Early remodelling of coronary stenoses after thrombolytic treatment in patients with acute myocardial infarction

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Abstract

Objective—To assess the frequency of early remodelling of coronary stenosis morphology after thrombolytic treatment in patients with acute myocardial infarction.

Design—Coronary angiograms were analysed by a computerised edge detection analysis system. Coronary stenosis severity was measured and morphology classified as smooth or complex.

Patients—Coronary arteriograms were obtained approximately 90 min and 24 h after thrombolytic treatment from 40 patients with acute myocardial infarction.

Main results—Stenosis morphology was complex in 22 patients (65%) and smooth in 11 (32%) 90 min after thrombolysis. The morphology of 11 (50%) complex coronary stenoses and three (27%) smooth stenoses had changed at 24 h ($P < 0.05$). The transition from complex to smooth was associated with a reduction in stenosis severity from 65 (4)% to 51 (5)% ($P < 0.05$). The stenosis severity was 63 (4)% and 60 (5)% in those with persistently complex morphology, and 56 (7)% and 50 (5)% in those with persistently smooth morphology at 90 min and 24 h respectively (NS).

Conclusions—Transition of morphology from complex to smooth within 24 h is common. This transition is associated with a reduction in stenosis severity of a degree greater than that found in persistently smooth stenoses over the same interval. 50% of stenoses are smooth at 24 h.

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Keywords: myocardial infarction; stenosis morphology; coronary artery patency

Angiographic studies performed before and after thrombolytic treatment in patients with acute myocardial infarction show an incidence of reperfusion of between 60 and 75 per cent within 90 min.¹⁻⁸ Combined angiographic and histopathological studies⁹⁻²² have shown that the presence of acute coronary thrombus is usually associated with complex lesion morphology characterized angiographically by an irregular border. The severity of residual stenosis is variable²³ and despite successful thrombolysis 15-25 per cent of patients

develop early reocclusion.^{1,27} There is evidence that remodelling of residual stenosis occurs after treatment,²⁴ but the relation between early coronary stenosis morphology and remodelling has not previously been described. We therefore investigated the angiographic morphology and severity of the residual infarct related coronary stenosis at approximately 90 min and 24 h after the start of streptokinase or tissue plasminogen activator (rtPA) treatment in patients with acute myocardial infarction.

Patients and methods

STUDY PATIENTS

Forty consecutive patients (31 men and nine women of mean (SEM) (range) age 55 (7) (36-71) years presenting with their first myocardial infarction were included in the study. All presented with persistent chest pain typical of acute myocardial ischaemia of more than 30 min duration and electrocardiographic ST segment elevation (≥ 0.2 mV in $\geq$ two leads of the standard 12 lead surface electrocardiogram) resistant to a 2 mg intravenous bolus of isosorbide dinitrate. The duration of chest pain at the time of initiation of fibrinolytic treatment was < 6 h in all cases. Patients were included in the study only if they were able to give fully informed, written consent to the study. They were excluded from the study if any of the following were present: (1) conditions that increased the risk of haemorrhagic complication with thrombolytic treatment; (2) cardiogenic shock (systolic blood pressure < 80 mm Hg) or pulmonary oedema; and (3) severely impaired renal or hepatic function.

The study protocol was approved by the Research Ethics Committee of Hammersmith Hospital. As soon as possible after admission patients were transferred to the cardiac catheterization laboratory from the accident and emergency department or from the coronary care unit. After insertion of short femoral arterial and venous sheaths a bolus of 5000-10 000 IU of heparin was administered intravenously. Intracoronary isosorbide dinitrate (2 mg) was administered into the ostium of the infarct related artery followed by a 2 ml saline flush.

Fourteen patients received a continuous intracoronary infusion of streptokinase (5000 IU/ml normal saline at 1 ml/min). The streptokinase infusion was continued throughout the procedure until stable patency of the

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infarct related artery was achieved or a maximum dose of 600 000 IU had been administered (total duration 120 min). Some 14 patients received an intravenous infusion of 40 clot lysis MU of double chain rtPA (alteplase) over 90 min, followed by infusion of 20 MU over 5 h (cumulative dose 60 MU); 12 patients received four intravenous bolus injections of 10 clot lysis MU of double chain rtPA at 20 min intervals (total duration 60 min).

