Consequences of Reocclusion After Successful Reperfusion Therapy in Acute Myocardial Infarction

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To determine the clinical consequences of reocclusion of an infarct-related artery after reperfusion therapy, we evaluated 810 patients with acute myocardial infarction. Patients were admitted into four sequential studies with similar entry criteria in which patency of the infarct-related artery was assessed by coronary arteriography 90 minutes after onset of thrombolytic therapy. Successful reperfusion was established acutely in 733 patients. Thrombolytic therapy included tissue-type plasminogen activator (t-PA) in 517, urokinase in 87, and a combination of t-PA and urokinase in 129 patients. All patients received aspirin, intravenous heparin and nitroglycerin, and diltiazem during the recovery phase. A repeat coronary arteriogram was performed in 88% of patients at a median of 7 days after the onset of symptoms. Reocclusion of the infarct-related artery occurred in 91 patients (12.4%), and 58% of these were symptomatic. Angiographic characteristics at 90 minutes after thrombolytic therapy that were associated with reocclusion compared with sustained coronary artery patency were right coronary infarct-related artery (65% versus 44%, respectively) and Thrombolysis in Myocardial Infarction (TIMI) flow 0 or 1 (21% versus 10%, respectively) before further intervention. Median (interquartile value) degree of stenosis in the infarct-related artery at 90 minutes was similar between groups: 99% for reoccluded (value, 90/100%) compared with 95% for patent (value, 80/99%). Patients with reocclusion had similar left ventricular ejection fractions compared with patients with sustained patency at follow-up. However, patients with reocclusion at follow-up had worse infarct-zone function at −2.7 (value, −3.2/−1.8) versus −2.4 (SD/chord) (value, −3.1/−1.3) ($p=0.016$). The recovery of both global and infarct-zone function was impaired by reocclusion of the infarct-related artery compared with maintained patency; median Δ ejection fraction was −2 compared with 1 ($p=0.006$) and median Δ infarct-zone wall motion was −0.10 compared with 0.34 SD/chord ($p=0.011$), respectively. In addition, patients with reocclusion had more complicated hospital courses and higher in-hospital mortality rates (11.0% versus 4.5%, respectively; $p=0.01$). We conclude that reocclusion of the infarct-related artery after successful reperfusion is associated with substantial morbidity and mortality rates. Reocclusion is also detrimental to the functional recovery of both global and infarct-zone regional left ventricular function. Thus, new strategies in the postinfarction period need to be developed to prevent reocclusion of the infarct-related artery. (*Circulation* 1990;82:781–791)

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The use of thrombolytic therapy in patients with acute myocardial infarction has led to substantial reduction in both in-hospital and long-term mortality rates.[1] The predominant efficacy of intravenous thrombolytic therapy lies in its ability to achieve coronary patency soon after onset of symptoms and by limiting infarct size. Although this salvage of jeopardized myocardium has led to improvement in myocardial function,[2,3] there is also evidence to suggest that long-term mortality rates

may be related to patency of the infarct-related artery at the time of discharge,[1,4–6] independent of standard measures of left ventricular function. Therefore, the potential benefits of thrombolytic therapy may be reduced if reocclusion of a patent infarct-related artery occurs, both by impairing the healing of the myocardium and by negating the beneficial effects of a patent infarct-related artery on survival.

Reocclusion after successful thrombolytic therapy may occur with symptoms or hemodynamic instability or as a reinfarction, but a proportion of reocclusion events display no signs or symptoms. Therefore, the true magnitude of the problem of reocclusion can be adequately addressed only in populations in which coronary artery patency has been documented during the early phase of infarction and later reassessed with coronary arteriography. Because no previous studies have systematically evaluated patients with reocclusion after successful thrombolytic therapy, the impact of the event on mortality rates and ventricular function is largely unknown. The aim of this study was to determine the incidence and consequences of reocclusion of the infarct-related artery in a large cohort of patients in whom patency was achieved during the early phase of acute myocardial infarction and in whom repeat coronary arteriography was performed before hospital discharge.

