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NEW DIRECTIONS

Coronary Angioplasty in Patients With Unstable Angina Pectoris: Is There a Role for Thrombolysis?

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Management of unstable angina has evolved progressively, and coronary angioplasty has recently been shown to be an effective treatment strategy for unstable angina. However, the procedure-related major complication rate is higher when compared with that for angioplasty in stable angina. The underlying pathophysiology may explain this higher complication rate. Rupture of an atherosclerotic plaque associated with thrombus formation is frequent in the pathogenesis of unstable angina. These processes lead to a critical reduction in myocardial blood supply, and coronary angioplasty may effectively interrupt this process. In contrast, coronary angioplasty itself may cause further injury of the already ulcerated intima, have the potential to intensify the ongoing thrombogenic process and lead to an increased frequency of abrupt closure of the artery during the procedure. Therefore, intracoronary streptokinase was used in the procedure in those patients with abrupt closure of the artery immediately after dilation to attempt to improve the immediate result.

Coronary angioplasty was attempted in 200 consecutive patients with unstable angina. Initial success in crossing the obstructed artery was achieved in 196 patients; however, an abrupt closure immediately after dilation occurred in 21 of these patients. Of these 21 patients, 12 were also treated with intracoronary streptokinase, and successful dilation was achieved in 9 patients without evidence of necrosis or the need for emergency bypass surgery. Of the remaining nine patients, four successfully underwent redilation with a larger-sized balloon, four underwent urgent surgery (one death postoperatively) and one was treated conventionally. Final success was achieved in 188 patients (94%) without death, the need for emergency surgery or evidence of myocardial necrosis. These beneficial results suggest that, in some cases, coronary angioplasty may need to be supplemented by additional intracoronary thrombolysis to improve immediate outcome by avoiding urgent surgery and procedure-related myocardial infarction.

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The clinical syndrome of unstable angina causes great concern to clinicians because of the perceived high risk of progression to myocardial infarction or cardiac death (1,2). Only limited information is available on the merits of pharmacologic treatment, coronary bypass surgery or coronary angioplasty from controlled randomized trials in these patients. Management of unstable angina has evolved despite this lack of trial data and, recently, coronary angioplasty was shown to be relatively safe and to result in significant symptomatic relief. However, the major complication rate (myocardial infarction, emergency bypass surgery and in-hospital mortality) is rather high when compared with that in patients with stable angina (3–5). In an early series (3) of 200 patients with unstable angina, we reported that coronary angioplasty could be performed with a high initial success rate (89.5%) but at an increased risk of major procedure-related complications (10.5%). The reasons for this relatively high complication rate are apparently related to the underlying pathophysiology leading to the clinical instability and an increased risk of abrupt closure after attempted angioplasty as a result of the formation of an acute occlusive thrombus (6,7). The present study was, therefore, undertaken to investigate whether additional thrombolytic therapy in instances of abrupt vessel closure could improve the immediate results of coronary angioplasty in patients with unstable angina pectoris.

Methods

Study patients. Between January 1986 and December 1987, coronary angioplasty was attempted in 200 consecutive patients with unstable angina pectoris (Table 1). They represented 20% of our total number of patients undergoing coronary angioplasty during the study period. All were treated intensively with a beta-adrenergic blocking agent, a

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Table 1. Clinical and Angiographic Characteristics of 200 Patients With Unstable Angina

Age (median) (yr)	59 (range 29 to 83)
Men (no.)	148 (74%)
Time from angiography to PTCA (median) (days)	2 (range 0 to 75)
Postinfarction unstable angina (no.)	94 (47%)
Previous CABG/PTCA (no.)	39 (20%)
Single vessel disease (no.)	120 (60%)
Double vessel disease (no.)	56 (28%)
Triple vessel disease (no.)	24 (12%)
Single vessel dilation (no.)	180 (90%)
Multivessel dilation (no.)	20 (10%)
Angiographic evidence of intracoronary thrombus (no.)	43 (22%)

CABG = coronary artery bypass surgery; no. = number of patients; PTCA = coronary angioplasty.

calcium antagonist, intravenous nitroglycerin and heparin. Patients were selected for angioplasty if the ischemia-related coronary lesion was suitable for dilation. The stenotic artery was considered to be ischemia related in patients with single vessel disease, whereas in patients with multivessel disease, the ischemia-related artery was determined by correlation with documented rest ST segment changes on the electrocardiogram (ECG), as described previously (3).

