spasm has been proved to be the cause of ischemia in Prinzmetal's angina and spasm has been observed in some patients with unstable rest angina. Hemodynamic abnormalities do not precede the onset of ischemia in most of these patients, as discussed earlier. The similarity between Prinzmetal's angina, unstable rest angina and acute transmural infarction, viz, rest pain with ST-segment changes, suggest a common initiating mechanism—reduced coronary blood flow due to spasm.

Coronary Arteriography Before, During and After Infarction

Spasm has been demonstrated by coronary arteriography in seven of ten patients with an acute inferior infarction studied within six hours from the onset of symptoms. After more than six hours
have elapsed, spasm is infrequently demonstrable, perhaps because an occlusive thrombus forms. Spasm is also infrequently detected in patients with an anterior infarction. This could be due to a reduced tendency of the left anterior descending coronary artery to develop spasm for a variety of anatomic or physiologic reasons or to inability of intracoronary nitroglycerin to reach the point of obstruction in sufficient concentration to relieve spasm. Spasm may be refractory to intracoronary nitroglycerin and occasionally massive doses relieve spasm when usual doses fail.44 Spasm has also been found shortly before an infarction. Four patients with coronary artery disease and spontaneous angina with ST-segment elevation had transient spasm at the site of a severe atherosclerotic narrowing one hour to five days before an acute transmural infarction.16 In one case, spasm involved the circumflex and was associated with transient inferior-lateral ischemia. Minutes after reversible spasm was demonstrated, an acute inferior-lateral infarction occurred. The circumflex artery was occluded and could not be opened by intracoronary nitroglycerin. At autopsy six hours later, the circumflex artery was severely narrowed and a small platelet fibrin-thrombus was located at the site of narrowing, but no occlusive thrombus had formed by the time of death. Thus, in this instance spasm unresponsive to intracoronary nitroglycerin superimposed on a severe atherosclerotic narrowing led to complete occlusion of the vessel and an acute myocardial infarction, but at autopsy the vessel was patent. Three other patients had transient spasm of the left anterior descending several days before an acute transmural anterior infarction. These observations suggest, and in one instance prove, that spasm can act in concert with a fixed atherosclerotic lesion to produce infarction. However, since all four of these patients had preceding rest angina with ST-segment elevation characteristic of Prinzmetal's angina—a subset of patients well known to have a proclivity to develop spasm—the relevance of this information to unselected patients with acute myocardial infarction is unclear.

A patent vessel supplying the infarcted region is found by coronary arteriography in about 35 percent of patients investigated within six months after a transmural infarction.45 Interestingly, about 20 percent of these patients have only a 50 percent to 75 percent narrowing. Moreover, several patients who had a coronary arteriogram done before and after an acute anterior infarction had a virtually unchanged 75 percent obstruction of the left anterior descending artery with new akinesis of the anterior wall after the infarction. These observations suggest that spasm, platelet aggregates or a thrombus transiently occluded the lumen long enough to produce infarction and then resolved in a substantial number of cases.

**Coronary Reactivity Before and After Infarction**

Additional information suggests that a phase of enhanced coronary reactivity may precede and follow an acute transmural infarction. Spasm could be provoked by methergine in 20 percent of patients with a recent transmural infarction and in 37 percent with rest angina, but only 2 percent of patients with stable effort angina had provokable spasm.46,47 Among patients with unstable angina, one third of the coronary arteries initially obstructed by an 80-95 percent narrowing became totally occluded over a four-month interval, while in patients with stable effort angina no detectable change in the severity of coronary stenosis occurred over a comparable time.48 Moreover, 50 percent of the patients with unstable angina who developed new occlusions also sustained an acute myocardial infarction. These observations suggest that transient coronary occlusion (probably due to spasm) often occurs in patients with unstable angina and may proceed to permanent occlusion and an acute myocardial infarction.

**Pathophysiologic Considerations**

In light of this information, it has been proposed that a dynamic, potentially reversible interaction among an intimal defect, platelet aggregates and spasm initiates the process of acute myocardial infarction and precedes permanent occlusion of the coronary artery by a thrombus.49 Spasm seems to be the trigger event in some cases, but the sequence of events is not yet established and may not be the same in every instance. The exact time when a thrombus forms and whether it is occlusive or non-occlusive may depend upon the extent of intimal disruption, the aggregability of platelets, and the duration of spasm. It seems plausible that spasm initially produces endothelial damage and plaque rupture which, in turn, leads to platelet aggregation on subintimal collagen and, subsequently, fibrin deposition and thrombus formation. This concept is consonant with the absence of an occlusive thrombus immediately after the onset of infarction, the prodrome experienced by some patients and the occurrence of an infarction during rest or low level physical activity, akin to the activity level in Prinzmetal's angina and unstable rest angina where spasm has been either established or strongly inferred to initiate ischemia. Nevertheless, this mech-
anism remains speculative and more clinical and pathologic observations closer to the time of infarction will help elucidate its pathogenesis.

