Editorial

Successful and unsuccessful coronary thrombolysis

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Coronary thrombosis is a consequence of the exposure of subendothelial connective tissue, including types I and III collagen, to platelets passing over an atheromatous plaque.¹ This exposure may be the result of either superficial or deep intimal injury to the plaque; the two injury processes differ in some important aspects.²

Deep injury is the result of tears or fissures that extend from the arterial lumen into the depths of the intima and lead initially to the formation of thrombus within the plaque, which rapidly alters in shape and increases in size. A plaque undetected as causing a significant stenosis at angiography may subsequently undergo fissuring.^{3,4} Intraluminal thrombus subsequently forms over the tear and is at first dominated by platelets. The final occluding thrombus is, however, rich in fibrin and red cells with few platelets.^{3,4}

In superficial intimal injury the endothelium alone is lost; there is no deep intimal tear and thus no intraplaque thrombosis. Factors predisposing to a loss of the endothelial coat include a high grade stenosis and infiltration of the intima by monocytic cells containing lipid. Necropsy studies show that deep injury of the intima is three times more likely to be associated with occlusive thrombi than superficial injury.^{5,6}

Fibrinolytic treatment often, but by no means always, restores antegrade flow in an occluded coronary artery.^{3,7,8} This is not surprising to the pathologist because the final stage of an occluding thrombus, and in particular any distal propagation of the thrombus, is almost entirely composed of a loose network of fibrin packed with red cells, which would be expected to be susceptible to lysis. Thrombolytic

treatment can, however, only reverse the thrombotic sequence of events to leave the residual plaque, which may have grown rapidly having an exposed intimal tear or merely have been denuded of endothelium. Clinical experience has led to the increased recognition of the short term factors that predispose to further occlusion from recurring intraluminal thrombus.⁹

The effect of thrombolysis on the coronary lesion

The process of recanalisation after fibrinolysis in the artery subtending a regional myocardial infarct has been followed by high resolution angiography.³ As soon as some antegrade flow was restored, a lobulated mass of thrombus was seen in the lumen and adhering to a high grade stenosis which was often irregular in outline. Initially flow was re-established in the space between the vessel wall and the thrombus, which steadily became smaller; but a portion of mural thrombus commonly resisted lysis for some time.¹⁰ In some reopened arteries (<20%) the appearance of a small crater (aneurysm) suggested that the intraplaque thrombus had also been lysed.³ Complex irregular stenoses with residual intraluminal filling defects may persist up to a month after recanalisation.¹¹ Some arterial occlusions that were also presumed to be caused by thrombosis could not be reopened by thrombolytic treatment.

The rapid increase in the numbers of reports on the clinical aspects of fibrinolysis for acute coronary occlusion has not been matched by necropsy reports of either successful or unsuccessful fibrinolytic treatment and several important questions, which could have been answered by such studies, remain unanswered. Two papers in this issue of the *British Heart Journal* partly redress this imbalance.

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Onodera and his colleagues studied the pathological findings in 21 arteries in which occlusion had been treated by selective intracoronary fibrinolysis with urokinase.¹² This was successful in 15 and unsuccessful in six vessels; all the patients died within a week from cardiogenic shock or cardiac rupture. In 14 of the fifteen successfully reopened arteries all the intraluminal thrombus was removed, and there was a plaque fissure with residual intraplaque thrombus in 13. In the six arteries that were not reopened, residual thrombus remained within the lumen in five and there was also plaque fissuring. This study therefore confirmed the dominant role of plaque fissuring in invoking thrombosis, but found no clear morphological reason for the failures to reopen—except that in all six there was a proximal patent branch vessel that might have diverted flow of the fibrinolytic agent from the thrombus. None of the three occluded circumflex arteries was reopened.

The study by Richardson and his colleagues of five arteries that were successfully reopened by intravenous streptokinase also found that intraluminal thrombi were absent but found an underlying residual plaque fissure in only one artery.¹³ In three arteries that remained occluded after thrombolysis, intraluminal thrombus was still present and there was an underlying deep intimal injury caused by a plaque fissure. If the pathological techniques were sound, and the methods described in the paper suggest that they were, these findings imply that thrombosis caused by superficial intimal injury is more easily treated by fibrinolytic treatment than that resulting from deep intimal injury.

There are good theoretical reasons why thrombi caused by major plaque fissures might be difficult to treat and might need more specific fibrinolytic agents, higher doses for longer periods, or intracoronary injection. Some fissures are so large that a flap of intima is raised, with extrusion of a plug of cholesterol and fragments of collagen which occlude the lumen. In other instances the intrainimal component of thrombus is so large that occlusion is the result of the mass of thrombus expanding the plaque itself. The fibrinolytic agent may not reach the interior of the plaque in all such cases; but the subsequent appearance of a small crater with overhanging edges in the angiogram suggests that it has in some reopened arteries.³ Finally, a component of the intraluminal thrombus may be inherently more resistant to lysis; sequential angiograms suggest that this may be the area over the fissure itself.³ Such sealing of the fissure orifice may be of benefit because it prevents more blood entering and expanding the plaque.