Coronary arteriography was repeated about 90 (range 60–120) min after the start of fibrinolytic treatment and also in the event of relief of chest pain or resolution of ST segment elevation. This coronary arteriogram is subsequently referred to as the 90 min arteriogram. At the end of the procedure the femoral arterial and venous sheaths were left in situ and the patients were transferred to the coronary care unit. Patency of the sheaths was maintained by slow infusion of heparinized saline and an intravenous infusion of heparin was administered over a period of 24 h to maintain an activated partial thromboplastin time of two to three times normal. An intravenous infusion of glyceryl trinitrate was administered at a rate of 1–10 mg/h titrated against systolic blood pressure. Oral aspirin (75 mg daily) and diltiazem (60 mg every 8 h) were prescribed. Coronary arteriography was repeated about 24 (range 18–36) h later. This coronary arteriogram is subsequently referred to as the 24 h arteriogram. After this arteriogram patients received routine clinical care.

QUANTITATIVE CORONARY ANGIOGRAPHY

The state of perfusion of the infarct related vessel on the coronary arteriograms was graded by two blinded observers from 0 (complete occlusion) to 3 (full patency), according to the classification criteria of the Thrombolysis In Myocardial Infarction (TIMI) Study Group.²⁵ We defined coronary occlusion as TIMI grade 0 or 1 and patency as grade 2 or 3. Coronary artery stenoses were analysed in random order using quantitative computerised analysis with an automated edge contour detection analysis system (Computerized Angiographic Analysis System (CAAS), Version 2V2; Pie Data Medical, Maastricht, The Netherlands).²⁶ End diastolic frames from each arteriogram were selected for analysis. The angiographic catheter was used as a scaling device and this together with pincushion distortion correction allowed the diameters to be recorded as absolute values (expressed in mm). Recorded variables before, 60–120 min after thrombolysis, and after 24 h were: (1) the location of stenoses, defined as the site of minimal lumen diameter relative to side branch origins; (2) the minimum diameter of stenoses in mm; (3) minimum luminal diameter as a percentage of that of the adjacent “normal” segment; and (4) qualitative and quantitative classification of stenosis morphology.

Stenoses were morphologically classified qualitatively as smooth (concentric or eccentric) or “complex” by two blinded indepen-

dent observers on the basis of visual inspection of arteriograms recorded in two orthogonal projections. This classification of stenoses into concentric or eccentric was compared with that obtained by computerised symmetry analysis (CAAS symmetry index)^{27,28} of the same coronary lesions. The symmetry index was measured from the predefined centre line of the vessel and given a value between 0 and 1, with 1 representing a perfectly concentric lesion and 0 representing the most severe case of eccentric lesion. Concentric stenoses were defined as those producing symmetric narrowing, with smooth borders or only very mild irregularity (symmetry index >0.5–1) that looked similar in orthogonal projections. Eccentric stenoses were defined as asymmetric narrowing with smooth borders and a broad neck (symmetry index 0.0–≤0.5). Complex stenoses were defined as asymmetric narrowings with irregular borders or overhanging edges, or type II of Ambrose *et al.*,^{17,18} or both, or with an “abrupt proximal face”¹⁹ or a “rough” or “sawtooth” component.¹⁹

Coronary stenosis remodelling was defined as a change in morphology from smooth (eccentric or concentric) to complex, or to occlusion, and vice versa. Clear angiographic evidence of intraluminal thrombus was found in three patients and was analysed as a part of the stenoses. A change in stenosis severity was not required to define remodelling. However, the completely occluded vessels at 90 min were unclassifiable. Quantitative analysis of coronary arteriograms was carried out by two independent observers, who blindly reanalysed the films at a remote time for reproducibility of the method. No significant intra- or inter-observer variability was found ($F = 0.3$, $P = 0.75$). The inter/intraobserver variability for the qualitative assessment of stenosis morphology was 95 per cent and 98 per cent respectively and any differences in classification were resolved by consensus. Agreement between computer symmetry analysis and qualitative assessment was 98 per cent for lesions imaged at baseline. In a separate study, we analysed the intra- and inter-observer variability of the CAAS system in our institution. Twenty four arterial segments were analysed by two independent observers and reanalysed at a remote time. The mean intraobserver variation, expressed as the standard error of the estimate (SEE), was 0.12 mm. The interobserver variation (SEE) was 0.10 mm.