Methods

Patient Population

The study population comprised 810 patients who had been enrolled into four sequential studies with thrombolytic therapy at five centers. The entry criteria for these studies were similar and have been described in detail previously.[7–10] In brief, patients with symptoms of acute myocardial infarction for from 30 minutes to 6 hours were included if ST segment elevation of at least 0.1 mV was present in at least two contiguous leads of a standard 12-lead electrocardiogram or there was ST segment depression of the precordial leads (V_1–V_4) consistent with posterior injury. The standard contraindications to thrombolytic therapy, including history of risk factors for serious hemorrhage, were observed. Specifically, the following factors were considered contraindications to entry into any of the protocols: suspected pregnancy; recent (less than 6 months) trauma or stroke; major surgery within 2 weeks; recent active internal bleeding (gastrointestinal or genitourinary); structural brain disease, including tumor or vascular malformations; uncontrolled hypertension (diastolic blood pressure of more than 120 mm Hg by several measurements); other serious advanced illnesses, such as cancer; or prolonged cardiopulmonary resuscitation within 2 weeks. Additionally, patients more than 75 years old or having a previous Q wave infarction in the distribution of the infarct-related artery or cardiogenic shock (systolic pressure of less than 85 mm Hg unresponsive to volume expanders) on presentation were excluded. The first 386 patients were enrolled into the Thrombolysis and Angioplasty in Myocardial Infarction trial (TAMI I) in which patients, after receiving tissue-type plasminogen activator (t-PA), were randomized to either delayed or immediate percutaneous transluminal coronary angioplasty (PTCA).[7] The next 147 patients were entered into a pilot study (TAMI II) that examined the efficacy of combination thrombolytic therapy—all patients received a combination of t-PA and urokinase.[8] An additional 175 patients received t-PA and were randomized to early or late intravenous heparin (TAMI III).[9] The final 102 patients received intravenous urokinase.[10]

Thrombolytic Therapy

All patients received an intravenous infusion of thrombolytic therapy as soon as possible after informed consent was obtained. Patients allocated to t-PA received predominantly single-chain t-PA (Genentech Inc., San Francisco) by a bolus injection of 10% of the first hour dose. The first 176 patients received 60 mg over the first hour, followed by 20 mg/hr for 2 hours and 10 mg/hr over the next 5 hours. The next 210 patients received 1 mg/kg over the first hour, with a maximum dose of 90 mg, followed by the remainder of a total dose of 150 mg over the next 5 hours. A total of 147 patients received a combination of t-PA and the low-molecular-weight form of urokinase (Abbott Laboratories, Chicago) concomitantly. The 34 patients randomized to low-dose t-PA (25 mg over 1 hour) did not receive a bolus, of whom 14 received 0.5 million units urokinase and 20 received 1.0 million units over 1 hour. The remaining 112 patients received 1 mg/kg t-PA with a maximum of 90 mg over 1 hour, with a 10% bolus injection. Of these patients, 24 received 0.5 million units urokinase, 33 received 1.0 million units urokinase, and 55 received 2.0 million units urokinase over 1 hour. Patients randomized to early versus late heparin received 1.5 mg/kg i.v. t-PA over 4 hours; the dose was 1.0 mg/kg over the first hour (maximum dose, 90 mg) with 10% given as a bolus. Over the next 3 hours, 0.5 mg/kg was given, not to exceed a total maintenance infusion of 45 mg. Eighty-two patients received early heparin—10,000 units with a bolus of t-PA; 82 patients received heparin at cardiac catheterization. An additional 11 patients received t-PA as outlined above but were not randomized to intravenous heparin. The first 60 of 102 patients treated with only urokinase received a total of 3 million units of the low-molecular-weight form over 45–60 minutes. The last 42 patients received a bolus of urokinase (1.5 million units) over 5 minutes, and the remaining 1.5 million units was infused over the subsequent 45–60 minutes.

Cardiac Catheterization and Coronary Angioplasty

After initiation of thrombolytic therapy, patients were transferred to the cardiac catheterization laboratory, where angiography of the infarct-related

artery was performed. Catheterization was performed by the femoral or brachial route. Immediately after obtaining vascular access, intravenous heparin (5,000 units) was administered except to patients randomized to late heparin therapy, in whom it was given after patency had been established. Arteriography of the infarct-related artery was performed within 60–90 minutes after thrombolytic therapy had been started. Several injections (as many as four) in various orthogonal and hemiaxial views were obtained. The flow pattern of the infarct-related vessel was graded according to Thrombolysis in Myocardial Infarction (TIMI) trial classification.[11] Injections were also made of the noninfarct vessels. Contrast ventriculography was performed in the right anterior oblique projection before additional intervention was instituted. The first 386 patients were triaged to immediate or late PTCA, to medical therapy, or in a few cases, to emergency coronary artery bypass graft surgery (CABG), the latter because of life-threatening coronary anatomy. Patients undergoing early PTCA did so if they had TIMI flow 0 or 1 or if coronary lesions were suitable for PTCA and the patients were randomized to early PTCA. Patients received medical therapy if coronary anatomy was deemed unsuitable for PTCA or the patients were randomized to deferred PTCA. In the remaining 424 patients, PTCA was attempted only in patients with TIMI flow 0 or 1 at the discretion of the investigator and in patients with ongoing ischemia (chest pain and more than 0.2-mV ST segment elevation) and reduced coronary blood flow (TIMI 2) in the infarct-related vessel. If residual thrombus was present at the arteriogram at 90 minutes or after angioplasty, additional thrombolytic therapy was given—either intracoronary urokinase or t-PA over 15 minutes. When PTCA was performed, additional heparin (5,000 units) was administered.

