PLATELETS AND VASCULAR OCCLUSION

Pathophysiology of coronary occlusion in acute infarction

Attilio Maseri, M.D., Sergio Chierchia, M.D., and Graham Davies, M.D.

ABSTRACT  Coronary angiography has proved beyond doubt that complete coronary occlusion is the rule in the very early hours of infarction. The 60% to 80% rate of coronary recanalization after thrombolytic therapy has proved that thrombosis is a major component of the occlusion at the time when the procedure is performed a few hours after the onset of symptoms. However, the trigger for coronary thrombosis and the causes of failure of thrombolytic therapy are still a matter of speculation. The relatively rare occurrence of acute coronary occlusion in the life of an individual with even severe coronary disease can be explained on the basis of the necessity of either (1) extremely powerful isolated stimuli, which only occurs rarely, or (2) the casual simultaneous presence in one coronary arterial segment of multiple unfavorable events, such as plaque fissuring, enhanced reactivity of coronary smooth muscle to constrictor stimuli and displacement of the thrombotic-thrombolytic equilibrium toward thrombosis. Coronary artery constriction possibly caused by vasoconstrictor substances released by thrombus, represents the potential element of a vicious cycle causing persistent coronary occlusion and reocclusion when reflow occurs with thrombolysis.


THE NOTION of coronary artery occlusion is traditionally associated with that of myocardial infarction. However, total coronary occlusions in the absence of infarction are frequently observed both during angiographic and postmortem examination in patients without symptoms or signs of ischemic events. Coronary occlusions are most likely to cause myocardial necrosis when occurring suddenly in vessels that are not already critically obstructed and have no adequate or no functional distal collaterals. Conversely, when occlusions are not associated with detectable ischemic events they probably developed gradually in vessels with distal functioning collaterals. The alternative view, that coronary occlusion may be a consequence rather than a cause of infarction, although attractively explaining some puzzling observations, lacks objective evidence. Thus it seems reasonable to assume that the development of infarction is usually determined by the balance between four factors: (1) the rate of progression of the occlusion, (2) its duration or intermittence, (3) the extent of collateral blood flow, and (4) the coronary and myocardial response to ischemia.

We will consider only the mechanisms of acute coronary occlusion, attempting to separate facts from extrapolations so that future lines of research can be defined from a more rational basis.

Evidence for coronary occlusion in the early phases of infarction. The angiographic studies by De Wood et al. have definitively clarified the issue by showing beyond doubt that, in the first 4 hr of the onset of symptoms, the coronary artery supplying the infarcted area is indeed occluded in over 87% of patients and is patent, although severely narrowed, in the remaining 13%. These findings have been largely confirmed by subsequent reports on intracoronary thrombolysis. It is conceivable that in the few cases in which the artery was found to be patent, it may have been occluded previously, since occlusions do tend to recanalize spontaneously and patent vessels are found in 32% of patients within 12 hr and in about 50% at 2 to 3 weeks.

Therefore, because enough evidence has now been gathered to establish that the coronary artery supplying the infarcted region in indeed totally occluded, at least in the early phases of infarction, it is appropriate to discuss the nature of the occlusion and its initiating mechanisms.

Nature of the acute coronary occlusion. From a theoretical point of view, acute coronary occlusion may be caused by intravascular plugging by blood constituents, by some form of vasoconstriction (see below), by embolization, by intraplaque hemorrhage, or possibly more often by a variable combination of these factors.
The relative role of these mechanisms is probably not the same in all patients and may vary in time as the acute event evolves.

Established myocardial infarction. Undoubtedly thrombosis must play a major role at 2 to 6 hr from the onset of symptoms, when thrombolysis is usually performed, considering the very high incidence of recanalization resulting from the procedure. Conversely, within this same period, spasm (at least of the type responsible for variant angina, which is usually promptly relieved by nitrates) seems to play a minor role because, with a single exception, all reports show a low incidence of recanalization after intracoronary nitroglycerin.5-11 No definite explanation is yet available for the 20% to 30% of cases in which both nitrates and thrombolysis are ineffective in reopening the artery. In two such cases no thrombus was found at postmortem examination at the site of severe stenosis.9 Thrombus not reached by or resistant to thrombolytic agents, or spasm refractory to nitrates, are possible alternatives.