**Effort Angina**

The conventional concept that classic effort angina is due to increased myocardial oxygen requirements superimposed upon fixed atherosclerotic narrowings is currently being reassessed. Unquestionably, most patients with effort angina have fixed obstructions of their coronary arteries, but this does not preclude spasm or normal vasomotion acting in concert with fixed obstructions to produce ischemia. In order to assess the relative contributions of fixed obstructions and dynamic alterations of coronary vascular tone, the first step is to elicit a careful history. Specifically, it is important to establish the level of exercise the patient can attain without angina on good and bad days. If the levels are disparate, this suggests that a variable, transient reduction of myocardial oxygen supply coexists with increased oxygen demands. If the levels are similar, this indicates that the ischemia is primarily related to increased oxygen demands being unsatisfied because of fixed obstructions. The exercise stress test is useful because it can objectively document the maximal level of stress which can be tolerated without ischemia and how this relates to exertional symptoms during ordinary daily activities. Similarly, the ambulatory electrocardiogram can provide objective information by indicating the heart rate at which ischemia occurs. If ischemia develops at a heart rate substantially lower than shown during stress testing or if ischemia bears no relationship to heart rate, it is reasonable to infer that the episode is not due to increased myocardial oxygen demands.

Continuous electrocardiographic monitoring of subjects with stable effort angina performing normal daily activities has provided inferential evidence that spasm may be more prevalent in effort angina than previously suspected. Frequent episodes of ST depression occur without any appreciable increase of heart rate. Moreover, many of these ischemic attacks are painless and most occur while the patient is recumbent, sitting or performing very light physical activity. These findings suggest that either unrecognized elevations of blood pressure occur or that myocardial oxygen supply is transiently reduced by spasm or platelet aggregates, or both.

**Coronary Arteriography during Effort Angina**

The actual demonstration of spasm during exercise has been accomplished infrequently. Yasue et al. provided the most convincing evidence by showing spasm at the site of a severe fixed narrowing during exercise associated with ST segment depression in three patients. In one patient, effort angina was not affected by propranolol treatment while calcium channel blockers prevented the attacks. In the other two patients, both propranolol and calcium blockers partially suppressed effort angina, suggesting that the angina was caused by both increased myocardial oxygen consumption and spasm. Attempts to provoke spasm with ergot derivatives in patients with effort angina have generally been unsuccessful.

**Vasomotion of Epicardial and Intramyocardial Coronary Arteries**

Thus, other mechanisms of reducing coronary blood flow should be considered. Human coronary arteries normally display vasomotion with the ability to vary luminal diameter by ±20 percent. Luminal diameter is also narrower in the early morning than in the afternoon. Even atherosclerotic human coronary arteries display spontaneous rhythmic contractions in vitro and can be provoked to contract by a variety of substances. Conversely, atherosclerotic narrowings can dilate in response to nitroglycerin and isosorbide dinitrate. An increase of coronary tone within the physiologic realm could cause significant narrowing of an epicardial vessel with only a 50 percent obstruction. In fact, a mere 9 percent reduction of external diameter at the site of a 50 percent narrowing could produce complete occlusion. Hence, normal degrees of epicardial coronary artery vasomotion or transient increases of adrenergically-mediated tone may alter the resistance of a fixed obstruction and produce variations in angina threshold.

Intramyocardial resistance vessels may also contribute to the pathogenesis of effort angina. Normally, these vessels dilate in response to ischemia in order to augment flow to the ischemic region. But recent experimental studies, not yet confirmed in man, have shown that distal vessel dilation may actually increase resistance at the site of a fixed stenosis by allowing passive collapse of the vessel wall. Moreover, in running dogs, the expected exercise-induced vasodilatation of small intramyocardial arterioles is lessened by concomitant alpha-receptor stimulation. Similarly, the cold pressor test increases coronary vascular resistance in subjects with effort angina, presumably by causing constriction of these intramyocardial resistance vessels through alpha-receptor stimulation. Thus, in coronary artery disease, the vasodilatory response
to exercise may be overridden or attenuated by increased stenotic resistance or constriction of resistance vessels distal to a fixed obstruction.

*Interactions between Fixed Obstructions and Coronary Vasomotion*

Considering the currently available information, it is probable that effort angina is due to a spectrum of interactions between fixed obstructions and dynamic narrowing of the coronary arteries. At one end of the spectrum are those patients whose effort angina occurs at a predictable rate-pressure product. Under these circumstances, the obstructions prevent a sufficient increase in coronary blood flow to meet demands. At the other end are those patients with a variable threshold of effort angina, or angina which occurs primarily in the morning. Here an element of spasm or vasoconstriction of epicardial or intramyocardial vessels may contribute to the ischemic process. Vasoconstriction of an epicardial vessel accentuates a fixed obstruction since the resistance across a stenosis is inversely related to the fourth power of the lumen diameter. Inappropriate vasoconstriction or inadequate vasodilatation of intramyocardial resistance vessels during exercise may also affect myocardial oxygen supply.

