Thrombolytic therapy and myocardial infarction

C. L. BERRY

From the Department of Pathology, Guy's Hospital Medical School, London

SYNOPSIS Examination of 27 hearts from patients treated by streptokinase following myocardial infarction showed one major histopathological difference from controls, the presence of massive interstitial haemorrhage into the necrotic tissue in some cases. This change is presumably related to the re-establishment of the circulation to infarcted areas.

As part of a multicentre trial of the effectiveness of streptokinase in acute myocardial infarction a comparative study of the morbid anatomy and histopathology of hearts from treated and untreated patients dying within the trial has been carried out. The details of the design of the trial, the criteria for inclusion, and the prognostic criteria by which patients were allocated to particular categories are discussed in detail elsewhere (Aber, Berry, Caeson, Hamblin, Howitt, MacIver, Portal, Rafertey, Rousell, and Stock, 1975).

The only requirement for entry to the trial was a diagnosis of myocardial infarction within the previous 24 hours. In the final analysis the diagnosis of acute infarction was not accepted unless there was a significant elevation of either serum aspartate aminotransferase (glutamic oxaloacetic transaminase, SGOT) or lactate dehydrogenase (LDT) or both. Both sexes were accepted and no upper age limit was prescribed. Patients were excluded from the trial if there was a history of a known haemorrhagic disorder, a gastrointestinal haemorrhage within the previous six months, or a history of peptic ulceration. A recent surgical operation, diastolic blood pressure over 120 mmHg, or a history of significant hypertension or liver disease were also grounds for exclusion, as were previous streptokinase therapy or previous entry to the trial. Once the decision to admit a patient to the trial was made he or she was randomly allocated to the streptokinase or control group.

Streptokinase was administered by intravenous infusion in 25 ml of 5% dextrose. A loading dose of 250 000 iu was given over a period of 30 minutes. In the succeeding 7½ hours a continuous infusion of 750 000 units in a volume of 200 ml was followed by 750 000 iu in each of two further eight-hour periods.

Thus a total of 2 500 000 iu was administered in a volume of 625 ml over a period of 24 hours.

Neither the streptokinase nor the control group was given any anticoagulant therapy unless this became clinically necessary following thrombo-embolic events.

For analysis the patients in the trial were grouped by means of a simple prognostic index modification from Norris (see Aber *et al*, 1975) based on age and blood pressure at the time of entry. This index was one in which the sum of the individual scores for age and systolic blood pressure assigned patients to one of three groups A, B, or C. Group C contained the patients deemed to be at highest risk by virtue of their greatest age and lowest blood pressure on admission.

Five hundred and seventy-six patients of the 639 admitted remained in the trial after the exclusion of 58 in whom the diagnosis of myocardial infarction could not be confirmed, and five cases in which the protocol was not followed. There remained 282 patients in the streptokinase group and 294 controls. The two groups were closely comparable with regard to age, history of angina and previous infarction, interval between infarction and admission, and initial blood pressure. At the conclusion of the pathological study there had been 55 deaths in the control group and 57 in the streptokinase group.

Intact hearts were sent to the author from centres at Hull, Stoke-on-Trent, Southend, Manchester, and Harrow.

Material and Methods

Twenty-six hearts from control patients and 27 from streptokinase treated patients were available for examination. At the time of study the status of each heart was unknown. Subsequently two control hearts were excluded because of extensive dissection

Hospital:
Patient name:
Hosp. No:
Group: Trial No:
Time interval from infarct to death hours
Serious external cardiac massage: YES ☐ NO ☐
(Please tick)

Fig 1 Diagram of record card

before dispatch and two streptokinase hearts when it was found that these patients had had no thrombolytic therapy before death.

The outline of any visible recent or old infarction was outlined on a record form (fig 1, after Spalteholz (1924) on which the site and nature of coronary artery lesions was also noted, these vessels having been cut transversely at 0.5 cm intervals. A comment on the patency of the coronary ostia was added. The thickness of each ventricle was measured, and blocks were taken from the edge of any visible infarctions, from the left and right ventricles, and from the posteromedial papillary muscle of the left ventricle. In cases in which death had occurred before macroscopically visible evidence of infarction had developed, electrocardiographic data were obtained to enable blocks of relevant areas to be taken. Sections were stained by haematoxylin and eosin (H and E), elastic-Van-Gieson (EVG), and a modification of the acid fuchsin technique described by Selye (Berry, 1967). Arterial sections were stained by Lendrum's MSB in addition to H and E and EVG stains. Where appropriate 'step' or serial sections of arterial occlusive lesions were also cut.

Results

In 12 control hearts and 11 streptokinase treated

patients there was evidence of ischaemic injury antedating the episode causing hospitalization. In only seven cases (4 control and 3 streptokinase) was there a previous history of infarction. The evidence consisted of left ventricular fibrosis and thinning (fig 2) which in two instances was aneurysmal in type (fig 3), or the histological changes of interstitial fibrosis.

Fig 2 Thinning of the left ventricular wall. Evidence of recent infarction is seen below the scale (control heart).