STATISTICAL ANALYSIS

All data are expressed as mean (SEM). For comparisons of haemodynamic data and coronary artery diameters (in mm), a one-way analysis of variance, with an allowance for repeated measures, was performed. When an F value was found to be significant, a two tailed Student's t test for paired observations with the Bonferroni correction was used to test differences among means. Discrete data were analysed by the χ^2 test. A P value < 0.05 was considered significant.

Results

PATIENT CHARACTERISTICS

Twenty six patients received rtPA within 3.0 (0.22) h of the onset of symptoms: 10 had anterior ST segment elevation with left anterior descending artery occlusion, 11 had inferior ST segment elevation with right coronary artery occlusion, and five had true posterolateral ST segment change with dominant circumflex coronary artery occlusion.

Fourteen patients received streptokinase within 2.8 (0.32) h of the onset of symptoms: six had anterior ST segment elevation with left anterior descending artery occlusion, five had inferior ST segment elevation with right coronary artery occlusion, and three had true posterolateral ST segment change with dominant circumflex coronary artery occlusion.

The infarct related coronary arteries were patent (TIMI grade 2 or 3) in two patients receiving streptokinase and two receiving rtPA before thrombolytic treatment, but with an angiographic filling defect suggestive of intraluminal thrombus; these patients were included in the study. The infarct related stenosis morphology was complex in two of these patients.

STENOSIS SEVERITY AND MORPHOLOGY 90 MIN AFTER TREATMENT

Some 90 min after fibrinolytic treatment the infarct related artery was patent in 34 patients (85 per cent) (12 after streptokinase and 22 after rtPA) with a minimum luminal diameter at the site of residual stenosis of 1.16 (0.10) mm. The residual stenosis morphology was complex in 22 patients (65 per cent) and smooth in 11 (32 per cent) ($P < 0.01$). There was no residual stenosis in one patient. The minimum luminal diameter was 1.07 (0.09) mm at complex stenoses and 1.19 (0.20) mm at smooth stenoses ($P =$ not significant). There was no difference in patency rate (86 per cent *v* 84 per cent) or minimum luminal diameter (1.12 (0.15) *v* 1.18 (0.13) mm)

between streptokinase and tPA treated patients.

STENOSIS SEVERITY AND MORPHOLOGY AT 24 H

At 24 h the infarct related artery was patent in 32 (80 per cent) patients (12 after streptokinase and 20 after rtPA) with a minimum luminal diameter of 1.33 (0.11) mm. The stenosis morphology was complex in 14 patients (44 per cent) and smooth in 16 (50 per cent), and there was no residual stenosis in two. The minimum luminal diameter was 1.15 (0.13) mm at complex stenoses and 1.32 (0.13) mm at smooth stenoses ($P =$ not significant). There was no difference in patency rate (86 per cent *v* 77 per cent) or minimum luminal diameter (1.32 (0.18) *v* 1.34 (0.14) mm) between streptokinase and rtPA treated patients.

CHANGE IN STENOSIS SEVERITY AND MORPHOLOGY

At 24 h remodelling of morphology was observed in 11 of 22 (50 per cent) complex coronary stenoses (four lesions had occluded and seven had become smooth) and in three of 11 (27 per cent) smooth stenoses (one lesion had occluded, one had become complex, and one had become a normal segment). The difference in the incidence of remodelling and reocclusion of smooth and complex stenoses over time was significant ($P < 0.05$). The transition of seven stenoses from complex to smooth was associated with a reduction in stenosis severity from 65 (4) to 51 (5) per cent ($P < 0.05$) and with an increase in the mean luminal diameter from 0.95 (0.15) to 1.41 (0.24) mm ($P < 0.05$) (table 1, figs 1 and 2). In contrast, in those with persistent complex morphology severity was 63 (4) and 60 (5) per cent, at 90 min and 24 h, and in those with persistent smooth ($n = 8$) morphology it was 56 (7) and 50 (5) per cent respectively ($P =$ not significant) (table 1).