Medical Therapy

All patients were admitted to the coronary care unit and monitored for 24 hours. Patients were treated with intravenous heparin, started at 500–1,000 units/hr and adjusted to prolong the activated partial thromboplastin time for twofold to 2.5-fold that of control, for at least 3 days. During the first 24 hours, the patients received intravenous nitroglycerin and lidocaine unless contraindicated. Patients also received 1 aspirin tablet (325 mg) per day, 75 mg t.i.d. dipyridamole, and 30–60 mg q.i.d. diltiazem soon after hospitalization. β-Blockers were not given unless clinically indicated (e.g., angina, hypertension, or supraventricular tachycardia).

Repeat Catheterization and Revascularization

Urgent repeat cardiac catheterization was performed for recurrent ischemia, which was defined as 20 minutes or more of chest discomfort associated with electrocardiographic ST segment elevation. Patients' occluded vessels were opened by either angioplasty or intracoronary thrombolytic therapy. If PTCA failed, patients were transferred immediately to receive CABG. Patients with recurrent ischemia also underwent CABG at the discretion of the attending cardiologist. Patients with significant left main disease or other life-threatening anatomy had revascularization by surgery at the earliest opportunity. Patients, including those who had CABG, underwent repeat cardiac catheterization when clinically stable to establish patency of the infarct-related artery and ventricular function according to protocol. The majority of patients had coronary arteriography and ventriculography between 7 and 10 days after myocardial infarction. Angioplasty of the infarct-related artery was only performed if there was significant residual stenosis. Patients with severe multivessel disease or coronary anatomy unsuitable for PTCA underwent CABG before discharge.

Core Angiographic Laboratory

All cineangiograms underwent blinded review by one observer at the Core Angiographic Laboratory. The perfusion status, quantitative stenosis, and ventricular function were assessed. Images were displayed, and silhouettes of end-diastolic and end-systolic frames were drawn with a light-pen system. Next, cardiac silhouettes were digitized and stored. Image processing was performed with a digital radiographic computer system (Adac Labs, Sunnyvale, Calif.). Global ventricular function was determined by the area-length method and expressed as ejection fraction. Regional wall motion of the infarct zone was quantified as SD per chord by the centerline chord method.[12] Technically inadequate studies due to lack of opacification or frequent premature ventricular beats were not included in the analysis.

Coagulation Variables

Blood samples were collected on 0.01 M citrate and 200 kIU/ml aprotinin at baseline and at 3–4, 5–8, and 24 hours after fibrinolytic therapy. Samples were immediately processed and kept frozen at −20° C until assayed in the core laboratory. Fibrinogen was determined by a coagulation rate assay, as described by Clauss.[13] Fibrinogen degradation products were analyzed by a hema-agglutination inhibition method.[14]

Statistics

Values are given as median and interquartile range (25th and 75th) unless otherwise specified. For continuous variables, the Wilcoxon rank-sum test was used to examine differences. The comparison for discrete variables was by the χ^2 test. To adjust for the relation between thrombolytic therapy and invasive strategy and to examine the consequences of reocclusion of the infarct-related artery, a general linear regression analysis was used. A p value of less than 0.05 was considered statistically significant.

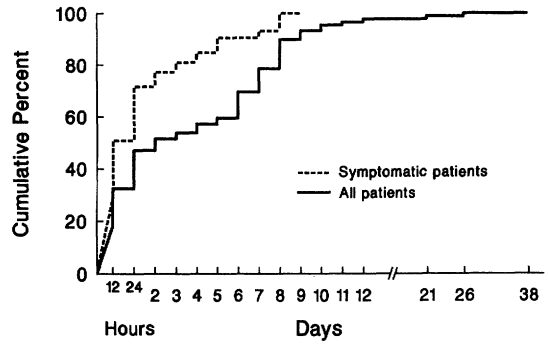

FIGURE 1. *Graph of time to angiographically documented reocclusion of infarct-related artery for patients with symptoms of reocclusion (broken line) and all patients (solid line). Cumulative percent of patients with reocclusion is displayed on vertical axis and time to reocclusion is displayed on horizontal axis. Median time to symptomatic reocclusion (n=53) was 0.91 days; in total cohort (n=91), it was 2.2 days.*

Results

Study Group

A total of 810 patients received thrombolytic therapy within 6 hours of onset of symptoms. Cardiac catheterization at 90 minutes after thrombolytic therapy administration was not performed in 13 patients: Three died soon after receiving therapy, four patients did not undergo coronary arteriography for technical reasons, and six patients were deemed not to be suffering from myocardial ischemia and were excluded from the analysis. In 64 of the remaining 797 patients (8.0%), the infarct-related artery remained closed despite attempts to achieve patency by both pharmacological and mechanical means. Therefore, 733 patients left the cardiac catheterization laboratory with a patent infarct-related artery. Follow-up cardiac catheterization was performed in 642 patients (87.6%). Repeat angiography was not done in 91 patients: Forty-one had CABG, and 18 had died by the time repeat procedure was scheduled by protocol; and follow-up catheterization was not performed in 32 patients because of technical reasons or patient refusal.