Developing myocardial infarction. In an earlier phase the mechanisms of occlusion seem to be complex as suggested by a recent study performed in our institution.12 In nine instances in which we could begin intracoronary streptokinase 45 to 120 min from the onset of symptoms, we observed reclosure (five patients) or occlusion of an initially patent artery (1 patient) while infusing the drug at 5000 IU/min; the occlusion was transient in four patients but irreversible in two; in two instances the vessel became patent promptly, but only transiently, after intracoronary administration of nitrates. Thrombosis still developing in spite of high concentrations of streptokinase, or spasm only transiently relieved or refractory to nitrates (see below), could account for our findings. An alternative explanation could be provided by subintimal hemorrhage into a plaque. However, postmortem studies suggest that this event is a rare cause of occlusion13-15 and it is usually confused with plaque fissuring, which, having a large opening toward the lumen, cannot cause obstructions by itself unless associated with thrombosis.

Coronary arterial lesions and composition of thrombi. Postmortem studies, although probably biased toward most severe lesions, provide us with some information on at least one type of patient with acute infarction: those that die. Thrombus is found in 21% to 54% of patients in one series of studies and in above 66% to 100% in another series.16 Patient selection, definitions, and method of examination account for these wide discrepancies. Thrombi are found less frequently in subendocardial and small recent infarcts than in large older infarcts complicated by pump failure. Early spontaneous recanalization as suggested by the studies of De Wood et al.,4 and of Bertrand et al13 may explain the absence of occlusive thrombus at postmortem study.

Systematic studies would be useful to assess the characteristics of the vessel wall at the site of thrombosis in relation to residual vascular lumen, length and severity of the preexisting atheromatous lesion, the presence of intimal damage, plaque fissure, intraplaque hemorrhage, the preservation of medial smooth muscle, and features of the adventitia with particular attention to vasa vasorum, nerve endings, and inflammatory cells.

A careful postmortem study of the composition of thrombi, when possible, would provide clues to their origin. If platelets and fibrin are the main components of at least one section of the occlusion, the “white thrombus” must have developed gradually in flowing blood. Conversely, if red cells are present in all segments of the thrombus in the same percentage as in circulating blood, without any trace of white thrombus, the “red thrombus” or clot must be secondary to total occlusion by other mechanisms. In turn, when platelet-rich white mural thrombi do not occlude the lumen completely, either postmortem release of spasm or partial lysis must be invoked to explain the absence of total occlusion. Although partial postmortem lysis cannot be excluded, this process is considered rather unlikely.14,17

A potential vicious cycle. Local coronary vasoconstriction caused by substances released by thrombi such as thromboxane A2,18 serotonin,19 and thrombin20 is a possible mechanism of persistent or recurring occlusion. Theoretically, if the local constrictor response of the arterial wall is sufficiently great, these compounds could be the elements of a potential vicious cycle determining total occlusion by spasm in the presence of intraintimal and mural thrombosis and favoring reclosure whenever release of spasm brings blood flow and hence more platelets.21 Conversely, during thrombolytic therapy, release of spasm would allow delivery of thrombolytic agents over the whole length of the thrombus.

Initial causes of occlusion. Although the predominant role of thrombosis in acute coronary occlusion is unquestionable, the mechanisms responsible for its initiation and progression are still speculative.

Plaque fissuring. Fissuring of plaques seems a most likely triggering event for coronary thrombosis. Studies based on microanatomic reconstruction of vascular segments with fresh thrombi in acute infarction22,23 consistently showed the presence of a fissured plaque with intraintimal thrombus extending into the lumen.
Plaque fissure with variable degree of intraintimal hemorrhage extending toward the media was also frequently observed by Falk in patients with unstable angina who came to postmortem examination. This author suggested, as we have done in the past, that plaque rupture with variable degree of intimal hemorrhage and luminal thrombosis could represent the missing link between morphology (atherosclerosis) and function (spasm).

