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Reocclusion: The Flip Side of Coronary Thrombolysis

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Since the introduction of thrombolytic therapy for acute myocardial infarction, the incidence of coronary artery reocclusion has been intensively studied. Also, the prediction and diagnosis of reocclusion by angiographic and clinical variables, as well its invasive and pharmacologic prevention, have gained much attention.

By angiographic definition, reocclusion requires three angiographic observations: one with an occluded artery, one with a reperfused artery and a third for the assessment of subsequent occlusion (true reocclusion). Since the introduction of early intravenous reperfusion therapy, most studies use only two angiograms: one with a patent and one with a nonpatent infarct-related artery. A search for all published reocclusion studies revealed 61 studies (6,061 patients) with at least two angiograms. The median time interval between the first angiogram after thrombolysis and the second was 16 days (range 0.1 to 365). Reocclusion was observed in 666 (11%) of 6,061 cases. Interestingly, the 28 true reocclusion studies showed an incidence of reocclusion of 16 ± 10% (mean ± SD), and the 33 studies with only two angiograms 10 ± 8% (p = 0.04), suggesting that proven initial occlusion of the infarct-related artery is a risk factor for reocclusion after successful thrombolysis. The other predictors for reocclusion are probably severity of residual stenosis of the infarct-related artery after thrombolysis and perhaps the flow state after lysis. Reocclusion is most frequently seen in the early weeks after thrombolysis. The clinical course in patients with reocclusion is more complicated than in those without this complication. Left ventricular contractile recovery after thrombolysis is hampered by reocclusion.

Routine invasive strategies have not been proven effective against reocclusion. In the prevention of reocclusion, both antiplatelet and antithrombin strategies have been tested, including hirudin and hirulog, but the safety of these agents in thrombolysis is still questionable.

Thus, reocclusion after thrombolysis is an early phenomenon and is more frequent after proven initial occlusion of the infarct-related artery. Reocclusion can be predicted by angiography after thrombolysis. Because reocclusion is detrimental, strategies to prevent it should be developed and carried out after thrombolytic therapy for acute myocardial infarction as soon as they are deemed safe.

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Besides bleeding, a major drawback of thrombolytic therapy for acute myocardial infarction is the increased incidence of recurrent ischemia, probably a result of coronary artery reocclusion (1). This review deals with the pathologic, clinical, angiographic, therapeutic and prognostic aspects of coronary reocclusion after thrombolytic therapy for acute myocardial infarction, as well as the strategies to prevent it.

Definition of Reocclusion

The angiographic definition of coronary reocclusion is literally that it occurs after 1) angiographically proven initial occlusion of the infarct-related vessel, 2) angiographically proven subsequent successful coronary recanalization, and 3) angiographically proven subsequent occlusion of the infarct-related vessel. Although angiography is still the reference standard for defining reocclusion, its snapshot characteristic makes it almost useless in clinical practice. Clinical signs of reperfusion and reocclusion are better guidelines, but they lack sensitivity and specificity. Interestingly, in patients with chest pain and ST segment elevation, angiographic "spontaneous" reperfusion is seen in 18% to 20% of cases (2,3). Since the introduction of early intravenous thrombolysis, angiography is mostly performed after initial treatment. Loss of coronary patency between two angiographic observations is usually called reocclusion. Because of these reasons, single angiographic observations showing an occluded infarct-related artery after thrombolysis can hardly represent reocclusion, although sometimes clinicians erroneously call lack of patency reocclusion.

The angiographic classification of patency is important to note. Two grading systems have been used: the European Cooperative Study Group (4) and the Thrombolysis in Myocardial Infarction (TIMI) flow grade classification (2). Currently the TIMI flow grade classification is most widely used, and recently it was shown that insufficient flow, like TIMI flow grade 2, is clinically almost identical to TIMI flow grade 0 to 1

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(5,6). With this in mind, reocclusion in the most clinically used way means the evolution of TIMI flow grade 3 to absent or low clinical flow states (TIMI flow grade 0 to 2). The large combined outcome and angiographic Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) study yielded insight into the clinical consequences of the several flow states in reperfusion therapy for acute myocardial infarction (6).