Unstable angina pectoris was defined as symptoms of angina at rest lasting for at least 15 min and associated with ST-T changes without evidence of further myocardial necrosis, as defined by either cardiac enzyme elevation (creatine kinase twice the normal value) or development of new pathologic Q waves. Intracoronary thrombus was defined as a definite contrast filling defect or contrast staining during angiography in at least two orthogonal views observed by at least two angiographers. In addition, patients with an ischemia-related occluded vessel were considered to have thrombus.

Coronary angioplasty. This procedure was performed with preformed guiding catheters, steerable dilating balloon catheters and a pneumatic inflation device. A 7F pacing electrode catheter was positioned in the right atrium. Before the procedure, 10,000 U of heparin and 250 mg of aspirin were administered intravenously. Two ECG leads and aortic pressure were monitored continuously. Initially balloon inflation pressure was 2 atm, with subsequent inflations ranging up to 12 atm. All procedures were carried out with a cardiac surgical team on standby. The current study differs from the previous one (3) in regard to the management of complications during angioplasty. In case of abrupt vessel closure after angioplasty, emergency recanalization was attempted by repeat dilation with use of the same or a larger sized balloon. If this approach failed, immediate surgery was performed in those patients with major coronary dissection, whereas intracoronary streptokinase was given to those patients in whom abrupt occlusion was presumably due to acute thrombosis (Fig. 1). After the procedure, all patients were followed up for 24 h in the coronary care unit, where the ECG and cardiac enzyme levels were monitored. A peri-interventional myocardial infarction was diagnosed if either new pathologic Q waves developed or an abnormal cardiac enzyme elevation was documented.

Angioplasty was considered successful when a reduction in the severity of the obstruction to <50% luminal diameter narrowing was achieved with the abolition of acute ischemic symptoms and without progression to myocardial infarction, emergency surgery or death. Only the ischemia-related vessel was dilated in the majority (60 of 80) of the patients with multivessel disease. The clinical and angiographic characteristics are shown in Table 1.

Results

In the 200 patients who underwent coronary angioplasty for unstable angina pectoris, 221 lesions were dilated (115 in the left anterior descending, 49 in the left circumflex and 48 in the right coronary artery and 9 in a bypass graft). Single vessel dilation was performed in 180 patients, including 25 multilesion dilations in the same artery. Double artery dilation was performed in 19 patients, and triple artery dilation in 1.

Intracoronary streptokinase in abrupt closure after angioplasty. Technical failure to cross the lesion occurred in four patients whose ischemia-related artery was found to be occluded at the time of attempted angioplasty; three of these underwent elective coronary bypass surgery and one was treated conservatively. The obstructed artery was crossed and dilated in 196 patients; however, an abrupt closure immediately after attempted dilation occurred in 21 (11%) of these patients. Closure was presumably due to occlusive thrombus in 12 patients who were treated with 250,000 U of intracoronary streptokinase, and successful dilation was achieved in 9 of these patients without evidence of further necrosis or the need for emergency surgery. Major coronary dissection was observed in four patients who underwent emergency bypass surgery. Of the remaining five patients, in whom the mechanism of abrupt occlusion was uncertain, four had successful redilation with use of a larger sized balloon and one was treated conservatively (Table 2). In these 21 patients with abrupt closure after attempted angioplasty, 12 had angiographic evidence of intracoronary thrombus before angioplasty.

Peri-interventional myocardial infarction, defined by either cardiac enzyme elevation or new Q waves, was documented in six patients, of whom four underwent emergency bypass surgery, with one death postoperatively (Table 2). Thus, among these 200 patients who underwent coronary angioplasty for unstable angina, final success in dilating the obstructed artery was achieved in 188 patients (209 lesions) without death, evidence of myocardial necrosis or the need for emergency surgery.