However, it is possible that the arterial segment corresponding to the fissured plaque develops occlusive spasm in response to constrictor substances released by the intraintimal and mural thrombi, only if coronary smooth muscle hypereacts to constrictor stimuli.

In 100 cases of sudden coronary death, Davies and Thomas found plaque fissures with intraintimal thrombus in 74%; in 44% a large thrombus extended into the residual lumen and reduced it by more than 50%; in an additional 30% mural thrombi were attached to the intima. However, they also found plaque fissuring with intraintimal thrombus in 10% of control hearts, suggesting that this alteration is quite frequent in the general population. Occurrence of plaque rupture in atherosclerotic coronary arteries is not surprising, considering that these vessels are continuously subjected to rhythmic motion and undergo frequent changes in distending pressure and smooth muscle tone.

Critical stenosis. Turbulence at the site of a critical stenosis creating high shear stress was proposed to cause platelet damage and aggregation either directly or because of ADP release by damaged red cells. In animals, transient platelet plug formation only at the site of an acute stenosis narrowing the lumen more than 95% and reducing slightly even resting blood flow. Lumen reductions of lesser severity (up to 70%) still allow a 300% to 400% increase of flow during reactive hyperemia. Therefore it appears that only a very severe stenosis coupled with high flow rates can produce sufficiently high shear stress to damage platelets and red cells. In patients who died after acute infarction, the preexisting obstruction at the site of thrombosis is found to reduce the lumen by 70% or more in 80% to 90% of the cases; collaterals are often present in patients with the most severe stenoses reducing forward flow. However, less severe or even minimal lesions are found in 10% to 20% of cases.

Thrombus formation. Endothelial damage undergoes a repair process that is self-limiting, although less severe forms of wall damage result in a much more limited reaction than larger ones, involving deeper layers of the vessel wall. A dynamic equilibrium between thrombosis and thrombolysis has been postulated and this view seems to be gaining acceptance. High flow rates tend to limit thrombus size in three ways: (1) the substances that cause platelet aggregation and can initiate coagulation locally are rapidly diluted in the blood stream (thus limiting thrombus growth); (2) plasmin, which has a very short half life, can be formed by newly delivered plasminogen and its activators (thus favoring thrombolysis); (3) the superficial layers of thrombus will tend to be dislodged because of the shear effects of flow (and indeed platelet emboli can be found distally to a fresh thrombus).

Thus, although it is understandable that large thrombi may form at the site of major obstructive plaques with large tears, the mechanisms of thrombotic occlusion in segments of arteries with only minor or with no detectable fissures and without critically obstructive plaques are less clear. In this case, local factors such as spasm and/or marked displacement of the thrombotic-thrombolytic equilibrium toward thrombosis may play an important role. The persistent tendency of thrombosis to recur in discrete episodes at the same site observed in patients with unstable angina is also difficult to explain, since usually endothelial repair after thrombosis is rapid, at least in normal arteries.

Coronary spasm. The reduction of caliber of epicardial coronary arteries in response to constrictor stimuli is rather small both in dogs and man, and it can impair flow only in pliable segments of arteries with a critical subintimal plaque. Conversely, spasm as seen in "variant" angina causes total occlusion, even in vessels without critical lesions, in response to stimuli that cause only moderate or no detectable constriction in patients who are not in an acute phase of this syndrome. Excessive smooth muscle response can be seen in the same patient after adrenergic, serotoninergic, and histaminergic stimuli. At present, no stimuli capable of producing occlusive spasm in the absence of a local hyperreactivity and/or of a critical subintimal plaque are known.

