

## Mechanisms of Disease

# Unstable angina

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Unstable angina has only been recognized as a distinct entity for about 50 years. The term is used to describe a symptom complex that is neither stable angina pectoris nor acute myocardial infarction. There are a number of other terms used to describe essentially the same symptom complex; these include pre-infarction angina, crescendo angina, intermediate coronary syndrome and threatening infarction. This entity excites interest since it represents a change in the pattern of symptoms. Some of the reasons for this change in pattern are beginning to be become clearer and have become more relevant since there is a large choice of treatment available. However there is considerable debate as to the circumstances in which a particular therapy might best be used. A better understanding of the complex pathophysiology of unstable angina may help determine the optimal form of treatment, may help prevent the problem and may also indicate the direction of future research.

For many years it was believed that unstable angina was due to episodic changes in myocardial oxygen demand superimposed on advanced fixed narrowings of the coronary arteries. It is now apparent that there are alternative or additional mechanisms. These include episodic reductions in the myocardial oxygen supply due to coronary artery spasm,<sup>1,2</sup> platelet activation and transient thrombus formation.

### The pathology of unstable angina

Coronary artery thrombi are now thought to be directly involved in all three clinical pictures of acute ischaemia, namely myocardial infarction, unstable angina and sudden ischaemic death (Figure 1). A better understanding of the various mechanisms involved has come from recent

pathological studies using post-mortem coronary arteriography and histological reconstruction of the microanatomy of occlusive lesions,<sup>3,4</sup> from coronary angiography in patients with acute infarction and unstable angina, and from direct fiberoptic angiography.

Pathological studies show that atheromatous plaques bulge outwards towards the media and not inwards as previously described in arteries that had been fixed and processed in the undistended state. These lipid rich plaques are separated from the lumen by a fibrous cap. A rupture of this fibrous cap allows blood from the lumen to dissect into the intima and into the lipid pool of the plaque (Figure 1, A). A thrombus, rich in platelets but also containing some red cells and fibrin, forms within the intima and leads to considerable expansion of the plaque. Over the site of rupture, thrombus forms in the lumen. This mass of luminal thrombus initially does not occlude the lumen, but waxes and wanes in size over hours or even days. Some patients may have a massive thrombotic response within the lumen with only minimal fissuring. The intraluminal thrombus may grow to become totally occlusive or may become completely lysed and the plaque fissure resealed.

The earlier stages of plaque fissuring are found in patients with unstable angina or those who suffer sudden ischaemic death. Patients who develop an established regional infarct are those in whom the thrombus has occluded the lumen at least for long enough to induce myocardial necrosis (Figure 1, B). This does not explain why some patients should die suddenly before the arterial lesion is fully occlusive. Death may be caused by an arrhythmia provoked by platelet emboli rising from the thrombus<sup>5,6</sup> (Figure 1, C). Sudden death may thus be the myocardial equivalent of transient cerebral ischaemic attacks due to platelet emboli. Support for this mechanism comes from a very elegant study in which a significant difference was found in the incidence of intramyocardial platelet aggregation in patients who died suddenly with angina of recent