Before thrombolytic treatment TIMI flow

Table 1 Minimum luminal diameter and severity after thrombolysis of complex stenoses with persistently complex morphology or transition to smooth morphology

No of stenoses	90 min			24 h		
	Morphology	Diameter (mm)	Severity (%)	Morphology	Diameter (mm)	Severity (%)
7	Complex	0.95 (0.15)	65.0 (4)	Smooth	1.41 (0.24)*	51.0 (5)†
11	Complex	1.16 (0.15)	63.0 (4)	Complex	1.321 (0.15)	60.0 (5)

* $P < 0.05$ compared with minimum luminal diameter at 90 min; † $P < 0.05$ compared with severity at 90 min. Student's paired *t* test.

Table 2 Patency of the infarct related coronary artery before, and 90 min and 24 h after thrombolytic treatment

Coronary patency (TIMI grade)	Arteries with remodelling			Arteries without remodelling		
	Before	90 min	24 h	Before	90 min	24 h
0	7	0	4	23	6	3
1	4	0	1	2	0	0
2	2	2*	0	0	1†	1
3	1	12	9	1	19	22

*One stenosis had TIMI flow grade 0 and another TIMI flow grade 1 at 24 h after thrombolysis. †TIMI flow grade 3 at 24 h after thrombolysis. TIMI, thrombolysis in myocardial infarction.

Figure 1 Coronary angiograms showing examples of remodelling of complex coronary stenoses to a smooth morphology 24 h after thrombolysis. Top: right coronary arteriograms (A) before, (B) during, and (C) 90 min and (D) 24 h after thrombolytic treatment. The occluded artery has become patent with a severe complex stenosis during treatment; the stenosis is less complicated at 90 min and mild and smooth at 24 h. Middle: right coronary arteriograms (E) before, (F) during, and (G) 90 min and (H) 24 h after thrombolytic treatment. The stenosis is complex before treatment; it is severe but less complex during treatment and a small piece of thrombus has broken off. It has become smooth but is still severe at 24 h. Bottom: left coronary arteriograms (I) before, and (J) 90 min and (K) 24 h after thrombolytic treatment. The stenosis remains complex at 90 min but is a little less severe. It has become smooth and very mild by 24 h.

grades 0, 1, 2, and 3 were found in 30, six, two and two arteries respectively. Some 90 min after thrombolytic treatment TIMI flow grades 0, 2, and 3 were found in six, three, and 31 arteries respectively. At 24 h after thrombolytic treatment TIMI flow grades 0, 1, 2, and 3 were found in 7, one, one, and 31

Figure 2 Coronary stenosis expressed as minimum luminal diameter in individual patients, before, and 90 min and 24 h after thrombolytic treatment. Mean (SEM) is shown.

arteries respectively (table 2). Of the 11 complex stenoses that remodelled between 90 min and 24 h, 10 were associated with TIMI flow grade 3 and one with TIMI flow grade 2 at 90 min. Of the three smooth stenoses that remodelled, two had TIMI flow grade 3 and one TIMI flow grade 2 at 90 min. Both the stenoses with TIMI flow grade 2 at 90 min had become completely occluded by 24 h. Table 2 shows the flow grades according to the presence or absence of remodelling.

Five of the 34 patent vessels became occluded at 24 h, three of six occluded vessels became patent at 24 h yielding a total of 32 patent arteries at 24 h. Three of eight occlusions at 24 h were unchanged from 90 min, but five had developed from stenoses which previously were relatively mild (73 per cent, 44 per cent, 55 per cent, 59 per cent, 64 per cent) and four of these were complex. Three occlusions at 90 min after thrombolysis had become patent at 24 h (two with smooth morphology and one complex).

Discussion

This study shows that considerable remodelling of residual coronary artery stenosis occurs in the first 24 h after initial patency has been obtained in response to thrombolytic drugs. Furthermore, the likelihood of remodelling is related to morphology of the residual lesion immediately after thrombolysis. Some 90 min after rtPA or streptokinase administration the infarct related artery was patent in 85 per cent of patients with a residual stenosis of variable severity in all but one patient. Sixty five per cent of these stenoses were of complex morphology and 32 per cent were of smooth. Remodelling of complex stenoses caused a transition between 90 min and 24 h to occlusion in 18 per cent and to smooth morphology in 32 per cent. Transition to smooth morphology was associated with a reduction in stenosis severity of a degree greater than that found in persistently smooth stenoses over the same time interval, the latter reaching a similar final luminal diameter at 24 h from a greater absolute diameter at 90 min.