Incidence and Management

Reocclusion occurred in 91 patients (12.4%) throughout the hospitalization period and was clinically suspected in 58% of patients at a median of 0.91 days (value, 0.45/2.60 days) after thrombolytic therapy (Figure 1). Of the 38 patients with silent reocclusion, 36 (95%) were treated medically, and two underwent successful angioplasty. The majority of patients (87%) with clinically detected reocclusion had angioplasty, which was successful (less than 50% residual stenosis) in 67% (31 of 46). In the 15 patients in whom angioplasty was unsuccessful, seven underwent CABG, and eight had medical therapy. A minority of patients underwent a nonemergency revascularization procedure between acute cardiac catheterization and follow-up cardiac catheterization. Eleven patients had CABG (1.5%), and 6% had PTCA.

TABLE 1. **Baseline Characteristics**

Variables	Patent IRA (n=642)	Reoccluded IRA (n=91)
Age (yr) (value)	57 (49/65)	56 (50/64)
Male gender (%)	81.2	76.9
Hypertension (%)	41.0	41.8
Hyperlipidemia (%)	12.2	14.3
Diabetes mellitus (%)	14.2	16.5
Peripheral vascular disease (%)	5.1	7.7
History of smoking (%)	62.9	72.5
Aspirin use before myocardial infarction (%)	21.3	20.9
Three-vessel coronary artery disease (%)	16.9	14.3
Infarct location (%)		
Anterior	42.1	31.9
Inferior	57.1	67.0

IRA, infarct-related artery.

Patient Characteristics

Baseline characteristics of patients who reoccluded and who remained patent are shown in Table 1. The median time to thrombolytic therapy in patients who reoccluded was 160 minutes (range, 120–210 minutes) and in those who did not was 172 minutes (range, 125–220 minutes).

Angiographic Characteristics

Patients with TIMI flow 0 or 1 at the 90-minute coronary arteriogram who achieved infarct artery patency via a rescue procedure (PTCA or intracoronary thrombolytic therapy) had a highly significant rate of reocclusion at 21.2% (38 of 179) compared with 9.7% (53 of 544) in patients with TIMI flow 2 or 3 ($p<0.0001$). The median degree of stenosis of the infarct-related vessel at 90 minutes after thrombolytic therapy was similar between those who reoccluded and those who remained patent [99% (value, 90/100%) versus 95% (value, 80/99%), respectively]. Reocclusion was more common in the right coronary artery compared with the left anterior descending and circumflex coronary arteries, but the location of the lesion within the coronary artery was similar, as shown in Table 2.

Hematological Variables

Baseline fibrinogen levels did not differ between patients with and without reocclusion [2.5 (value, 2.2/2.8) versus 2.8 (value, 2.3/3.6) g/l]. Patients who reoccluded tended to have a smaller drop in fibrinogen levels [Δ fibrinogen, 1.2 (value, 0.7/1.9) versus 1.9 (value, 1.1/2.7) g/l]. Median peak fibrinogen degradation products were also lower in those who reoccluded [60 (value, 14/400) versus 210 (value, 31/900) μg/ml, $p=0.0016$].

TABLE 2. Angiographic Variables

Variables	Patent IRA (n=642)	Reoccluded IRA (n=91)
IRA (%)		
Left anterior descending	41.1	31.9
Left circumflex	14.2	3.3
Right coronary	44.1	64.8
Other (left main or graft)	0.6	0.0
Location within IRA (%)		
Proximal	54.5	49.5
Middle	33.5	37.4
Distal	11.3	13.2
TIMI flow in IRA at 90 minutes (%)		
0	17.1	36.2
1	5.2	5.5
2	17.6	23.1
3	60.1	35.2

IRA, infarct-related artery.

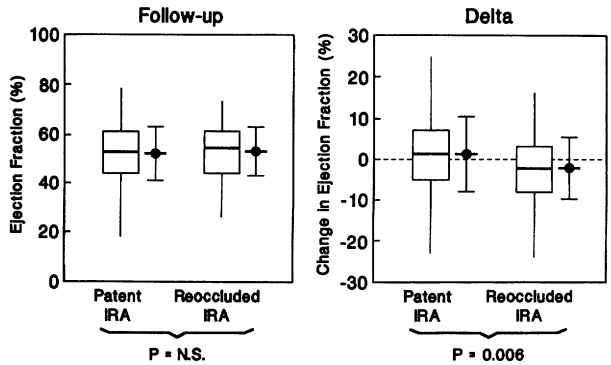

FIGURE 2. *Box (median and interquartile values) and whisker (mean±1 SD) plots of global left ventricular function in patients with patent* (n=*479) and reoccluded* (n=*72) *infarct-related arteries at follow-up cardiac catheterization at a median of 7 days* (left panel). *Δ ejection fraction (acute minus follow-up) is given in* right panel. *There was a highly significant difference in change in ejection fraction between patients with patent* (n=*444) and reoccluded infarct-related arteries* (n=*65) (p=0.006). IRA, infarct-related artery; Delta, difference in ejection fraction between acute and follow-up left ventricular arteriography.