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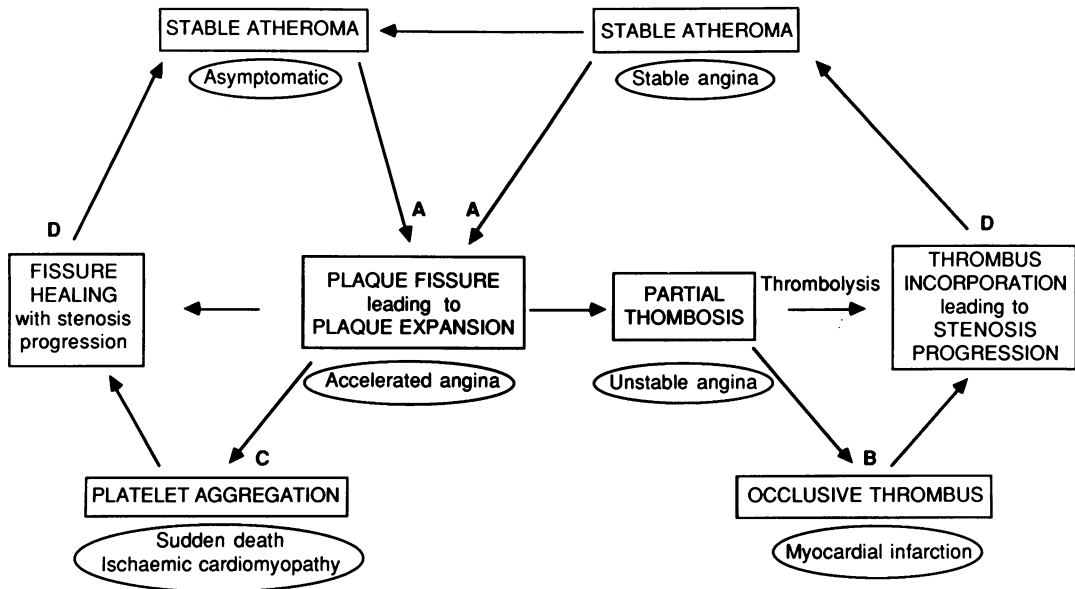


Figure 1 Cycle of atheromatous coronary artery disease.

onset compared with those who died with a preceding history of stable angina. Platelet aggregation was found only in those segments of myocardium that were downstream from the atheromatous plaque and thrombus in those patients with angina of recent onset.<sup>7</sup> The patient with a plaque fissure who escapes one of these manifestations will be left with an atheromatous plaque larger than previously (Figure 1, D). This episodic plaque growth is an important factor in the development of stable angina.

Arteriography has also produced further valuable information which corresponds to the pathological findings. Atherosclerosis produces lumens which approximate to being circular but are often placed eccentrically to the midline of the vessel forming elliptical and D shaped lumens. This can be recognized angiographically but may lead to difficulty in assessing accurately the degree of stenosis. Since part of the wall is not involved in the atherosclerotic process, it is reasonable to assume that this segment is still able to contract and relax and thus alter the degree of obstruction. Angiographic studies have shown that spasm usually occurs in abnormal coronary arteries at the site of atherosclerotic plaques. Slit-like and crescentic lumens do not occur with stable angina; they can, however, be demonstrated with rapidly evolving lesions caused by plaque fissuring and

associated thrombus formation. A number of studies have shown that thrombus is demonstrated considerably more frequently when the arteriogram is performed either during, or soon after an episode of chest pain than if the arteriogram is performed several days later.<sup>8</sup> Direct fibre optic angiography has also demonstrated a difference between patients with a stable and unstable angina.<sup>9,10</sup> In the former, only smooth, non-ulcerated lesions without haemorrhage or thrombus are found. In the group of patients with unstable rest angina, there are fresh and, at times, occlusive thrombi which undulate in size during cold cardioplegia flusing in front of the lens.

#### Haemostatic factors

The speed at which thrombi evolve and regress over a relatively short period of time emphasizes the importance of the haemostatic and fibrinolytic systems, both as part of the acute or sub-acute complications of atheroma and also more chronically in the initial development of the atheromatous lesion.<sup>11-13</sup> Many of these haemostatic factors can be rapidly modified by stressful stimuli. There is thus a distinct possibility that the actual stress of suggesting and then performing coronary arteriography, may modify these factors in an

adverse manner. Indeed platelet activation and secretion of platelet factor 4 and  $\beta$ -thromboglobulin can be demonstrated with emotional stress.<sup>14</sup> This secretion is not blocked by aspirin suggesting that such activation occurs independently of the cyclo-oxygenase pathway.

