Jubilee Editorial

Coronary thrombolysis

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Fifty years ago, when the Cardiac Society of Great Britain and Ireland was founded, myocardial infarction was a well recognised, but hardly a commonplace, diagnosis. A quarter century before, Obrastzow and Straschenko,¹ and then Herrick,² had recognised the clinical syndrome of coronary thrombosis, and in the intervening years Pardee,³ Parkinson and Bedford,⁴ and Wilson *et al*⁵ had defined the crucial role of electrocardiography in diagnosis. Yet Gilchrist, president of the Cardiac Society in its foundation year, had diagnosed the first case of myocardial infarction to be recognised in the Royal Infirmary of Edinburgh less than a decade earlier. It could be argued that in any event diagnosis of myocardial infarction in 1937 was of prognostic, rather than therapeutic, importance, because apart from analgesia and bed rest (for at least a month, very strict for the first fortnight⁶) there was little else to offer: quinidine for ventricular arrhythmias; digitalis for atrial fibrillation; mercurial diuretics. There were no bedside monitors, defibrillators, β blockers, or loop diuretics. Yet, ironically, Tillett and Garner had already identified the fibrinolytic activity of streptococci,⁷ heparin was in use for venous thrombosis,⁸ and within five years coumarin anticoagulants would have their first trials.⁹ It took another twenty years before these concepts were first assembled into a fundamental attack on the immediate cause of infarction.¹⁰

How does it work?

Coronary thrombosis, usually at the site of a ruptured atheromatous plaque, causes the majority of acute myocardial infarcts.¹¹⁻¹³ The thrombus can

be dissolved by intracoronary or intravenous administration of thrombolytic drugs without causing unacceptable bleeding complications.¹⁴⁻¹⁶ Assessment of success in restoring coronary patency is complicated by spontaneous reperfusion.^{17 18} Coronary patency rates assessed by a single angiogram 90 minutes after thrombolytic treatment are usually 15-20% higher than reperfusion rates in vessels shown by pretreatment angiography to be occluded. On the other hand, the delay introduced by pretreatment angiography may reduce the likelihood of successful thrombolysis. The patency rate associated with intravenous streptokinase is probably in the range 55-75% if treatment is given during the critical period when limitation of myocardial damage is possible.¹⁶ About 70% of reperfused vessels are left with a significant degree of coronary stenosis at the site of initial occlusion.^{19 20} The rate of early reocclusion is high in vessels with a very tight residual stenosis,²¹ but it is arguable whether the limited amount of blood flow that such vessels provide is of much value in maintaining myocardial viability. In patients with lesser degrees of obstruction the severity of the residual stenosis tends to diminish with time.²²

Estimates of reocclusion rates after coronary thrombolysis range from 12% to 40%.^{16 23} There was clinical or angiographic evidence (or both) of reocclusion in 15% of the first 80 patients treated in Edinburgh who were followed up for a year or longer. Half the reocclusions occurred within the first week and three quarters within the first month.

Is it worth while?

Does coronary thrombolysis improve outcome in terms of survival and ventricular function, and which patients should have thrombolysis? Early trials were too small to answer these questions or not

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designed to answer them. A pooled overview by Yusuf and colleagues suggested an increase in survival of 10–15% that was independent of any treatment delay within the first 24 hours,²⁴ but more recent large individual studies give a different view. In the GISSI study 11 806 patients (out of 31 826 screened for entry) were randomised to receive either placebo or 1 500 000 units of streptokinase infused over an hour.²⁵ Twenty one day survival was 10.7% in the treated group and 13.0% in the untreated group ($p < 0.0002$)—a reduction in mortality of 17%. Prospective stratification according to the delay between time of onset and symptoms indicated that the effect was almost entirely the result of improved survival in the groups treated within three hours of infarction (9.2% *vs* 12%) or between three and six hours (11.7 *vs* 14.1%). When the results in over 1000 patients treated within one hour were analysed an even greater effect was found—mortality was 8.2% in the treated group and 15.4% in the untreated group, an improvement of 46% in the chances of survival.

The Netherlands interuniversity study confirmed the importance of early treatment in 533 patients randomised to a control group or a streptokinase group with or without coronary angioplasty. Infarct size (measured by plasma hydroxybutyrate dehydrogenase activity) was reduced by 51% in patients treated within an hour, by 31% in those treated between one and two hours, and by 13% in those treated between two and four hours.²⁶ Left ventricular ejection fraction, measured by predischARGE cineangiography, was higher after thrombolysis both in patients with anterior infarcts and in those with inferior infarcts.²⁷

The measurement of left ventricular function after infarction and thrombolysis is complex and results depend on the technique used and the time it is applied. Gated blood pool radionuclide ventriculography probably underestimates the effects of inferior infarction, whereas cineangiography must take account of changes in phase of left ventricular wall movement as well as changes in amplitude. In the GISSI study the reduction in mortality was most pronounced in those with anterior infarction—survival after inferior infarction was good in both the treated and untreated groups. Improved survival was also more likely after first infarcts than after recurrent infarcts, perhaps because these are associated with reduced myocardial reserve and need more effective restoration of perfusion than that provided by the GISSI protocol. The importance of early treatment in preserving myocardial function accords with laboratory studies of the rate of myocardial necrosis after coronary occlusion.²⁸ Very early treatment may not only limit infarction but may also prevent it.^{29 30}

Who should get thrombolytic treatment?