Pathogenesis of Reocclusion

The pathologic and angiographic observations with thrombolytic therapy have firmly established the role of thrombosis in the pathogenesis of acute myocardial infarction. Plaque rupture probably causes activation of blood platelets and the coagulation cascade, resulting in total thrombotic occlusion of a coronary artery. Depending on the area at risk, collateral blood flow and the duration of occlusion, the resulting infarct will be large or small with little sequelae or with deleterious consequences to the patient. Reperfusion therapy is aimed at early restoration of blood flow by dissolving or removing thrombotic material at the site of the coronary lesion. Because the nidus of coronary thrombus usually is not removed, rethrombosis can easily occur. Because thrombosis and thrombolysis probably represent a subtle balance, reestablishment of the thrombotic state may lead to coronary rethrombosis. Remarkably, plasminogen activation with exogenous compounds has the paradoxic effect of activating both platelets and thrombin in the acute phase (7–10). Also, incomplete lysis of thrombus (11) and plaque swelling after thrombolysis (12) may be stimuli for rethrombosis.

The natural history of residual stenosis after thrombolysis shows decremental stenosis severity in the majority of patients, suggesting ongoing thrombus resolution and plaque repair (13). Platelets cannot only be activated by reexposure to the damaged vessel, but also by high shear rates (14). After thrombolysis a high grade residual stenosis might activate platelets by this mechanism. Experimental studies have shown that fibrin-rich thrombus may be replaced by platelet-rich thrombus that may be highly resistant to lysis (7). However, other processes like inflammation and tissue proliferation caused by growth factors cannot be excluded, although they have not been studied in the setting of reocclusion.

Reocclusion is probably a time-dependent process. However, some vessels show total obstruction early after thrombolytic therapy and are patent when studied later. Therefore, it seems likely that prothrombotic and antithrombotic processes continue long after thrombolytic therapy vessel wall repair is finished.

Incidence of Reocclusion

The incidence of reocclusion has been intensively studied since the introduction of thrombolytic therapy for acute myocardial infarction. Through EMBASE a search for reocclusion studies was done using the key words *reocclusion* and *thrombolytic therapy*. Between 1980 and 1994, 60 studies with at least one follow-up angiogram after angiographically successful thrombolytic therapy have been published. They included 6,061 patients, of whom 666 (11%) sustained reocclusion of the infarct-related artery. The median time between the first postthrombolysis angiogram and the follow-up angiogram was 16 days (range 0.1 to 365). The postthrombolysis angiogram showed an "open" infarct-related artery or "successful" reperfusion and the follow-up angiogram an "occluded" artery. Studies with three angiograms (one with an occluded artery, one with a reperfused artery and a third for the assessment of reocclusion) are true reocclusion studies. The 28 true reocclusion studies (1,037 patients) show an incidence of reocclusion of 16 ± 10% (mean ± SD). The 33 studies (5,024 patients) with only two angiograms (one with an open artery and a second for the assessment of reocclusion) report a reocclusion incidence of 10 ± 8% ($p = 0.04$ vs. true reocclusion studies). This indicates that angiographically proven initial occlusion of the infarct-related artery is a risk factor for reocclusion. Two of the studies with three angiograms have specifically analyzed the difference in reocclusion after angiographically proven initial occlusion and angiographically proven initial patency. Serruys et al. (15) showed reocclusion of 2 (6%) of 36 initially open vessels compared with 19 (21%) of 91 initially occluded vessels ($p < 0.05$). For TIMI-I (2), these figures were 2 (5%) of 40 and 19 (21%) of 91 ($p < 0.05$).