### Platelet aggregation

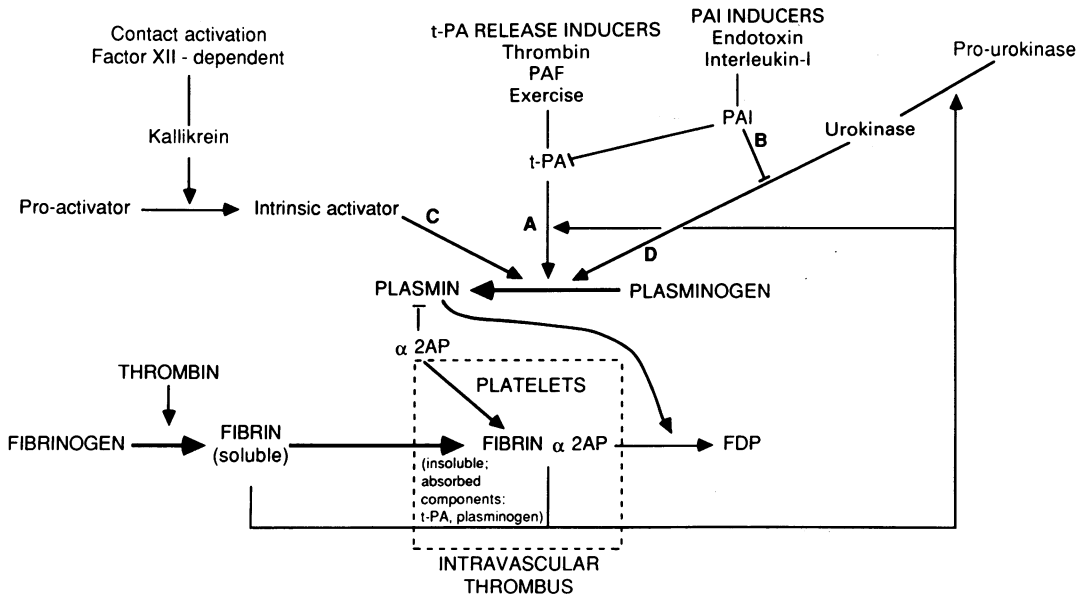
It is worthwhile reviewing briefly the factors involved in platelet aggregation, thrombus formation and fibrinolysis. From the therapeutic standpoint, an understanding of these factors and how they interrelate, is becoming more important. The vascular endothelium synthesizes prostacyclin which is a potent vasodilator and has anti-aggregatory properties. The endothelium also activates or inactivates a number of vasoactive substances present in the blood, influences the amount of vasoactive substances reaching the deeper layers of the blood vessel wall and modifies the responsiveness of the vascular smooth muscle of the media. Platelets can produce a number of vasoactive substances which include serotonin, thromboxane, adenine nucleotides, vasopressin and platelet activating substance. Each of these substances produce constriction of the smooth muscle of coronary arteries when there is a damaged endothelium. In the presence of an intact endothelium, relaxation occurs. How are these opposite effects explained? It is postulated that the endothelium derived relaxing factor (EDRF) or a component of it, plays a crucial role. If platelets begin to aggregate in a normal artery with an intact endothelium, the response of the smooth muscle to the substances released from the platelets is that of relaxation mediated by EDRF. This is reinforced if the platelet aggregation sets the coagulation cascade in motion causing the formation of thrombin. If the endothelium is damaged or not functioning properly, the response of the coronary vessels to the platelet products and thrombin is that of contraction which further reduces the lumen and increases the obstruction to blood flow. Platelet activation can be demonstrated during episodes of unstable or variant angina.<sup>15</sup> In contrast, platelet activation is not demonstrable at rest nor during exercise-induced ischaemia in patients with stable angina.