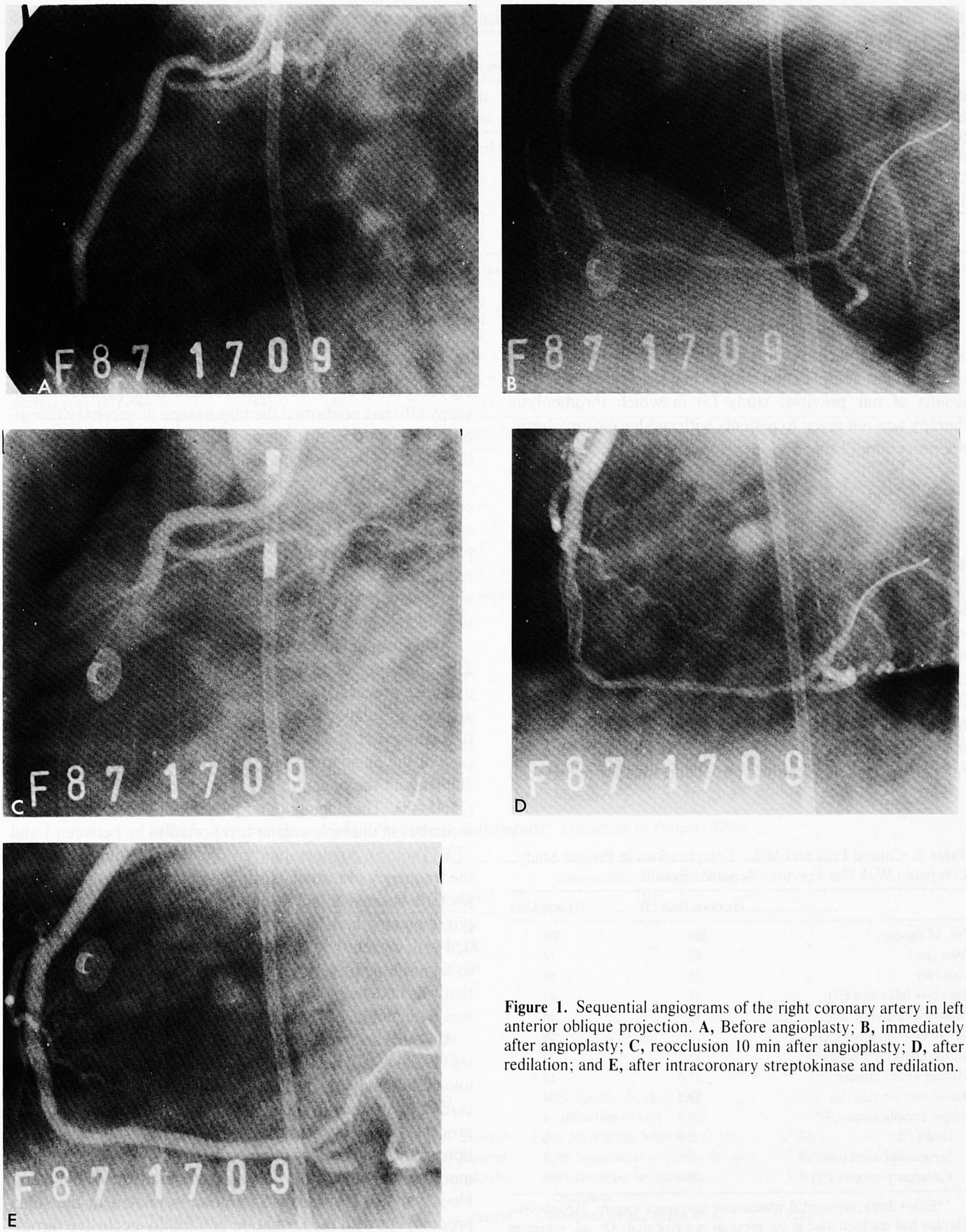

Figure 1. Sequential angiograms of the right coronary artery in left anterior oblique projection. **A,** Before angioplasty; **B,** immediately after angioplasty; **C,** reocclusion 10 min after angioplasty; **D,** after redilation; and **E,** after intracoronary streptokinase and redilation.

Table 2. Management and Outcome of 21 Patients With Acute Vessel Closure During Coronary Angioplasty

	n	MI
Redilation*	4	0
IC SK + redilation	10	1
IC SK + acute surgery	2	1
Emergency surgery	4	3†
Conservative treatment	1	1
Total	21	6

*Prolonged inflations with larger size balloon; †one patient died postoperatively. IC = intracoronary; MI = myocardial infarction; SK = streptokinase.