Fig 3 Aneurysmal dilatation of the left ventricle (control heart).

Fig 4 Endocardial thrombus overlying infarcted myocardium (streptokinase treated heart).

Ten control hearts and 11 streptokinase treated patients showed extensive endocardial thrombosis (fig 4); subsequent enquiries revealed that one case in each group had evidence of a cerebrovascular accident at necropsy, that in the control group being a cerebral haemorrhage and in the test group a basilar artery thrombosis.

There were nine cases with myocardial tears, seven of which had apparently occurred ante mortem. Table I shows the time after infarction at which the myocardial rupture occurred. In one case in each group the tear was in the ventricular septum (fig 5).

In 11 cases there was no conventional histological evidence of myocardial infarction, although six of these showed fuchsinophilia of varying degrees,

Time (hours) after clinical onset of infarction	
Control	Streptokinase treated
16	2
23	13
48	34
70	36
	42

Table I Myocardial rupture

Fig 5 Ventricular septal defect following myocardial rupture. An extensive haemorrhagic infarction is seen (streptokinase treated heart).

indicating muscle fibre injury. Table II shows the interval between clinical onset and death in these patients.

In 13 controls and 14 streptokinase treated patients, recent occluding lesions were found in the coronary vessels. Thrombosis of a lumen greatly reduced in diameter by atheroma was found most frequently (in 7 controls and 11 treated cases). Plaque fissure (Constantinides, 1966) or haemorrhage into a

Interval between clinical onset and death (hours)

<i>Control</i>	<i>Streptokinase treated</i>
4 ¹	4 ¹
6 (2) ¹	5
7	8
11 ¹	14 ¹
12	
17 ¹	

Table II *No conventional evidence of infarction*¹These cases showed myocardial fuchsinophilia.

plaque was found in six controls and three streptokinase patients. In three hearts in each group severe stenosis (lumen less than 10% of original diameter) of large coronary arteries was the only lesion found. In six controls and eight treated hearts evidence of a long-standing occlusion was found, most frequently a calcified atheromatous mass, but represented in some instances as a partly recanalized vessel containing many haemosiderin filled macrophages.

Fig 6 *The edge of an haemorrhagic infarction from a streptokinase treated heart. Ischaemic injury of adjacent myocardium is evident. (H and E $\times 83$).*

There was one striking difference between the two groups. Three patients exposed to thrombolytic therapy had haemorrhagic myocardial infarctions (see fig 5). Two of these had ruptured. Microscopically massive red cell extravasation had occurred into the myocardium which was unrecognizable in small fields. The edge of one such lesion is seen in figure 6. These three lesions were found in cases dying 48, 96, and 108 hours post infarction respectively.

In general, the progression of histological changes in the resolution of the infarctions resembled that described by Lodge-Patch (1951). There was an impression that development of the cellular reaction at the margin of necrosis occurred more rapidly in the streptokinase treated patients, but too few hearts were available to assess this point critically.

Discussion

The two groups differed significantly in only one particular, the development of haemorrhagic infarction. This change has been reported previously after thrombolytic therapy, Schachenmayr and Haferkamp (1972) describing four streptokinase treated patients, one with myocardial rupture. Phenprocoumon had been given in these cases after completion of thrombolytic therapy, but the change was not seen after heparin alone. These authors pointed out that in myocardial infarction one may see small interstitial haemorrhages (as described by Fischer (1963)) but these were seldom extensive or disruptive. Microscopical evidence of injury to the myocardium is evident after a few hours in some infarctions and myocardial cell death has obviously occurred before this (Jennings, Sommers, Smyth, Flack, and Linn, 1960). It is possible that the re-establishment of circulation to such areas after thrombolysis, or the prevention of thrombosis in the microvasculature at the edge of the necrotic area, may produce subsequent extravasation of blood. Arterial thrombi were present in the vessels supplying the infarcted areas in two of the three 'haemorrhagic' cases; presumably blood had reached the area via collaterals in these instances. An acceleration of the rate of development of the cellular reaction to infarction may also depend on recirculation, as found in the dog (Jennings, Sommers, Kaltenbach, and West, 1964), but there is insufficient material in this series to document this possibility fully.

The higher proportion of myocardial tears found when this series is compared with others (Sievers, 1966) is presumably related to the treatment of all cases in intensive care units where, without exception, vigorous resuscitative measures were taken as a

matter of course. This also accounts for the occurrence of rupture at an earlier stage in the natural history of infarction than is generally described.

The demonstration of fuchsinophilia, as evidence of early myocardial injury, proved a reliable technique in our hands providing rigorous controls were used. It was found to be more easily assessed than the change described by Bouchardy and Majno (1974). Fuchsinophilia demonstrates a reversible change, and myocardial ischaemia in experimental systems may be reversible if corrected within six hours (Cox, McLaughlin, Flowers, and Horan, 1968). This may be true in man, and much shorter periods have been considered to be critical when therapeutic aims in thrombolysis are considered (Betty *et al.* 1973). It may be that thrombolytic therapy will be of most value in situations in which thrombosis is developing.

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