### Fibrinolysis

Fibrin is the natural substrate of the fibrinolytic system. It is formed from circulating fibrinogen by

the action of thrombin. Together with the interaction of the platelets, it forms the scaffolding of the intravascular thrombus or haemostatic plug. Fibrin also plays a decisive role in its own dissolution by accumulating various components of the fibrinolytic system and by accelerating the action of tissue-type plasminogen activator (t-PA) on plasminogen. Plasmin, formed by activation of plasminogen, is the key enzyme in the fibrinolytic system (Figure 2). Its non-specific proteolytic activity in the circulation is controlled by protease inhibitors, the most important of which is  $\alpha$ 2 antiplasmin ( $\alpha$ 2AP). The major role of  $\alpha$ 2AP is to neutralize plasmin in the circulation. It is also incorporated into growing fibrin clots where it is bound by the action of clotting factor XIII. It thus has a regulatory role in fibrinolysis. Both plasminogen and  $\alpha$ 2AP are themselves modulated by several factors. Plasminogen activation is the main regulatory process of the fibrinolytic system. There are at least three different routes of activation that can be distinguished and quantified. Of the three, the pathway catalysed by the tissue-type plasminogen activator (t-PA) has received most attention (Figure 2,A). t-PA is secreted by endothelial cells into the circulation. The recent discovery of fast-acting plasminogen activator inhibitor (PAI) has caused a reassessment of the interpretation of some assays of fibrinolytic activity which have measured the overall effect of t-PA and PAI.<sup>16</sup> It is now clear that the diurnal variation in fibrinolytic activity, the reduced t-PA after surgery or after a myocardial infarction, is due mainly to changes in PAI (Figure 2,B). The measurement of the circulating components will only partly reflect the local situation at the site of the blood clot. The discovery of PAI has also had consequences for the study of fibrinolysis-related risk factors for thrombosis. A number of essential interacting factors are selectively adsorbed onto the growing fibrin network; platelets contribute additional PAI and the vessel wall can react with the release of extra t-PA. Once fibrinolysis has started, the stimulatory effect of fibrin on plasminogen activation in the clot matrix may increase many times.

The two other main pathways influencing plasminogen activation are the Factor XII-dependent pathway (Figure 2,C) and the Factor XII-independent pathway (Figure 2,D) which account for about half of the intrinsic activation system; the latter is also known as the urokinase related pathway. Attempts at anti-thrombotic intervention have been based on one of two principles; either using anticoagulants to slow down the formation of thrombi or alternatively using drugs



**Figure 2** An outline of the fibrinolytic system. —→, conversion, stimulation; —|, binding, inhibition; t-PA, tissue-type plasminogen activator; PAI, fast acting plasminogen activator inhibitor;  $\alpha$ 2AP,  $\alpha$ 2 antiplasmin; FDP, fibrin degradation product; PAF, platelet activation factor.

to speed up their dissolution. It has become clear from studies of patients with myocardial infarction that thrombolysis is achieved with a much smaller dosage if the drug is introduced early in the development of thrombus; it seems likely that the same will apply to patients with unstable angina.

The amount of injury to the myocardium will depend on a number of factors which will include the time and the extent that the vessel is narrowed by the thrombus, the degree of coronary artery spasm, the collateral blood supply to the ischaemic zone as well as the balance between the thrombotic tendency and the fibrinolytic system. Three degrees of ischaemic injury have been described which may help determine the practicability of tissue salvage.<sup>17</sup> Tolerable ischaemia, in which the coronary flow is

reduced by up to 50% and the tissue energy stores are hardly depleted, is tolerated reasonably well. Critical ischaemia, in which the coronary flow is reduced by as much as 80%, causes a rapid reduction in energy stores and tissue is jeopardized within minutes. Reperfusion within  $\frac{1}{2}$ –4 hours can lead to recovery of some of the tissue. In lethal ischaemia the reduction in flow exceeds 80% with a very rapid depletion of energy stores and death or necrosis of tissue. It seems reasonable to speculate that patients with tolerable ischaemia will do well with medical treatment; patients with critical or lethal ischaemia might be further helped by thrombolysis, bypass surgery or percutaneous transluminal angioplasty.<sup>18</sup>

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