These results show a high initial success rate of coronary angioplasty in patients with unstable angina pectoris and a lower major complication rate when compared with the results of our previous study (3) in which thrombolytic therapy was not given to patients with sudden closure during the procedure (Table 3).

Discussion

Coronary angioplasty, as an alternative to bypass surgery, has recently been shown to be effective in the treatment of unstable angina pectoris (Table 4). The reported lower angioplasty procedural success rates of 63 to 76% were achieved with the nonsteerable dilation catheters. The more recent reports of improved results were achieved with the more advanced steerable dilation system. However, these results were obtained in selected patients with predominantly single vessel disease and well preserved left ventricular function. Despite these improved results with time, the rate of major complications (procedure-related myocardial infarction and emergency surgery) is rather high compared with elective coronary angioplasty, ranging from 8 to 13% (3,8–23), although Meyer et al. (13) reported a lower complication rate.

Table 3. Clinical Data and Major Complications in Present Study Compared With Our Previous Reported Results

	Previous Data (3)	Present Data
No. of patients	200	200
Men (no.)	82	74
Age (yr)	56	59
Previous infarction (%)	37	47
Multivessel disease (%)	33	40
Multivessel dilations (%)	0	10
Intracoronary thrombus (%)	15	22
Abrupt vessel closure (%)	11.5	10.5
Initial success rate (%)	89.5	94
Major complications (%)*	10.5	4
Death (%)	0.5	0.5
Myocardial infarction (%)	8	3
Emergency surgery (%)	9	3

*Either death, myocardial infarction or emergency surgery. Thrombolytic therapy had not been used in our previous reported study (3). no. = percent of patients.

Reasons for higher complication rate for angioplasty in unstable angina. The reasons for this high complication rate are apparently related to the underlying pathophysiology. Almost all patients with unstable angina pectoris have a high grade fixed coronary stenosis (24,25), and in addition to this fixed stenosis, other dynamic conditions may also play a role, such as plaque fissuring with platelet aggregation, increased vasomotor tone and formation of a partial or even intermittent occlusive thrombus (26–30). Evidence derived from postmortem pathologic studies (29,30), postmortem coronary arteriography (31), serial coronary arteriography (25,32,33), lysis of intracoronary thrombi (34), surgery during acute coronary syndromes (35) and intraoperative angioscopy (36) has confirmed the importance of coronary thrombosis as a factor in unstable angina. Further clinical evidence (28,37–42) to support the role of intracoronary thrombus comes from the observation that thrombolytic therapy in patients with unstable angina did lyse the thrombus in a considerable number of patients (Table 5). The role of platelets in intracoronary thrombus is also shown by the reduction in the incidence of death and nonfatal myocardial infarction after the administration of aspirin to patients with unstable angina (43,44).

Angiographic identification of intracoronary thrombus. The formation of an intracoronary thrombus is an active dynamic process. Identification of such a thrombus with angiography depends on the timing of the angiogram after the acute event, the size of the intracoronary thrombus at the time of the angiogram, the severity of illness in the patient studied and the angiographic criteria used for identification (28,45–48). The angiographic presence of an intracoronary thrombus in unstable angina is reported to be between 1 and 52% (Table 6). Angiographic criteria probably underestimate the frequency of thrombosis in patients with unstable angina pectoris because a mural (nonocclusive) thrombus superimposed on an atherosclerotic plaque cannot always be identified with currently available techniques. In a pilot study (36) using intraoperative angioscopy, an intracoronary thrombus that was undetectable on review of the coronary angiograms was detected in 7 of 10 patients with unstable angina.