The overall message of the two papers is that the bigger the event in the intima that caused thrombosis

the more difficult it may be to reopen the vessel by thrombolysis.

In an earlier necropsy study of arteries after recanalisation there was little evidence that fibrinolytic treatment had led to continuing growth of the plaque because of bleeding from the lumen into the intima, except when angioplasty and fibrinolysis were performed together.¹⁴ Severe haemorrhage was seen around the angioplasty site in four patients who had been treated with fibrinolysis; in one the haematoma compressed the lumen externally. In contrast, five patients treated by angioplasty alone did not have such haemorrhage and in nine patients treated by streptokinase alone there was no recent intraplaque haemorrhage. The risk of combining angioplasty with fibrinolytic treatment derives from the intimal splits that are an integral part of successful procedures to relieve stenosis and that can extend into the medial/intimal junction in a plane in which there is a natural cleavage, allowing a haematoma to form. This plane is not entered by the intimal tears of natural plaque fissures.

The effect of thrombolysis on the myocardium

Restoration of flow to an infarcted area of myocardium leads to a striking and characteristic naked eye appearance at necropsy of haemorrhagic infarction (fig). A review of 93 necropsies of deaths after fibrinolytic treatment showed that 43% of the infarcts were red, whereas 95% of cases without reperfusion had a pale anaemic infarction.¹⁴ The myocardium was red because of extensive haemorrhage into the interstitial tissues between the myocytes.¹⁵ Interstitial haemorrhage is usually attributed to reperfusion of a capillary bed in which the endothelium has been damaged by hypoxia. Haemorrhagic infarction was reported to be less common after reperfusion by angioplasty without thrombolysis¹⁴ suggesting that the thrombus or the lytic agent might release substances that damage the capillary endothelium.

A red infarction is of special consequence only if the haemorrhage extends outside the area of myocyte necrosis or alters the progress of repair by fibrosis. In animal models in which reversible ligation of the coronary artery was used to re-establish flow to an area of infarction, haemorrhage did not extend outside the area of myocardium at risk even when fibrinolytic treatment was given.¹⁶ Nor did careful necropsy studies in man suggest that haemorrhage extended outside the areas in which there was evidence of ischaemic damage to myocytes.^{13 15}

Some claim that intramyocardial haemorrhage can become so extensive that it prevents the expected

Figure Haemorrhagic infarction seen at necropsy in a reperfused area of ischaemic necrosis.

improvement in ventricular function after successful reperfusion,¹⁴ but there is no firm proof of this. There are reports in some patients of pooling of angiographic media within the myocardium after fibrinolytic treatment.^{17,18} These patients probably developed an intramyocardial haematoma; which raises the question whether the risk of myocardial rupture is higher after fibrinolysis. A further possible factor predisposing to rupture is a suggested delay in repair by fibrosis in haemorrhagic infarcts.¹⁹ The evidence for this in man is based largely on a comparison of the histological appearances of an anaemic infarct and a haemorrhagic infarct in the same patient. The clinical evidence that both infarcts were the same age was not strong, and the hypothesis was not confirmed in experimental models of haemorrhagic infarction.²⁰

Five (24%) of the series of 21 patients reported by Onodera *et al* who died soon after fibrinolytic had external cardiac rupture,¹² whereas cardiac rupture was reported in 10 and 20% in two necropsy studies of in hospital infarction without fibrinolytic treatment.^{21,22} External rupture of an infarct may occur early (within 24 hours) if there is shearing at the border between viable and non-viable myocardium, or later if an established infarct expands and softens.²³ Two large multicentre studies suggested a slight preponderance of early deaths (0–1 day) in those treated with streptokinase, and analysis of the data indicated that the preponderance was the result of cardiac rupture, which was reduced in frequency by intravenous atenolol.^{24,25} If the myocardium ruptures some time after the onset of infarction, an endocardial tear and intramyocardial haematoma often precede the formation of either a haemopericardium or ventricular aneurysm. This process could be

exacerbated by fibrinolytic treatment. Large trials of fibrinolytic treatment in which the cause of death is accurately established by necropsy will be needed to establish whether this is so. In the ISAM trial there were 10 cases of cardiac rupture in the treated group and 13 in the placebo group²⁶; in the ISIS-2 trial there were more cardiac ruptures in the placebo group than in those treated with streptokinase (76/74), aspirin (81/69), or both (38/31).²⁷ A review of the reported data from eight trials up to 1979 showed equal numbers of cardiac ruptures in the treated and placebo groups.²⁸ If fibrinolytic treatment has any effect on late cardiac rupture it is likely to reduce the rate slightly because it limits infarct size.

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