CORRELATION BETWEEN ANGIOGRAPHIC LESION MORPHOLOGY AND HISTOLOGICAL FINDINGS IN ACUTE MYOCARDIAL INFARCTION

Previous studies^{17 19} have described the close association between type of stenosis morphology and acute coronary syndromes. Ambrose *et al*^{17 18 22} have shown that the type II eccentric lesion (smooth with narrow neck or irregular borders) is found in many patients with acute presentation of unstable angina and in those with acute or recent myocardial infarction without totally occluded vessels. Other angiographic studies have identified either intraluminal filling defects, consistent with thrombus, or eccentric lesions with irregular borders in patients with unstable angina.^{22 29 30} The type II lesion is the most common morphological finding in infarct related vessels after reperfusion with streptokinase. Comparison of postmortem angiographic and histological findings in patients with coronary artery disease has shown that these irregular lesions may represent not only sites of intraluminal partially occlusive or partially lysed thrombus but also of plaque rupture, plaque haemorrhage, or organised thrombus.^{11 20 21} At postmortem examination plaque rupture was found in 64 per cent of patients with unstable angina, 90 per cent of those with acute myocardial infarction and 38 per cent of those who had died suddenly and unexpectedly.³¹ Many patients in our study showed this complex stenosis morphology 90 min after coronary thrombolysis, but by 24 h 50 per cent of stenoses were smooth. As ruptured plaques would be expected to have a complex morphology it raises the possibility that at least 50 per cent of patients who survive a myocardial infarction probably have not had a plaque rupture. This is in contrast to postmortem studies^{11 20} in which a higher incidence of plaque rupture has been reported. It is conceivable that myocardial infarction due to plaque rupture is more likely to be fatal than those caused by superficial thrombosis.

The importance of thrombus in the development of coronary occlusion in acute myocardial infarction is firmly established on the basis of previous studies of thrombolytic therapy.³²⁻³⁴ The infarct related coronary artery patency at any selected time of study may represent only a transient phase of a dynamic event involving dissolution and reformation of intracoronary thrombus. The intensity of the thrombotic stimulus may be related to the degree of vessel injury, but a systemic alteration in blood coagulability or low blood flow velocity, or both, may determine which fissured plaques are complicated by thrombotic occlusion.

CORONARY LUMINAL REMODELLING

Changes in coronary stenosis severity and morphology have been observed after successful thrombolysis in patients with myocardial infarction.^{24 34} Davies *et al*²⁴ showed, at repeat angiography 2–10 days after thrombolysis, that globular filling defects seen in eight patients had disappeared, while linear filling defects persisted in seven of 14 cases. Furthermore, with an increasing interval between thrombolysis and angiography, the observed frequency of irregular lesions and the ulceration index decreased. These changes have been attributed to re-endothelialisation of the ruptured plaque, resorption of associated haemorrhage, dissolution of residual thrombus as a result of continuing fibrinolysis, and altered vasomotor tone due to loss of endothelial function.

The results of the present study show that remodelling is an early phenomenon with considerable change in morphology and stenosis severity occurring within 24 h of initial patency. The process of remodelling and stabilization of the coronary plaque is marked by either a tendency to smoother less stenotic lesions or reocclusion. This transition from complex to smooth stenosis morphology would be compatible with healing of ruptured atheromatous plaque, but also with the further dissolution of thrombus or a combination of both mechanisms. We did not have follow up angiographic data indicating that the remodelled stenoses remained stable after 24 h. Other clinical studies,²⁴ however, indicate that early angiographic appearance predicts reocclusion at 3 months and that smooth stenoses seem to be more stable than complex stenoses. It is uncertain to what extent this early remodelling reflects the natural history or the effect of treatment, which included aspirin and heparin. Serruys *et al*³⁵ found an improvement in the per cent diameter stenosis and plaque area in patients maintained on heparin treatment after thrombolysis with recombinant rtPA, but morphological characteristics were not examined.

Almost all the infarct related arteries in this study were either occluded or had TIMI flow grade 3 at 90 min and no definite relation between TIMI flow grade and remodelling was found.