Unstable angina and non-Q wave infarction. Several studies (29,30,49–52) have emphasized the important pathophysiologic link between unstable angina and non-Q wave myocardial infarction. In unstable angina, the pathophysiologic process is limited to endothelial ulceration, platelet aggregation and thrombus formation, which may be intermittent or more permanent in the presence of an adequate collateral blood supply. Myocardial infarction is related to the same process, but with the formation of a totally occlusive thrombus. When the balance between intracoronary thrombus and

Table 4. Reported Results of Coronary Angioplasty for Unstable Angina (initially stabilized, refractory or early postinfarction)

Study (ref)/Year	No. of Pts	Success Rate (%)	Major Complication Rate			Coronary Events After Successful Angioplasty			Follow-up (mean no. of months)
			Death (%)	MI (%)	Acute Surgery (%)	Death (%)	MI (%)	AP (%)	
Initially Stabilized Unstable Angina									
Faxon et al. (8)*/1983†	442	63	0.9	8	—	1.7	1.5	18	18
Quigley et al. (9)/1986	25	81	4	12	12	0	0	32	18
de Feyter et al. (10)/1987	71	87	0	10	12	2	2	23	12
Steffenino et al. (11)/1987	89	90	0	5	5	0	1.5	23	10
Refractory Unstable Angina									
Williams et al. (12)*/1981	17	76	0	0	6	0	0	8	10.5
Meyer et al. (13)/1983	50	74	0	4	2	0	0	36	6
de Feyter et al. (14)/1985	60	93	0	7	7	2	0	13	9
Timmis et al. (15)/1987	56	70	5.4	7.1	12.5	3.3	3.3	39	6
Plokker et al. (16)/1988	469	88	1	4.9	3	1.5	0.1	21	19.3
Sharma et al. (17)/1988	40	88	0	0	12	0	0	34	11
Early Postinfarction Unstable Angina (≤ 30 days after MI)									
de Feyter et al. (18)/1986	53	89	0	8	8	0	4	26	9
Holt et al. (19)/1986	69	80	2	—	12	0	4	24	21
Gotlieb et al. (20)/1987	47	91	2	4	2	3	3	18	16.3
Safian‡ et al. (21)/1987	68	87	0	1.5	1.5	0	2	41	17
Suryapranata et al. (22)‡/1988	60	85	0	5	7	0	5	23	20
Hopkins et al. (23)/1988	54	81	0	0	4	0	2	25	11

*Use of a nonsteerable dilation system; †the majority of the patients were initially stabilized; ‡after non-Q wave myocardial infarction. AP = angina pectoris; Pts = patients; ref = reference number; other abbreviations as in Table 2.

antithrombotic natural and pharmacologic factors leans toward continued thrombus formation, persistent total coronary occlusion leading to acute myocardial infarction may occur. If the coronary artery remains occluded for a long period (>15 min), myocardial necrosis will occur. If very early clot lysis occurs with or without embolization to the distal coronary bed or if an adequate collateral blood supply is present, infarction will be limited (non-Q wave myocardial infarction), whereas it will be extended (Q wave myocardial infarction) when no or late clot lysis occurs. In addition, in a

Table 5. Reported Results of Fibrinolytic or Anticoagulant Treatment in Patients With Unstable Angina

Study (ref)	No. of Pts	Treatment	Angiographic Evidence of Lysis (%)	Clinical Outcome	Follow-Up
Vetrovec et al. (37)	13	IC SK	77		
Mandelkorn et al. (28)	9	IC SK	44		
Shapiro et al. (38)	18	IC SK	67		
Lawrence et al. (39)	20	IV SK (24h) + coumadin		5% Sudden death (1 pt)	6 mo
	20	Coumadin		40% Sudden death (4 pts), infarction (4 pts)	6 mo
Telford and Wilson (40)	100	Heparin + atenolol		3% Myocardial infarction (3 pts)	7 days
	114	Placebo or atenolol		15% Myocardial infarction (17 pts)	7 days
Gold et al. (41)	24	IV rt-PA or placebo		40% Decrease in recurrent ischemia	7 days
Topol et al. (42)	40	IV rt-PA or placebo		Improved pacing threshold to ischemia	7 days

IV = intravenous; rt-PA = recombinant tissue plasminogen activator; other abbreviations as in Table 2 and 4.