Consequences of Reocclusion

Patients who had reocclusion after successful thrombolytic therapy had a significantly higher in-hospital mortality rate (11.0%) compared with those who had patent infarct-related vessels (4.5%) (p=0.01). The 64 patients in whom the infarct-related vessel never opened at acute cardiac catheterization had a 17.2% mortality rate. Patients with a patent artery improved their ejection fraction and infarct regional wall motion. Those who reoccluded had significantly less improvement in both of these variables, as shown in Figures 2 and 3.

The incidence of angina from time of study entry to time of reocclusion or to the median time of reocclusion in those who remained patent was similar (24.2% versus 21.7%, respectively). Patients who reoccluded had more complicated hospital courses, as shown in Table 3.

Reocclusion after mechanical versus pharmacological patency. Of the 733 patients who left the cardiac catheterization laboratory with a patent infarct-related artery, 425 had achieved reperfusion by thrombolytic therapy alone. The incidence of reocclusion among these patients was 9.2%. There were higher rates of both in-hospital complications and mortality among the patients who failed to sustain patency of the infarct-related artery (Table 4). There was also less of an improvement in both global and infarct-zone left ventricular function.

Angioplasty was used under three different conditions in this cohort. First, 91 patients underwent angioplasty in conjunction with thrombolytic therapy as part of randomization in TAMI I (12.1% reoccluded).[7] Second, an additional 54 patients had angioplasty despite a patent infarct-related artery because of evidence of ongoing ischemia (14.8% reoccluded). Finally, 152 patients had rescue angioplasty because of persistent occlusion after intravenous thrombolytic therapy (21.1% reoccluded). Overall, 16.9% of patients who had emergency angioplasty failed to maintain patency of the infarct-related artery. There was a trend toward higher rates of in-hospital complications and mortality among the patients who reoccluded after thrombolytic therapy

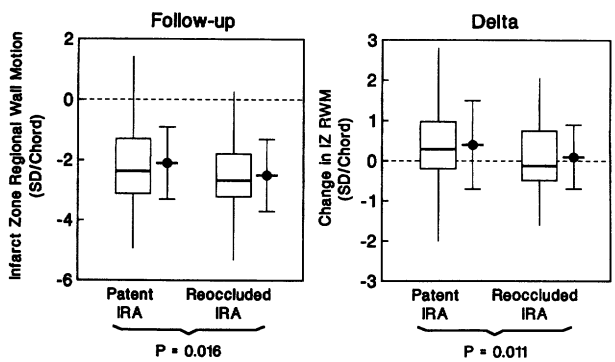

FIGURE 3. *Box (median and interquartile values) and whisker (mean±1 SD) plots of infarct-zone regional wall motion as determined by centerline method in patients with patent* (n=*480) and reoccluded* (n=*72) *infarct-related arteries* (left panel). *Patients with reocclusion of infarct-related artery had a significantly worse infarct-zone regional wall motion* (p=*0.016). Δ (acute minus follow-up) infarct-zone regional wall motion is shown in* right panel. *Patients with patent infarct-related artery* (n=*443) had a highly significant improvement in infarct-zone regional wall function compared with patients with reocclusions* (n=*65) (p=0.011). IRA, infarct-related artery; IZ RWM, infarct-zone regional wall motion; SD/Chord, SDs per chord; Delta, difference in infarct-zone regional wall motion between acute and follow-up left ventricular arteriography.*

TABLE 3. In-hospital Complications

Variable	Patent IRA (n=642)	Reoccluded IRA (n=91)
Killip class >1 (%)	21.1	23.0
Pulmonary edema* (%)	13.6	18.7
Sustained hypotension† (%)	16.5	25.3
Respiratory failure‡ (%)	8.3	13.2
Atrioventricular block (second or third degree) (%)	12.8	25.3

IRA, infarct-related artery.
*Documented by either physical findings or radiological appearances.
†Systolic blood pressure of less than 90 mm Hg for more than 1 hour.
‡Failure to adequately oxygenate leading to need for mechanical ventilatory support.

and emergency angioplasty (Table 5). Reocclusion was also detrimental to left ventricular function with an additional deterioration observed in patients who failed to maintain patency.