Because of the snapshot characteristic of the angiographic approach, other diagnostic criteria (see later) are eagerly awaited. In the meantime, reocclusion can only be detected by angiography, with its important limitations, such as cost and safety. The time window for the diagnosis of reocclusion is very important. The first observation of patency is usually performed between 60 and 180 min after initiation of thrombolytic therapy. Follow-up angiography can be performed as early as 24 h after the first angiogram. The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial, the largest study reporting on in-hospital reocclusion comprised 642 patients, demonstrated reocclusion of ~9% after successful thrombolytic therapy and 17% reocclusion after initially failed thrombolytic therapy followed by coronary angioplasty (16). Another reported large study of in-hospital reocclusion was GUSTO trial, which showed a low reocclusion rate of ~6% (6). Reocclusion in the first year after thrombolysis is more frequent. Probably the large time window between which the angiograms are obtained (e.g, the first days of thrombolysis followed by angiography at 3 months) forms the explanation for the high incidence. Reocclusion diagnosed at 3 months might be as high as 18% to 32% (17–19). Data on vessel patency 1 year after thrombolytic therapy revealed about the same incidence (20).

To study reocclusion over time, the incidence of reocclusion and the time of the second angiogram are plotted in Figure 1. Because reocclusion occurs in a minority of patients treated with thrombolysis, only the larger studies were taken into account. A cutoff point of 75 patients was chosen. Table 1 summarizes the 20 studies fulfilling these criteria (2,5,16,18,

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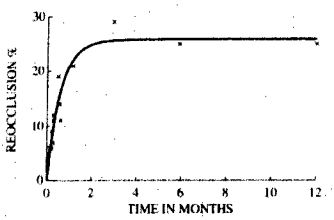

Figure 1. Incidence of reocclusion after thrombolysis in the published studies with >75 patients. The x axis represents the time between the initiation of thrombolytic therapy and the time of follow-up angiography.

20–33). Figure 1 clearly shows that reocclusion is most frequent in the first week after thrombolysis and its incidence levels off in the ensuing months. The incidence of reocclusion after thrombolytic therapy increases with the time window of observation. The snapshot approach is probably the cause of this phenomenon. In contrast, it is quite possible that vessels may reocclude intermittently, which is not diagnosed by the follow-up angiogram.

About 25% of patients treated with thrombolytic therapy for acute myocardial infarction fail to achieve reperfusion, leaving only 75% of successfully treated patients. It is clear from the GUSTO trial that early complete vessel patency with TIMI flow grade 3 is only observed in ~50% of patients undergoing thrombolytic therapy. Approximately 30% of patients will experience reocclusion in the subsequent months, leaving much less than 50% of patients with successful sustained full reperfusion. Thus, only a minority of patients will have full sustained benefit from thrombolytic therapy.

A 21% incidence of reocclusion after primary angioplasty for acute myocardial infarction was reported recently in the Primary Angioplasty Myocardial Infarction (PAMI) trial involving a limited number of patients: 33 of 154 patients had TIMI flow grade 0 to 2 six months after successful primary angioplasty (34). The incidence of restenosis was reported to be ~25% at 3 months (35) and 45% at 6 months (34). Reocclusion data on thrombolysis in the randomized trials of primary angioplasty versus thrombolysis are lacking.

Noninvasive Indicators of Reocclusion

Clinical variables have been intensely tested in the prediction and diagnosis of coronary reperfusion. In the absence of angiography, successful reperfusion is as difficult to diagnose as subsequent reocclusion. Relief of chest pain, disappearance of ST segment elevation and the occurrence of accelerated idioventricular rhythm are all indicators, but no proof of successful reperfusion. When they are combined, they are more indicative of reperfusion, and when none of them are present, persistent occlusion is likely. The introduction of continuous 12-lead ST segment monitoring has made the noninvasive diagnosis of failed reperfusion much more sensitive than the other clinical variables (36).

Recurrence of chest pain and ST segment elevation and reinfarction are probably indicators of reocclusion. Also, continuous 12-lead ST segment monitoring might be a more sensitive indicator of reocclusion after coronary thrombolysis (37). Other diagnostic tools like thallium-201 or technetium sestamibi have not been tested in the diagnosis of reocclusion.

Prediction of Reocclusion

After thrombolysis, smoking and the continuation of smoking have been identified as the only independent predictors of reinfarction (38), not of reocclusion, and because reinfarction is only a part of the spectrum of reocclusion, no clearcut clinical variables can be identified as risk determinants for reocclusion.