*Spasm during Exercise in Prinzmetal's Angina*

In contrast to the significance of spasm in classic effort angina, it is clear that in patients with Prinzmetal's angina exercise can induce spasm associated with ST depression or ST elevation. There is a widespread misconception that patients with Prinzmetal's angina cannot have effort angina. Gaasch summarized the literature in 1978 and found that about 50 percent of patients with Prinzmetal's angina also had an ischemic exercise test consonant with Prinzmetal's assertion that "it is not uncommon for both the variant and classic form of angina pectoris to occur together in the same patient." This does not contradict the fact that when a patient with variant angina is having frequent attacks of pain at rest, his exercise tolerance is good, while during a less "active" phase of his illness effort angina may occur.

ST-segment elevation and depression during exercise occur with almost equal frequency among those patients with both variant and effort angina. The direction of the ST shift may reflect different pathogenetic mechanisms of ischemia. ST elevation is due to spasm of a normal or severely stenosed vessel. ST depression usually reflects underlying significant fixed obstructive coronary disease, but it is unclear if spasm or increased metabolic demands cause the exercise-induced ST depression. Both mechanisms have been demonstrated but insufficient information is available to establish the frequency with which either mechanism is operative.

*Sudden Death*

This common expression of ischemic heart disease is usually due to ventricular fibrillation although about 30 percent of victims monitored soon after collapse have asystole or slow ventricular rhythms. But what causes these lethal arrhythmias? Only 16 percent of survivors develop electrocardiographic evidence of an acute myocardial infarction, but most have extensive coronary artery disease with segmental wall motion abnormalities, reduced ejection fraction and, not infrequently, a ventricular aneurysm. Ambulatory electrocardiographic monitoring shows frequent premature ventricular contractions which are often multifocal and occur during the vulnerable period. Thus, these patients have the anatomic substrate for temporal dispersion of refractory periods in ischemic tissue and electrical instability. There is no proof that spasm causes sudden death and perhaps no reason to consider it given the status of the myocardium and the electrical instability. But it seems imprudent to disregard the possibility that spasm causes or contributes to sudden death and there are some intriguing observations which whet one's intellect.

Intravenous ergonovine may produce irreversible spasm with ventricular fibrillation or asystole and oral ergotamine for migraine can cause sudden death in the presence of pathologically normal coronary arteries. Among patients with variant angina, roughly 15 percent die suddenly. Spasm previously engendered ventricular arrhythmias in some of these patients. Therefore, it seems reasonable to assume that spasm can cause ventricular fibrillation and sudden death in some patients with variant angina. Interestingly, arrhythmias often occur as the ST-segment elevation is waning or during the succeeding period of T-wave inversion. These electrical events correspond to the relief of spasm with consequent reperfusion of ischemic myocardium. Ventricular tachycardia and ventricular fibrillation frequently attend reperfusion and are probably related to sudden changes in the transmembrane potassium gradient of ischemic tissue. In a canine model, the frequency of reperfusion-induced ventricular fibrillation is less when reperfusion flow is attenuated. This favorable effect may be related to a reduction in the rate of trans-

Coronary Arterial Spasm and Vasomotion (Philip B. Olive)
membrane potassium flux or to a limitation of the availability of calcium ions which further damage ischemic cells.

**Catecholamines, Electrical Instability and Spasm**

Many patients dying suddenly display coagulative myocytolysis, a type of necrosis resembling that induced by catecholamines. It is possible that a sudden surge of catecholamines elicited by excitement, stress, anger or cigarette smoking results in spasm and myocardial damage, but it is more probable that catecholamines lower the ventricular fibrillation threshold and lead to sudden death without invoking spasm. In several instances sudden death has occurred during ambulatory monitoring of patients performing ordinary daily activities. Although no pattern has emerged, ventricular fibrillation is sometimes immediately preceded by ischemic electrocardiographic changes which could be due to either catecholamine-related increases of heart rate and/or blood pressure or to spasm. The potential interactions between catecholamines, electrical instability and spasm are illustrated by evidence, on the one hand indicating that stress can augment sympathetic activity and electrical instability thereby predisposing to ventricular tachycardia and ventricular fibrillation. On the other hand, stress induced by aversive stimuli can also produce marked coronary vasoconstriction in experimental animals.

The information presented suggests that spasm may be operative in sudden coronary death, but direct proof is absent. It is probable that sudden death is multifactorial and that poor ventricular function and electrical instability are often responsible. Nevertheless, the possibility of spasm should not be dismissed and it should not come as an apocalypse if spasm is someday shown to be a cause of sudden coronary death.

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