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Table 6. Reported Angiographic Evidence of Intracoronary Thrombus

Study	No. of Pts	IC Thrombus		Time Elapsed Between Acute Event and Angiography	Criteria Used*
		No. of Pts	%		
Holmes et al. (45)	1,202	16	1	3 mo	2A
Vetrovec et al. (46)	129	8	6	1 mo	2A
Mandelkorn et al. (28)	9	4	44	2 mo	3
Capone et al. (47)	119	44	37	14 days	2A
Capone et al. (47)	44	23	52	24 h	2A
Zack et al. (48)	83	10	12	3 mo	1, 2A, 2B

*Definition of intracoronary (IC) thrombus: 1 = occlusive thrombus; 2 = nonocclusive thrombus; A = intraluminal defect; B = intraluminal staining; 3 = reduction in severity of stenosis after streptokinase infusion.

patient with non-Q wave infarction, rethrombosis and reocclusion often occur, leading to repeat infarction affecting the same myocardial region (52).

Abrupt coronary occlusion during angioplasty. These data suggest that rupture of an atherosclerotic plaque with associated thrombus formation is frequent in both the pathogenesis of unstable angina and myocardial infarction. These processes will lead to a critical reduction in myocardial blood supply. Coronary angioplasty, designed to enlarge the stenosed lumen, may effectively interrupt this process, thereby normalizing myocardial blood flow. However, coronary angioplasty may act as a two-edged sword because angioplasty itself may cause further injury to the plaque and the already ulcerated intima (53), which has the potential to intensify the ongoing thrombogenic process, leading to an increased frequency of abrupt total occlusion during the procedure.

Incidence rates of abrupt closure after attempted angioplasty that vary between 2 and 12% have been reported (7,11,54,55). The management of this serious complication has changed over the past 10 years and remains controversial. There was a time when all patients with acute occlusion underwent emergency surgery. In earlier reported series (56–58), emergency surgery was performed in 5 to 13% of the patients in whom angioplasty was attempted. More recent reports (59) show a decline in emergency coronary bypass surgery to 2%, along with an increase in the frequency of myocardial infarction without surgery. Approximately 40 to 60% of patients who have emergency surgery after angioplasty have evidence of myocardial infarction, despite prompt operation, and mortality rates range from 0 to 6.4% (57–62).

Predictive factors for abrupt occlusion after angioplasty. The identification of factors associated with increased occlusion rates might be of great value in optimizing patient selection and developing treatment strategies for preventing this complication. Although the extent of myocardial ischemia resulting from acute occlusion can be predicted from the patient's diagnostic angiogram, the occurrence of abrupt occlusion is not foreseeable. However, in the patients presented here, there was a correlation between the presence of intracoronary thrombus before angioplasty and the subsequent development of complete coronary artery occlusion after attempted angioplasty. In patients with pre-existing intracoronary thrombus, abrupt occlusion occurred in 28% (12 of 43) compared with 6% (9 of 157) in those without angiographic evidence of intracoronary thrombus. This finding is consistent with other reports (7,63), and leads us to believe that the mechanism of occlusion in this series was an ongoing thrombogenic process. Coronary spasm as an alternative cause of abrupt occlusion was unlikely because intracoronary nitroglycerin and nifedipine were routinely administered. In addition, the use of intensive anticoagulant therapy (intravenous heparin 2 to 4 days before the procedure) and routine premedication with intravenous aspirin (250 mg) combined with heparin (10,000 U) during the dilation did not prevent abrupt vessel occlusion from occurring either during dilation or immediately after what appeared to be successful dilation. This is consistent with other clinical and experimental reports (7,63–65) showing that platelet thrombus deposition occurred despite continuous heparin use.

Role of thrombolytic therapy. Because thrombolytic therapy combined with coronary angioplasty has been widely and safely used in the setting of acute myocardial infarction, we felt justified in applying this strategy in our patients with unstable angina who have abrupt vessel occlusion after angioplasty. Therefore, since 1986, the use of emergency redilation (with the same or an oversized balloon) or intracoronary thrombolysis, or a combination of both, has been adopted as treatment for this complication. Intracoronary streptokinase was given to our patients in whom abrupt closure of the coronary artery immediately after dilation was presumably due to acute thrombosis. Of the 4 patients with major coronary dissection who underwent emergency surgery, 3 had myocardial infarction; in contrast, only 2 of the 12 patients who received intracoronary streptokinase had evidence of infarction. These findings compare favorably with those of our previous series (3) (Table 3), suggesting that, in some cases, thrombolytic therapy may improve the immediate outcome of angioplasty in unstable angina by avoiding urgent surgery and procedure-related myocardial infarction. However, because this was a retrospective study, we can only speculate about the reasons for the improvement in the result.