A comparison of patients who reoccluded regardless of whether angioplasty was performed acutely (Tables 4 and 5) reveals that the occlusion had similar effects on in-hospital complications, mortality rates, and left ventricular function. After adjusting for thrombolytic therapy and invasive strategy by

TABLE 4. Reocclusion After Thrombolytic Therapy Alone

	Patent IRA (n=380)	Reoccluded IRA (n=39)
In-hospital complications (%)		
Killip class >1	18.7	23.7
Pulmonary edema*	12.1	18.0
Sustained hypotension†	12.4	25.6
Respiratory failure‡	7.6	12.8
Atrioventricular block (second or third degree)	11.3	25.6
Mortality	4.0	12.8
IRA (%)		
Left anterior descending	40.8	33.3
Left circumflex	12.8	2.6
Right coronary	45.9	64.1
Final percent stenosis (values)	90 (75/95%)	95 (80/95%)
Left ventricular function		
Δ (acute minus follow-up) ejection fraction values (%)	1 (−5/8)	−2 (−9/4)
Δ (acute minus follow-up) infarct-zone regional wall motion (SD/chord) (values)	0.39 (−0.30/1.15)	0.07 (−0.49/0.80)

IRA, infarct-related artery.
*Documented by either physical findings or radiological appearances.
†Systolic blood pressure of less than 90 mm Hg for more than 1 hour.
‡Failure to adequately oxygenate leading to need for mechanical ventilatory support.

TABLE 5. Reocclusion After Thrombolytic Therapy and PTCA

	Patent IRA (n=256)	Reoccluded IRA (n=52)
In-hospital complications (%)		
Killip class >1	24.3	22.5
Pulmonary edema*	15.2	19.2
Sustained hypotension†	21.5	25.0
Respiratory failure‡	9.4	13.5
Atrioventricular block (second or third degree)	14.8	25.0
Mortality	4.7	9.6
IRA (%)		
Left anterior descending	41.8	30.8
Left circumflex	16.0	3.9
Right coronary	41.8	65.4
Final percent stenosis (values)	30 (20/48%)	38 (25/50%)
Left ventricular function		
Δ (acute minus follow-up) ejection fraction values (%)	1 (−5/6)	−3 (−7/3)
Δ (acute minus follow-up) infarct-zone regional wall motion (SD/chord) (values)	0.22 (−0.21/0.80)	−0.12 (−0.48/0.63)

IRA, infarct-related artery.
*Documented by either physical findings or radiological appearances.
†Systolic blood pressure of less than 90 mm Hg for more than 1 hour.
‡Failure to adequately oxygenate leading to need for mechanical ventilatory support.

performing a linear regression analysis, reocclusion remained significantly related to changes in infarct-zone regional wall motion (p=0.032), ejection fraction (p=0.007), and mortality (p=0.013).

Silent versus clinically detected reocclusions. Reocclusions were clinically detected in 53 patients (58%); the reocclusions were silent and were found at follow-up cardiac catheterization in 38 patients (42%). The angiographic and hemodynamic characteristics of patients with silent versus symptomatic reocclusion are given in Table 6. The infarct-related artery and TIMI flow were similarly distributed among patency with silent and symptomatic reocclusions. There was a tendency toward a worsening in infarct-zone regional wall motion in patients with silent reocclusions compared with reocclusions that were clinically detected.

Patients with silent reocclusions tended to have fewer in-hospital complications compared with patients with symptomatic reocclusions [pulmonary edema (13% versus 23%), sustained hypotension (5% versus 40%), and respiratory failure (3% versus 21%), respectively]. However, there was a similar incidence of atrioventricular block (25% versus 26%, respectively).

Angioplasty was attempted in 48 patients during the reocclusion of the infarct-related artery (46 symptomatic and two silent reocclusions). The procedure

TABLE 6. Silent Versus Symptomatic Reocclusion

	Symptomatic reocclusion (n=53)	Silent reocclusion (n=38)
Infarct-related artery (%)		
Left anterior descending	37.7	23.7
Left circumflex	3.8	2.6
Right coronary	58.5	73.7
Final percent stenosis (%) (values)	75 (30/95)	50 (30/80)
TIMI flow (%)		
2	30.2	15.8
3	69.8	84.2
Ejection fraction at follow-up cardiac catheterization (%) (values)	52 (44/60)	55 (44/61)*
Δ (acute minus follow-up) ejection fraction (%) (values)	−2 (−9/6)	−3 (−7/1)†
Infarct-zone regional wall motion at follow-up cardiac catheterization (SD/chord) (values)	−2.39 (−3.0/−1.7)	−2.99 (−3.5/−2.2)‡
Δ (acute follow-up) infarct-zone regional wall motion (SD/chord) (range)	0.12 (−0.5/0.8)	−0.23 (−0.5/0.6)*

*p=0.6, †p=0.8, ‡p=0.019.

was successful in 68.8%. In patients in whom angioplasty failed to restore patency, there was a high rate of morbidity compared with patients in whom the procedure was successful [sustained hypotension (46.7% versus 33.3%), respiratory failure (26.7% versus 12.1%), and high-degree atrioventricular block (33.3% versus 18.2%), respectively]. Mortality rates were also higher in patients who failed to have patency restored during reocclusion with angioplasty (26.7% versus 12.1%, respectively).