CLINICAL IMPLICATIONS

Smooth residual lesions seem to be more stable than complex ones. The relatively rapid morphological change therefore probably indicates a rapid process of stabilisation of the active coronary lesion. Further studies are required to investigate whether additional treatment after thrombolysis can accelerate the transition to stability. Use of early coronary arteriography to detect complex lesions might then be used to identify a subgroup of patients requiring additional treatment such as angioplasty or anticoagulation.

Conclusions

The likelihood of remodelling depends on the morphology of residual coronary stenosis immediately after thrombolysis. Complex coronary stenosis morphology 90 min after thrombolytic treatment represents an unstable state which tends to change within 24 h, to either occlusion or a smooth residual stenosis of lesser severity. Smooth coronary morphology tends to remain stable with persistent patency.

- 1 Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction and improved survival: should the paradigm be expanded? *Circulation* 1989;79:441-4.
- 2 Braunwald E. Optimizing thrombolytic therapy of acute myocardial infarction (editorial). *Circulation* 1990;82:1510-3.
- 3 O'Rourke M, Baron D, Keogh A, Kelly R, Nelson G, Barnes C, *et al.* Limitation of myocardial infarction by early infusion of recombinant tissue-type plasminogen activator. *Circulation* 1988;77:1311-5.
- 4 Kennedy JW, Martin GV, Davis KB, Maynard C, Stadius M, Sheehan FH, *et al.* The Western Washington intravenous streptokinase in acute myocardial infarction randomized trial. *Circulation* 1988;77:345-52.
- 5 White HD, Norris RM, Brown MA, Takayama M, Maslowski A, Bass NM, *et al.* Effects of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med* 1987;317:850-5.
- 6 Bassand J-P, Faivre R, Becque O, Habert C, Schuffenecker M, Patiteau PY, *et al.* Effects of early high-dose streptokinase intravenously on left ventricular function in acute myocardial infarction. *Am J Cardiol* 1987;60:435-9.
- 7 Braunwald E. Coronary artery patency in patients with myocardial infarction. *J Am Coll Cardiol* 1990;16:1550-2.
- 8 Lierde JV, Geest H, Verstraete M, Werf VF. Angiographic assessment of the infarct-related residual coronary stenosis after spontaneous or therapeutic thrombolysis. *J Am Coll Cardiol* 1990;16:1545-9.
- 9 Duber C, Jungbluth A, Rumpelt HJ, Erbel R, Meyer J, Thoenes W. Morphology of the coronary arteries after combined thrombolysis and percutaneous transluminal coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 1986;58:698-703.
- 10 Wilensky RL, Bourdillon PDV, Vix VA, Zeller JA. Intracoronary artery thrombus formation in unstable angina: a clinical biochemical and angiographic correlation. *J Am Coll Cardiol* 1993;21:692-9.
- 11 Falk E. Plaque rupture with a severe pre-existing stenosis precipitating coronary thrombosis: characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br Heart J* 1983;50:127-34.
- 12 Levin DC, Fallon JT. Significance of the angiographic morphology of localized coronary stenoses: histopathologic correlations. *Circulation* 1982;66:316-20.
- 13 Ridolfi RL, Hutchins GM. The relationship between coronary lesions and myocardial infarctions; ulceration of atherosclerotic plaques precipitates coronary thrombosis. *Am Heart J* 1977;93:468-86.
- 14 Wilson RF, Holida BS, White CW. Quantitative angiographic morphology of coronary stenoses leading to myocardial infarction or unstable angina. *Circulation* 1986;73:286-93.
- 15 Harrison DG, Ferguson DW, Collins SM, Skorton DJ, Erickson EE, Kioschos MJ, *et al.* Rethrombosis after reperfusion with streptokinase: importance of geometry of residual lesions. *Circulation* 1984;69:991-9.
- 16 Brown BG, Gallery CA, Badger RS, Kennedy JW, Mathey D, Bolson EL, *et al.* Incomplete lysis of thrombus in the moderate underlying atherosclerotic lesion during intracoronary infusion of streptokinase for acute myocardial infarction: quantitative angiographic observations. *Circulation* 1986;73:653-61.