In patients with variant angina, infarction is relatively rare considering the frequency of episodes of spasm. Out of over 7000 episodes of transient ischemia caused by spasm observed in a large group of patients with variant angina, we found only 28 episodes that progressed to infarction. However, although the mechanism leading to persistent coronary occlusion is most likely to be different from the form of spasm responsible for variant angina, spasm must in some way be related to infarction, since this occurred consistently in the area supplied by vessels shown to undergo spasm during transient ischemic episodes.
tients we were unable to reestablish patency by large doses of intracoronary nitrates, although the same vessel was patent 24 hr later. Angiography showed a pattern consistent with recanalized thrombus in two cases, and the post mortem examination revealed a mural platelet thrombus in another. Thrombosis was also observed in angiographically normal vessels after spasm.

In an unselected group of patients with recent myocardial infarction, Bertrand et al. observed that coronary arteries are supersensitive to spasmogenic stimuli; ergonovine produced spasm in 20% of their patients with a recent infarction, a smaller percentage than in patients with angina at rest (38%) but much greater than in patients with old infarction (6%) and in those with stable angina (4%).

Thus it seems possible that persistent coronary occlusion may result both from spasm causing a plaque to rupture and from plaque fissure in an arterial segment supersensitive to constrictor stimuli released by the developing thrombus. Also, the possible occurrence of spasm resistant or refractory to nitrates as observed in some cases after ergonovine provocation or after bypass surgery cannot be dismissed. Persistent spasm was observed at postmortem examination in patients with variant angina who died during an attack. Catheter-induced spasm of the brachial artery and vein is a typical example of severe vasospasm that cannot be relieved by sublingual, intravenous, and even locally injected nitrates or calcium antagonists. Extreme smooth muscle sensitivity to constrictor stimuli, persistence of the stimulus, or formation of latch bridges that require minimal energy expenditure to maintain contraction are possible explanations for persistent spasm resistant to vasodilators.

A unifying hypothesis. Acute coronary occlusion is an occasional event in the life of an individual even when extremely severe coronary atherosclerosis is present. Infarction is also relatively rare in patients with unstable angina: 13% within 6 months in the Edinburgh study and 8% within 1 month in the Rotterdam study. The relatively rare occurrence of acute coronary occlusion could be explained by the occurrence of (1) extremely powerful but rare stimuli or (2) the necessity for the simultaneous occurrence of multiple independent pathologic events in the same coronary arterial segment.

One such possible set of unfavorable events could be a plaque rupturing in an arterial segment supersensitive to vasoconstrictor stimuli with a local thrombotic thrombolytic equilibrium displaced toward thrombosis. (figure 1).

**Initial Mechanisms of Acute, Persistent Coronary Occlusion**

**FIGURE 1.** The probability of developing an acute persistent coronary occlusion in a patient with coronary disease over days, months, and years is small and it may result from the casual combination of events present at the same time. Three critical events, potentially linked by positive feedback mechanism, may be necessary to initiate coronary occlusion. Plaque fissuring (a) and spasm (b) are related to the local coronary artery pathology; the formation and progression of thrombus are related to local vascular anatomic and hemodynamic factors as well as to the balance between thrombotic and thrombolytic factors (c). Thus the probability of developing acute persistent coronary occlusion, P, can be seen as 1/(a × b × c), where a = development of plaque fissure, b = presence of local coronary artery supersensitivity to constrictive stimuli, and c = displacement of the thrombotic-thrombolytic equilibrium toward thrombosis. However, an extreme alteration of either a or b alone or a combined alteration of a and b, b and c, or a and c may be sufficient to cause occlusion.

Thus the probability of developing an acute persistent coronary occlusion (P) can be seen as:

\[ P = \frac{1}{a \times b \times c} \]

where a = development of plaque fissure, b = presence of local coronary artery supersensitivity to constrictive stimuli, and c = displacement of the thrombotic-thrombolytic equilibrium toward thrombosis.

However, an extreme alteration of any of these factors alone or a combination of a and b, b and c, or a and c may be sufficient to cause occlusion.