Discussion

Mortality rates after acute myocardial infarction in patients receiving thrombolytic therapy are approaching 5% in most large studies.[15–18] The majority of deaths now occur in subsets such as patients with severely depressed left ventricular function,[19] those who fail to reperfuse,[20] and as demonstrated by this study, those who suffer reocclusions of an infarct-related artery. Reocclusion of a previously patent coronary artery in our patient population was associated with twice the in-hospital mortality rate (11.0%) compared with that of those who remained patent (4.5%). The very low mortality rate in patients with sustained patency seen in the present study has also been documented in the TIMI I study, in which patients with sustained patency of the infarct-related artery at hospital discharge had a 1.9% mortality rate at 6 months and an additional 1.9% mortality rate at 1 year.[21] Similarly, the Western Washington study documented that patients treated with intracoronary streptokinase had a 2.5% mortality rate at 1 year if the infarct-related artery remained patent.[4] A therapeutic strategy that would prevent reocclusion might therefore further lower in-hospital and long-term mortality and morbidity rates in patients with acute myocardial infarction.

Left Ventricular Function

The present study documented that reocclusion is detrimental to preservation of left ventricular function after reperfusion therapy. Patients who sustained patency of the infarct-related artery had improved global and regional left ventricular function, whereas patients with reocclusion had a decline in these parameters. The importance of the patency and coronary flow to the infarct zone for ensuing myocardial function is supported by animal models of myocardial infarction and reperfusion. These studies have suggested that the flow in the infarct-related artery has important physiological effects on the healing of the myocardium after infarction.[22,23] Preliminary clinical observations have supported this concept in humans.[24] Our findings offer additional support for this hypothesis because reocclusion was associated with worsened infarct-zone regional function on follow-up.

Complications During Hospitalization

Patients who suffered reocclusion of the infarct-related artery had more complicated hospital courses compared with patients with sustained patency. The management of patients with clinically suspected reocclusion was directed to maintain coronary artery patency. Of patients with symptomatic and clinically suspected reocclusion, 86% had attempted angioplasty, which was successful in 67%. It is likely that this approach toward coronary artery patency may be related to some of the higher in-hospital complication rates in patients with symptomatic reocclusions compared with patients with silent reocclusions. However, this approach was associated with a better infarct-zone regional wall motion in patients with clinically detected reocclusion than in patients with silent reocclusion at follow-up.

Angiographic Variables and Reocclusion

The degree of residual stenosis in the infarct-related artery after thrombolysis has been suggested to be important for the occurrence of recurrent ischemic events and reocclusion after streptokinase therapy.[25–27] These studies have suggested that a high degree of residual stenosis was associated with a higher reocclusion rate, but each report was based on a study population of less than 60 patients. We have failed to demonstrate a relation between the residual stenosis after intravenous t-PA and recurrent ischemic events and reocclusion in 192 patients studied with quantitative angiography.[28] Emergency angioplasty was not performed in any of the 192 patients. In this report of 733 consecutive patients, in whom emergency angioplasty was used in 42%, we observed a similar degree of residual stenosis in the infarct-related artery acutely in patients who sustained either patency or reocclusion. Other factors may predispose the infarct-related artery to reocclude, although a previous extensive review of qualitative angiographic factors failed to predict reocclusion.[28]

The degree of coronary perfusion in the infarct-related artery after thrombolytic therapy has been linked to recurrent ischemic events. Wall et al[29] found a higher rate of reocclusion and recurrent ischemic events in patients with TIMI flow 2 compared with those with TIMI flow 3 after achieving patency without emergency angioplasty. A similar relation between suboptimal perfusion and reocclusion has been documented in patients in whom angioplasty was used in combination with thrombolytic therapy.[30] The present data further suggest a relation between reduced coronary flow and reocclusion because 65% of patients who reoccluded had less than TIMI flow 3 at acute cardiac catheterization.

Systemic Fibrinolysis and Reocclusion

The degree of systemic fibrinolysis may be important for the prevention of reocclusion.[31] This hypothesis is supported by the finding in the patients with reocclusion who had a lower formation of fibrin degradation products, suggesting a lower rate of systemic fibrinolysis compared with patients who did not suffer a reocclusion. In addition, it has been suggested that early reocclusion can be prevented by a maintenance infusion of t-PA,[27,32] thus prolonging the fibrinolytic state. Reocclusion rates after different thrombolytic agents used in this study cannot be assessed reliably because different strategies for thrombolytic therapy and angioplasty were used. Preliminary data from the recently completed TAMI 5 study, in which administration of intravenous urokinase, t-PA, and a combination of the two were examined, showed reocclusion rates for t-PA (14%) and urokinase (6%) identical to those of the present study.[33] A lower reocclusion rate with urokinase compared with t-PA has also been documented by the German Activator Urokinase Study (GAUS), in which the reocclusion rate after urokinase was 6.5% and after t-PA was 14.8%.[34] Thus, agents that either alone or in combination induce a systemic fibrinolytic state may be advantageous in reducing the reocclusion rate.