Subtle but nevertheless potentially important factors that may have contributed to the improved results include increased operator experience, the exclusive use of better X-ray equipment and advanced angioplasty systems, optimization of balloon size, longer observation period in the catheterization laboratory after dilation and less stringent

criteria for repeat dilation when the arterial segment appeared to be hazy on the angiogram. Although all of these procedural modifications may be exerting a favorable influence on the outcome of dilation, we believe that thrombolytic therapy itself has led to the more effective resolution of acute complications that occur during attempted angioplasty.

Recently reported randomized placebo-controlled trials of recombinant tissue-type plasminogen activator (rt-PA) in unstable angina (41,42) further confirm the potential of fibrinolytic therapy in this setting, particularly in patients with angiographic evidence of intracoronary thrombus. However, Ambrose et al. (66) recently reported that intracoronary streptokinase was usually ineffective in reducing the percent stenosis of the angina-producing vessel, measured quantitatively, in patients with unstable angina and non-Q wave myocardial infarction. Possible explanations for this finding include the possibility that there was no thrombus present at the time of angiography because of spontaneous lysis or heparin therapy, and that, in some patients with unstable angina, the thrombus deposited at the site of plaque disruption may already be organized within the coronary artery at the time of clinical presentation (30) and, therefore, is resistant to short infusions of streptokinase. To achieve thrombolysis, it may be necessary to administer thrombolytic therapy within hours of the onset of unstable symptoms. Furthermore, results of a small randomized placebo-controlled trial of rt-PA in unstable angina (41) have shown that a prolonged (12 h) infusion of rt-PA in combination with heparin effectively lyses thrombus and leads to stabilization of the clinical syndrome when compared with heparin alone. In this randomized trial, angiographic evidence of intracoronary thrombus was detected in 73% of placebo-treated patients but in none of the rt-PA–treated patients. A highly significant correlation was observed between the presence of thrombus and recurrent angina. However, bleeding was observed in 67% of the rt-PA–treated patients and in none of the placebo-treated group.

In our institution, thrombolysis has been used as a means to treat complications of angioplasty and not as a primary or preventive therapy. The reason for this approach is that we are concerned that the risk of thrombolytic agents may exceed the possible benefit in patients with unstable angina. Only 10% of the patients will develop serious complications with conventional therapy, and the hemorrhagic risks inherent to thrombolytic therapy with either a specific clot lysing agent or a systemic fibrinolytic agent are not negligible.

Recommendations. Studies to date have established the potential for thrombolytic therapy to alter the course of unstable angina. Future studies should be directed toward delineating the place of thrombolytic therapy in the management of patients with unstable angina, especially in those refractory to other pharmacologic therapy. First, thrombolytic therapy could be tested as a strategy to stabilize the patient's condition. In this strategy, the thrombolytic therapy would be given early, before angiographic documentation of the coronary anatomy. Second, it might be used as a preventive strategy to avoid complications during coronary angioplasty. With this strategy, thrombolytic therapy would be reserved for patients with angiographically visible thrombus. Finally, it could be used as a rescue strategy in case of abrupt vessel occlusion during attempted angioplasty. At present, we are conducting a double-blind randomized trial of intravenous rt-PA versus placebo in patients with unstable angina refractory to pharmacologic therapy who will undergo coronary angioplasty within 24 h.

Until further information becomes available, we are using the following practical approach. Patients with unstable angina should initially receive prompt management, with stepwise intensification of pharmacologic therapy with antiplatelet drugs and anticoagulation with heparin in an attempt to achieve stability. Early angiographic evaluation and revascularization are indicated if this approach fails and ischemic episodes continue despite maximal medical management. Coronary angioplasty is indicated when a stenosis that is technically suitable for dilation is found to be responsible for the unstable state. An intravenous thrombolytic agent is given before angioplasty in patients with angiographic evidence of intracoronary thrombus. In case of abrupt vessel occlusion during attempted angioplasty, intracoronary streptokinase and redilation are carried out.

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