Angiographic predictors of reocclusion may include flow status, stenosis severity and morphology of the culprit lesion. Studies specifically aimed at identifying the incidence of reocclusion, not recurrent ischemia (39), are the TAMI (16), TIMI-4 (33), Aspirin Versus Coumadin Trial (APRICOT) (40) and GUSTO (41) studies and the study by White et al. (20). A poor flow state (TIMI flow grade 0 or 1) of the infarct-related artery at 90 min after thrombolysis initiation was a significant predictor of subsequent reocclusion in the TAMI trials and the TIMI-4 study. However, this finding could not be confirmed in the GUSTO angiographic study (41). In the APRICOT study, reocclusion was the primary end point in 284 patients, and only patients with TIMI flow grade 3 were included. All patients with TIMI flow grade 2 or less were regarded as showing reocclusion on the second angiogram. It was clearly shown that stenosis severity is an independent risk factor (odds ratio 2.3) for the occurrence of reocclusion. Interestingly, a smooth morphology of the culprit lesion is also associated with reocclusion. Also, in the trial by White et al. (20) and the TIMI-4 study (33), residual stenosis severity proved to be a predictor of reocclusion in the year after successful thrombolysis.

As stated previously, angiographically proven initial occlusion of the infarct-related artery seems to be a risk factor for subsequent reocclusion. Thus, the risk of reocclusion can probably be predicted by early angiographic observation both before and after thrombolytic therapy.

Consequences of Reocclusion

The presence of both an initially open artery and salvaged myocardium may determine the clinical manifestations of reocclusion. Reocclusion may be associated with recurrent angina, reinfarction, pump failure and death. It may also occur without symptoms. Symptomless reocclusion may be associated with the presence of collateral channels protecting the salvaged myocardium against renewed damage at the time of reocclusion. In contrast, symptomless reocclusion may also indicate a lack of initially salvaged myocardium. This question has not yet been answered, and no conclusive studies evaluating the presence of myocardial viability and consequences of

Table 1. Reocclusion Rates After Successful Thrombolysis (summary of trials with at least 75 patients)

First Author or Study Name (ref no.)	No. of Pts*	Angiogram	Angiographic Time Window	Thrombolytic Agent	Average Reocclusion (%)
Serruys (15)	91	1st	Acute, serial	IC (+IV) SK	21
		2nd	2–8 wk		
Timmis (21)	95	1st	Acute, serial	IC SK	14
		2nd	10–24 d		
TIMI-I (2)	91	1st	Acute, serial	SK, tPA	19
		2nd	5–25 d		
TAMI-1 (22)	197	1st	90 min	tPA	12
		2nd	7–10 d		
Uebis-1 (23)	106	1st	Acute, serial	IC SK	6
		2nd	3 d		
Uebis-2 (23)	76	1st	Acute, serial	IC SK	25
		2nd	6 mo		
Anderson et al. (24)	77	1st	90 min	IC SK, APSAC	5
		2nd	<24 h		
PRIMI (30)	213	1st	45–75 min	pro-UK	3
		2nd	24–36 h		
Ohman (16)	419	1st	90 min	IV UK, tPA,	9
		2nd	7 d	IV UK+tPA	
TAMI 1–5 (26)	607	1st	90 min	IV UK, tPA,	11
		2nd	7–10 d	IV UK+tPA	
TEAM-2 (25)	190	1st	90–240 min	SK, APSAC	2
		2nd	1 d		
ARMS (28)	102	1st	90 min	APSAC	4
		2nd	24 h		
TAMI-7 (27)	157	1st	90 min	IV UK, tPA	7
		2nd	5–10 d		
TAPS-1 (29)	339	1st	90 min	APSAC, tPA	6
		2nd	24–48 h		
TAPS-2 (29)	339	1st	90 min	APSAC, tPA	11
		2nd	14–21 d		
HART (31)	98	1st	7–24 h	tPA	9
		2nd	7 d		
APRICOT (18)	248	1st	<48 h	SK, APSAC	29
		2nd	3 mo		
GUSTO (6)	586	1st	90 min	SK, tPA,	6
		2nd	5–7 d	SK+tPA	
TIMI-5 (32)	183	1st	90 min	tPA	4
		2nd	16–36 h		
White (20)	154	1st	4 wk	SK, tPA	25
		2nd	1 yr		
TIMI-4 (33)	278	1st	90 min	APSAC, tPA	5
		2nd	18–36 h		