Incidence of Reocclusion

The incidence of reocclusion in this large cohort was 12.3%, which is similar to the rate of 13% reported from pooled data of studies in which PTCA was used acutely.[35] More recently, the TIMI study group reported a reocclusion rate of 12.8% in the invasive strategy arm of patients who underwent PTCA.[18] Similar data have been reported by Stack et al[36] (10.2%) and by the European Cooperative Study Group[37] (11.7%). In general, reocclusion rates have been higher in studies in which PTCA was not performed with a pooled mean of 19%,[35] including rates as high as 33% with t-PA[37] and as low as 4% with urokinase.[39] The estimated reocclusion rate in the TIMI I study[40] was identical with either streptokinase (30%) or t-PA (29%). Thus, the reocclusion rate reported in the present study closely reflects a clinical practice with different thrombolytic agents in which PTCA was used acutely in 42%.

Silent Reocclusion

Only 58% of the patients in our series documented symptoms suggesting reocclusion of the infarct-related artery. However, silent reocclusion remains clinically important because patients without symptoms have degrees of global left ventricular dysfunction similar to those of patients with detected reocclusions. In addition, there was a tendency for a decline in infarct-zone ventricular function in patients with silent reocclusions. This group was predominantly treated medically; attempts to revascularize were used in only 5%.

The detrimental effect of symptomatic reocclusion is evident from results of this study. The mortality rate in patients in whom angioplasty failed to restore patency after reocclusion was high (26.7%). We have previously noted high morbidity and mortality rates in patients with reinfarction who failed to reperfuse.[41] In our experience, reinfarction represents the second most common mode of death after progressive cardiac failure in the thrombolytic era.[42] Hence, symptomatic reocclusion in the form of reinfarction represents a high-risk syndrome that needs to be prevented to enhance clinical outcome after thrombolytic therapy.

Timing and Detection of Reocclusion

Seventy-five percent of the clinically suspected reocclusions occurred during the first 3 days, and 50% occurred within the first 24 hours. Hence, strategies for detecting or preventing reocclusions should concentrate on the first 48–96 hours after myocardial infarction. The incidences of angina in patients with and without reocclusions were similar in one of every five patients; thus, angina per se will not aid in detecting patients at risk for reocclusion. Continuous recording with the 12-lead electrocardiogram may offer a simple method of noninvasively

detecting reocclusion[43,44] because many ischemic episodes, as evidenced by ST segment elevation, occur without symptoms.

Emergency Angioplasty and Reocclusion

The association between reocclusion and emergency angioplasty cannot be fully explored in the present study because angioplasty was applied both as a rescue procedure in patients with TIMI flow 0 or 1 and in patients with evidence of ischemia despite a patent infarct-related artery and as part of the randomization strategy in TAMI I.[7] The reocclusion rate was highest among patients who had rescue PTCA. Confirming our previous experience with rescue PTCA,[20,45] these data suggest that initial TIMI flow 0 or 1 may be a risk factor for reocclusion if patency is restored.

Study Limitations

All of the reocclusions were documented by angiography, which was performed in 88% of patients. This very high follow-up arteriographic rate is higher than that of the TIMI I study[40] (72%) and comparable to our previous data[36] (91%) and data from the European Cooperative Study Group[37] (93%) but does not exclude the possibility that silent reocclusions occurred in the remaining 12%. The majority of excluded patients had CABG soon after infarction and refused repeat arteriography. Because reocclusion tended to be less common in patients who had CABG, it is unlikely that results from this group would contribute significantly to the overall findings.

Our cohort was drawn from four sequential studies that had almost identical study protocols but used different thrombolytic agents and invasive strategies. Although this combination may reflect clinical practice, it offers some limitations to specific questions regarding the role of PTCA or of different thrombolytic agents and reocclusion rates. In addition, our dedicated approach toward achieving coronary artery patency after successful reperfusion may have led to a higher complication rate in this cohort.

The role of intervening revascularization procedures in determining the reocclusion rate cannot be addressed in the present study. The overall rate of nonacute interventions before repeat angiography was less than 10%; therefore, it would be unlikely to affect the overall outcome. In addition, data from a West Germany study[46] in which no interventions were performed during a 6-month period after acute myocardial infarction showed a similar rate of reocclusion.

Conclusions

Our findings from results of a study of a large cohort of patients treated aggressively with heparin and aspirin with documented patency and reocclusions after thrombolytic therapy suggest that reocclusion is common. The occurrence of reocclusion is associated with a more complicated hospital course, deterioration in both global and regional left ventricular function, and a higher in-hospital mortality rate. New strategies in the postinfarction period need to be developed to prevent this deleterious event.

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