The most obvious message coming from these clinical trials is that patients with anterior infarcts who have had major symptoms for less than three hours are the most likely to benefit. Clinical trials may produce their own artefacts, however, and uncertainty over the duration of symptoms may exclude patients with “stuttering” infarction who might benefit particularly. Global measurements of left ventricular function are also more sensitive to anteroapical akinesis than to the changes induced by right coronary artery occlusion. At present, it seems reasonable to propose that whatever the duration of symptoms patients with persistent ischaemic chest pain and ST elevation that are unresponsive to nitrates and patients with unstable angina and angiographically demonstrated intracoronary thrombus should be considered for thrombolysis.

The main contraindication to coronary thrombolysis is a risk of haemorrhage because of known peptic ulceration, head injury, traumatic resuscitation, or recent surgery. The individual risks must be weighed against the potential benefits.

How should it be done?

For practical reasons the intravenous route is much more widely applicable than the intracoronary one.³¹ Streptokinase is by far the most widely used thrombolytic drug. The cost of urokinase in many countries remains prohibitive, but its relative lack of antigenicity may be useful for repeated treatments. Tissue plasminogen activator^{32–34} and acylated plasminogen streptokinase complex (APSAC) (BRL 26921, Eminase)³⁵ are likely to be marketed in some countries in the near future, but at present they are available only for use in research studies. The most popular regimen for giving intravenous streptokinase is that developed by Schroder and colleagues¹⁵ from the original “high dose, short time” concept of Breddin *et al.*³⁶ 1 500 000 units of streptokinase are given intravenously over 60 minutes in 100 ml of 5% glucose. This may be preceded by chlorpheniramine 10 mg and a steroid—for example hydrocortisone 100 mg—to suppress allergic reactions. The possible role of platelets has been acknowledged in some regimens in which aspirin (100–300 mg) is given orally or intravenously (no parenteral aspirin preparation is currently available in the United Kingdom). Thrombolytic treatment should not distract attention from good medical care with analgesia, arrhythmia monitoring, and treatment of cardiac failure. Short term β blockade may help to protect the myocardium during thrombolysis, and this treatment is currently being evalu-

ated in at least two trials. Nitrates on their own are seldom effective in restoring coronary patency, but they may improve and maintain patency induced by thrombolysis.²⁹ On the other hand, excessive doses of nitrates may produce deleterious haemodynamic effects, especially in inferior infarction.

Indiscriminate venepuncture should be forbidden, and a single cannula is usually sufficient for blood sampling and drug administration. If they are needed, pacemaker electrodes or Swan-Ganz catheters should be inserted via an antecubital or femoral vein: subclavian puncture is safer once the initial wave of thrombolysis has passed. In about 50% of patients in whom an occluded vessel is reperfused this will be signalled by an arrhythmia—usually a short burst of idioventricular rhythm, but 5–10% will have ventricular tachycardia or fibrillation. Most, but not all, patients show a reduction in ST segment elevation.

Follow up after thrombolysis

Ideally an intravenous thrombolytic agent should be given as early as possible after infarction—perhaps at home or in an ambulance—and on arrival at hospital the patient should be taken immediately to the catheter laboratory.^{26 27} If the infarct related vessel is not adequately perfused, mechanical perforation with a guide wire or immediate angioplasty or both can be done. It can be argued^{37 38} that immediate angioplasty of a residual stenosis in a patent vessel will improve perfusion and help preserve the myocardium, but this remains to be tested in controlled trials.

Even if coronary angiography or angioplasty facilities are not immediately available it is worth while to give intravenous thrombolytic treatment. Reperfusion can often be inferred from relief of pain, reperfusion arrhythmias, sudden reduction of ST elevation, and a rapid release pattern of plasma creatine kinase activity. Patients whose condition remains unstable with recurring pain and fluctuating ST elevation should be transferred for emergency angiography; the remainder can have elective angiography later. There is no answer yet to the question of whether subsequent intervention in the latter group should be based on angiographic appearances or on evidence of persisting myocardial ischaemia such as angina, a positive exercise test, or perfusion scanning.

Our present policy is to perform elective coronary angiography four to six weeks after infarction in patients who have post-infarct angina or who are limited by symptoms to less than five minutes' exercise on a standard Bruce protocol. We refer patients for angioplasty or bypass grafting according to the

angiographic appearances. Using these criteria, which are similar to those we use for post-infarction patients who have not had thrombolysis,^{39 40} we refer approximately 25% of post-thrombolysis patients for coronary angioplasty or bypass grafting within a year of treatment. This proportion is similar to the intervention rate reported by the Belfast group.⁴¹ In their view, however, elective angiography should be performed in all patients. Many practitioners of thrombolysis believe that anticoagulation, at least for the first month after thrombolysis, is important in preventing reocclusion—but unfortunately evidence for this tends to be anecdotal rather than based on the results of comparative trials. It is our policy to anticoagulate with heparin for three days followed by warfarin for up to three months. The current Intravenous Short Term Infusion of Streptokinase and GISSI 2 trials may provide more evidence for or against the importance of anticoagulation, and paradoxically anticoagulation may prove to be more important with the more thrombus selective agents than with streptokinase.

What proportion of myocardial infarct patients should have thrombolytic treatment?

Murray *et al* concluded that only a small proportion of patients admitted to a London coronary care unit fulfilled the criteria for thrombolytic treatment.⁴² Jagger and colleagues from Birmingham were more optimistic, and reckoned that thrombolysis would have been suitable for 50% of admissions.⁴³ There are two problems with this type of study; first, the rigid entry criteria that are appropriate for a clinical trial of a new drug may not be so appropriate for therapeutic use. Second, the denominator should really be the number of patients having infarcts in the community—which is much more difficult to measure than the number of admissions. Several clinical trials are under way to study methods of administering thrombolytic treatment before hospital admission. Their results may provide a further incentive for the establishment and funding of rapid response or rapid admission schemes, which will need to be tailored to individual local requirements.

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