*With angiographically successful thrombolysis and with one or more follow-up angiograms. APRICOT = Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis; APSAC = anisoylated plasminogen streptokinase activator complex; ARMS = APSAC Reocclusion Multicenter Study; d = day; GUSTO = Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries; HART = Heparin-Aspirin Reperfusion Trial; IC = intracoronary; IV = intravenous; PRIMI = Pro-Urokinase in Myocardial Infarction; pro-UK = pro-urokinase; Pts = patients; ref = reference; SK = streptokinase; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction; TAPS = t-PA APSAC Patency Study; TEAM = Trial of Eminase Versus Alteplase in Myocardial Infarction; TIMI = Thrombolysis in Myocardial Infarction; tPA = tissue-type plasminogen activator; UK = urokinase.

collateral channels after reocclusion are available. Some large studies showed that reocclusion precludes left ventricular contractile recovery (16,20,42), especially in the infarcted region of the left ventricle. This occurs also in the absence of clinical reinfarction (41). Reocclusion in the anterior region of the left ventricle has the worst consequences for global left ventricular function (42). Apparently, reocclusion is deleterious for long-term left ventricular function and indirectly indicates that myocardial viability exists after successful thrombolysis.

Recurrent angina is a poor indicator of reocclusion. Angina is a symptom notoriously difficult to interpret. Reinfarction

Table 2. Randomized, Controlled Trials With Two Angiograms for Prevention of Reocclusion With Heparin After Successful Coronary Thrombolysis

Study (ref no.)	No. of Pts	1st Angiogram	2nd Angiogram	Reocclusion With Heparin [no. (%) of pts]	Reocclusion With Control [no. (%) of pts]	p Value
APRICOT (18)	155	23 h (median)	3 mo	24/81 (30%)*	24/74 (32%)†	NS
HART (31)	98	18 h (mean)	7 d	7/60 (12%)†	2/38 (5%)‡	NS

*Patients were not receiving aspirin; warfarin was started with heparin; heparin was discontinued when thromboplastin time was therapeutic. †Patients were not receiving aspirin. ‡Patients were receiving aspirin, 80 mg/day. Abbreviations as in Table 1.

early after thrombolytic therapy is probably due to reocclusion because its incidence is twice as high as that for with control treatment (3,43,44). Depending on the definition, the reinfarction rate can be as high as 13% (45). To our knowledge, a hard correlation between reocclusion and reinfarction has never been made. This correlation is scarcely possible because in the search for reocclusion, one is forced to use the snapshot approach. It is likely that reinfarction is the result of reocclusion. Because reocclusion impedes recovery of left ventricular function, it is understandable that mortality is higher with than without reocclusion (16). In the thrombolysis-only arms of the TAMI studies 5 (12.8%) of 39 patients with reocclusion died versus 15 (4%) of 380 patients without reocclusion ($p < 0.02$).

Prevention of Reocclusion

Strategies to prevent reocclusion may be invasive or noninvasive. Invasive strategies consisting of early angiography followed by angioplasty have been tested extensively in the prevention of reocclusion after successful coronary thrombolysis (46). The largest study, carried out in the United States, prospectively analyzed a routine invasive versus a routine conservative strategy after thrombolysis with tissue-type plasminogen activator (t-PA) (47). It was clearly shown that a routine invasive strategy does not prevent recurrent ischemia, reinfarction or death, nor does it preserve residual left ventricular function after thrombolytic therapy for acute myocardial infarction. Also, the long-term efficacy of this strategy has not been proven. Apparently, manipulation by angioplasty of a postthrombolytic coronary lesion, which contains or has contained thrombotic material, exposes the patient to untoward effects of angioplasty, like total occlusion or vessel dissection. Another invasive strategy to prevent reocclusion is aortic balloon counterpulsation immediately after thrombolysis. In one large trial (48), this proved to be effective, but these results should be confirmed in another study.