In diseased coronary arteries that remain occluded for a period of time, the development and extension of red thrombus may occur irrespective of the original cause of occlusion (figure 2). The possibility of late thrombus formation or of its extension has been demonstrated by the incorporation into thrombi of radiofibrinogen injected after the onset of symptoms and
Determinants of Coronary Thrombosis

SPASM  →  WHITE THROMBUS

Transient or persistent coronary occlusion

(overall balance of thrombosis - thrombolysis - platelets - spasm)

RED THROMBUS or CLOT

(consequence of occlusion ➔ cause of its' persistence and extension)

FIGURE 2. Initial acute coronary occlusion can be caused by white thrombus forming gradually in flowing blood, by spasm, or by their combination. Flowing blood tends to inhibit thrombus growth because it dilutes locally formed coagulant factors, it brings new plasminogen, and it tends to fragment un-stabilized thrombus. In occluded vessels red thrombus may form and extend depending on the balance between thrombotic and thrombolytic tendency, degree of vessel wall damage, and local hemodynamics. When a red thrombus has formed, the occlusion persists also when spasm has disappeared; conversely, restoration of flow by spontaneous thrombolysis or relief of spasm brings new platelets that can adhere to the damaged wall and release vasoconstrictor substances, which may favor recurrence of spasm and reobstruction. Intermittent coronary occlusion seems a frequent feature in the very early phases of myocardial infarction in patients.

previously suggested by some postmortem studies for patients with large infarcts and pump failure.

When an occlusive red thrombus is present, the vessel will remain occluded even when spasm is relieved.

Implications for the prevention of myocardial infarction. In terms of treatment of acute coronary occlusion in acute infarction, intracoronary and intravenous thrombolysis appears quite often effective in recanalizing the occlusion. The available evidence indicates that very early interventions (less than 2 hr) can prevent infarction in about 50% of cases; lysis at 2 to 4 hr is likely to reduce size rather than preventing infarction. The multiple factors involved in the genesis of infarction (figure 3) and the possible stuttering progression of the occlusion suggests that the time from onset of symptoms to irreversible necrosis maybe quite variable; thus decisions on maximum acceptable delay of thrombolytic attempts should not be based only on the time after the onset of pain but also on the stage of the electrocardiographic changes. Furthermore, considering the possible late occurrence of thrombus extension, even late interventions might contribute to reduction of the infarct size and to the propagation of occlusive clot along the vessel. The results with tissue-type plasminogen activator are promising, but even with this agent supposed to have a thrombolytic effect the rate of recanalization seems to be only 60% to 70% and patients who do not respond also fail to respond to streptokinase; reocclusion also seems to be a common problem, and bleeding is also observed.

On the basis of these arguments, it may be desirable to associate thrombolytic agents with drugs capable of effectively reducing coronary smooth muscle tone, but this may not be possible until the mechanisms of coronary constriction in acute persistent coronary occlusion are better understood.

In terms of prevention, aspirin appears to reduce significantly the occurrence of infarction and of sudden death in patients who went through a phase of unstable angina. However, the mechanisms of this beneficial effect are not clear. Intravenous heparin also was found to reduce the occurrence of infarction in the intermediate coronary syndrome; the result with antithrombin III anticoagulants are less clear. Thus the results obtained so far with thrombolytic and antithrombotic agents for the treatment and prevention of myocardial infarction can be considered promising but only partially successful.

The reported beneficial effects of \( \beta \)-blockers in postinfarction patients seem more related to prevention of arrhythmic deaths than to reduction of infarction. No large studies of the effects of calcium antagonists and/or nitrates on mortality in early infarction and in unstable angina are available, but theoretically it would seem reasonable to assume an additive effect of a combined prophylaxis with antivasospastic and antithrombotic agents.

The task of preventing acute persisting coronary occlusions, occurring unpredictably and very rarely in a patient’s life as a result of events localized in one
coronary arterial segment and caused by a variable combination of mechanisms, is arduous. The chances of success depend not only on the identification of the prevailing initiating and feedback mechanisms, but also on the possibility of intervening effectively in the varied local pathologic processes of the coronary artery wall.

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