- 17 Ambrose JA, Winters SL, Arora RR, Halt JJ, Goldstein J, Rentrop KP, *et al.* Coronary angiographic morphology in myocardial infarction: a link between the pathogenesis of unstable angina and myocardial infarction. *J Am Coll Cardiol* 1985;6:1233-8.
- 18 Ambrose JA, Winters SL, Arora RR, Eng A, Riccio A, Gorlin R, *et al.* Angiographic evolution of coronary artery morphology in unstable angina. *J Am Coll Cardiol* 1986;7:472-8.
- 19 Ellis S, Alderman EL, Cain K, Wright A, Bourassa M, Fisher L. Morphology of left anterior descending coronary territory lesions as a predictor of anterior myocardial infarction: a CASS registry study. *J Am Coll Cardiol* 1989;13:1481-91.
- 20 Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death and crescendo angina. *Br Heart J* 1985;53:363-73.
- 21 Davies MJ, Thomas A. Thrombosis and acute coronary lesions in sudden cardiac ischemic death. *N Engl J Med* 1984;310:1137-40.
- 22 Ambrose JA, Winters SL, Stern A, Eng A, Teichholz LE, Gorlin R, *et al.* Angiographic morphology and the pathogenesis of unstable angina pectoris. *J Am Coll Cardiol* 1985;5:609-16.
- 23 Hackett D, Davies G, Maseri A. Pre-existing coronary stenoses in patients with first myocardial infarction are not necessarily severe. *Eur Heart J* 1988;9:1317-23.
- 24 Davies SW, Marchard B, Lyons JP, Timmis AD, Rothman MT, Layton CA, *et al.* Coronary lesions morphology in acute myocardial infarction: demonstration of early remodeling after streptokinase treatment. *J Am Coll Cardiol* 1990;16:1079-86.
- 25 The TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial: phase I findings. *N Engl J Med* 1985;312:932-6.
- 26 Reiber JHC, Serruys PW, Koozman C, Wijns W, Slager C, Gerbrands JJ, *et al.* Assessment of short-, medium, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. *Circulation* 1985;71:280-8.
- 27 Tousoulis D, Kaski JC, Davies G, Pereira W, El-Tamimi H, McFadden E, *et al.* Preangioplasty complicated coronary stenosis morphology as a predictor to restenosis. *Am Heart J* 1992;123:15-20.
- 28 Kaski JC, Tousoulis D, Haider W, Gavielides S, Crea F, Maseri A. Reactivity of eccentric and concentric stenoses in chronic stable angina. *J Am Coll Cardiol* 1991;17:627-33.
- 29 Cowley MJ, DiSciascio G, Rehr RB, Vetrovec GW. Angiographic observations and clinical relevance of coronary thrombus in unstable angina pectoris. *Am J Cardiol* 1989;63:108-13E.
- 30 Gotoh K, Minamino T, Katoh O, Hamano Y, Funui S, Hori M, *et al.* The role of intracoronary thrombus in unstable angina: angiographic assessment and thrombolytic therapy during ongoing anginal attacks. *Circulation* 1988;77:526-34.
- 31 Kragel AH, Gertz DS, Roberts WC. Morphologic comparison of frequency and types of acute lesions in the major epicardial coronary arteries and unstable angina pectoris, sudden coronary death and acute myocardial infarction. *J Am Coll Cardiol* 1991;18:801-8.
- 32 Laffel GL, Braunwald E. Thrombolytic therapy: a new strategy for the treatment of acute myocardial infarction. *N Engl J Med* 1984;311:710-7.
- 33 Davies GJ, Chierchia S, Maseri A. Prevention of myocardial infarction by very early treatment with intracoronary streptokinase: some clinical observations. *N Engl J Med* 1984;311:1488-92.
- 34 Hackett D, Davies GJ, Chierchia S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction: value of combined thrombolytic and vasodilator therapy. *N Engl J Med* 1987;317:1055-9.
- 35 Serruys PW, Arnold AER, Brower RW, De Bono DP, Bokslag M, Lubsen J, *et al.* for the European Cooperative Study Group for recombinant tissue-type plasminogen activator. Effect of continued rt-PA administration on the residual stenosis after initially successful recanalization in acute myocardial infarction: a quantitative coronary study of a randomized trial. *Eur Heart J* 1987;8:1172-81.