Noninvasive methods to prevent reocclusion have also been evaluated and seem to be partially effective. However, in analyzing the data, one should clearly discriminate between early coronary patency and proven coronary reocclusion. For the diagnosis of early patency, one needs only one angiogram. For the diagnosis of reocclusion, one needs at least two angiograms: one with a patent and one with a subsequently occluded coronary lesion.

Heparin has been extensively tested after thrombolysis, especially with t-PA. Coronary patency evaluated in the first hours or days after thrombolytic therapy with t-PA is better with than that without intravenous heparin (31,49,50). These data do not necessarily prove that heparin, when used in conjunction with t-PA, actually prevents reocclusion. Randomized, controlled studies on the effect of intravenous heparin in the prevention of reocclusion after angiographically proven successful coronary thrombolysis are scarce and have a negative outcome (Table 2). Intravenous heparin followed by warfarin sodium (Coumadin) does not prevent long-term reocclusion either (18). Heparin infusion after t-PA for acute myocardial infarction is probably necessary during a short time and can be discontinued 24 h after thrombolytic therapy (51). Heparin therapy is notoriously difficult to monitor, which might be the reason for its apparent ineffectiveness in preventing reocclusion. Partial activated thromboplastin time is the usual measure for heparin anticoagulation. There is a correlation between adequacy of heparinization and coronary patency (49), but its relation to reocclusion after successful thrombolysis has not been systematically studied. Close monitoring of heparin therapy after thrombolysis is mandatory not only for patency and possibly reocclusion but also for the prevention of bleeding. Partial activated thromboplastin time values >90 s after thrombolysis are correlated with an unacceptable risk of cerebral bleeding (52,53). Hirudin and hirulog, highly specific antithrombin agents, seem to be more effective than heparin in the prevention of reocclusion after t-PA (32) or streptokinase (54) (Table 3). However, patient numbers in these trials are small, and although more simple than with heparin, hirudin

Table 3. Randomized, Heparin-Controlled Trial With Two Angiograms for Prevention of Reocclusion With Hirudin or Hirulog After Successful Coronary Thrombolysis

1st Author or Study Name (ref no.)	No. of Pts	Agent	1st Angiogram	2nd Angiogram	Reocclusion With Agent [no. (%) of pts]	Reocclusion With Heparin [no. (%) of pts]	p Value
TIMI-5 (32)	165	Hirudin	90 min	16–36 h	1/105 (1%)	4/60 (7%)	0.05
Lidon (54)	45	Hirulog	90 min	5 d	0/30 (0%)	1/15 (7%)	NS

Abbreviations as in Table 1.

Table 4. Randomized, Controlled Trials With Two Angiograms for Prevention of Reocclusion With Aspirin After Successful Coronary Thrombolysis

1st Author or Study Name (ref no.)	No. of Pts	1st Angiogram	2nd Angiogram	Reocclusion With Aspirin [no. (%) of pts]	Reocclusion With Control [no. (%) of pts]	p Value
APRICOT (18)	167	23 h (median)	3 mo	23/93 (25%)	24/74 (32%)	NS
White (20)	154	4 wk	1 yr	18/79 (23%)	20/75 (27%)	NS
HART (31)	98	18 h (mean)	7 d	2/38 (5%)	7/60 (12%)†	NS

*Combined with dipyridamole, 200 mg twice a day. †Patients were receiving intravenous heparin with a partial activated thromboplastin time between 1.5 and 2.0 s. Abbreviations as in Table 1.

also needs close monitoring, because it is associated with more cerebral bleedings than heparin (52,53,55).

The role of antiplatelet therapy after thrombolytic therapy in the prevention of reinfarction has been firmly established (43). However, the mechanism by which this benefit is achieved is not clear (56). Many believe that antiplatelet therapy prevents reocclusion after thrombolysis, but this has never been proved. Patency after thrombolysis is better with aspirin than without it (57), but this does not prove aspirin prevents reocclusion. Placebo-controlled studies with aspirin in successfully thrombolyzed patients with follow-up angiograms are scarce. They show that aspirin only tends to prevent reocclusion (18,20,57) (Table 4).

Because the reocclusion trials with heparin and aspirin are few in number and small in size, large-scale angiographic studies are necessary to identify the role of these agents in the prevention of reocclusion. However, placebo-controlled studies cannot be carried out any more because the place of these drugs in the standard thrombolytic strategies for optimal patency and reduction of reinfarction has been firmly established.

Primary angioplasty without the use of thrombolysis might eliminate factors in the culprit lesion leading to reocclusion. However, as stated before, the reocclusion rate after this therapy has been reported in only a limited number of patients and does not seem to differ from reocclusion after thrombolysis, although more data from randomized trials are necessary.

Currently several antiplatelet and antithrombin strategies after thrombolytic therapy are being clinically tested.

Treatment of Reocclusion

As stated previously, coronary occlusion is detrimental to left ventricular contractile recovery, even in the absence of clinical reinfarction. Many believe that once reocclusion is diagnosed, thrombolytic therapy for acute myocardial infarction has failed. Interestingly, ~50% of reocclusions are not accompanied by clinical recurrent infarction or recurrent ischemia (16) and thus are silent. Reperfusion therapy with angioplasty even weeks after myocardial infarction seems to be beneficial in selected patients in terms of left ventricular functional recovery (58). Therefore, it seems that myocardial viability exists even after the occurrence of reocclusion. If silent reocclusion leaves myocardial tissue viable, it could be treated. If it occurs early, rethrombolysis is an option, although revascularization seems to be a more definite solution.

The optimal time for angiography after thrombolytic therapy for acute myocardial infarction is probably several days before hospital discharge. The patency of the infarct-related vessel can be used for risk stratification for either reocclusion or further left ventricular functional recovery. Culprit lesion severity tends to diminish over time (13) and a not severely stenosed infarct-related artery will not reocclude easily (40). When the infarct-related vessel is open but severely stenosed, revascularization seems to be indicated, because these vessels tend to reocclude (13,20). If the infarct-related vessel is occluded, angioplasty can be carried out to allow left ventricular contractile recovery (58). Patients with minimal infarction in relation to estimated risk area and those in whom viable myocardium can be shown to be present with nuclear techniques (59,60) or dobutamine stress echocardiography (61,62) might benefit from this procedure. Angioplasty of the infarct-related artery a few days before hospital discharge is feasible because the vascular occlusion must be very recent, and is probably also safer than angioplasty early after thrombolysis. However, a strategy of predischarge angiography with subsequent revascularisation of severely stenosed or occluded infarct-related arteries supplying viable myocardium has not been tested yet in a large randomized trial. For this purpose at least 300 patients should be randomized to show, with a power of 80%, a statistically significant 50% reduction of an expected 25% reocclusion of very tightly stenosed or occluded infarct vessels that are dilated at hospital discharge. As yet, invasive strategies in the prevention and treatment of reocclusion after thrombolysis cannot be recommended for routine clinical practice.

Conclusions

Reocclusion after thrombolytic therapy for acute myocardial infarction remains a major problem in everyday cardiology. It is probably thrombotic in origin and its incidence varies strongly at the time of diagnosis: from 5% to 30%. The highest incidence is seen after proven initial occlusion of the infarct-related artery. The incidence is ~5% to 10% during the hospital stay for the index infarction and levels off to ~30% in the first year. Reocclusion interferes with left ventricular contractile recovery and also seems to be associated with high

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morbidity and mortality. It might be predicted by early angiography, but so far invasive strategies have failed to prevent it. Whether reocclusion can be prevented by the use of antithrombotic agents is still unclear. Both heparin and aspirin are associated with better patency, but randomized, controlled trials with these agents in the prevention of angiographically proven reocclusion are small and inconclusive. More antithrombotic and antiplatelet drugs need to be tested in the prevention of reocclusion.

Because reocclusion is often silent, it is possible that viable myocardium remains even after reocclusion. Therefore, invasive treatment of coronary reocclusion may be an option in the further improvement of thrombolytic therapy, but this should be tested first in a randomized trial. Both the prevention and treatment of reocclusion after thrombolytic therapy are main fields of future clinical research.

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