JACC Vol. 21, No. 6
May 1993:1391–5

Impact of Early Perfusion Status of the Infarct-Related Artery on Short-Term Mortality After Thrombolysis for Acute Myocardial Infarction: Retrospective Analysis of Four German Multicenter Studies

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Objective. This study evaluated the impact of early patency of the infarct-related vessel on short-term mortality after thrombolysis for acute myocardial infarction.

Background. Different thrombolytic regimens for acute myocardial infarction proved to be equally effective in large scale mortality trials despite significant differences in their efficacy with respect to early infarct-related vessel patency as shown in smaller angiographic trials.

Methods. Patients from four German multicenter studies of thrombolysis in acute myocardial infarction were retrospectively evaluated. Of 939 patients with acute myocardial infarction (duration of symptoms <6 h) treated with thrombolysis, 907 (96.6%) had an angiogram of the infarct-related artery 90 min after the initiation of thrombolytic therapy. The perfusion status was graded according to the Thrombolysis in Myocardial Infarction (TIMI) study criteria.

Results. Complete reperfusion (TIMI grade 3) was found in 561 of 907 patients and partial reperfusion (TIMI grade 2) in 122 of 907. Overall, the in-hospital mortality rate was 4.6% (43 patients). In patients with complete reperfusion of the infarct-related vessel, the mortality rate was only 2.7% versus 7.1% in patients with an occluded vessel at the 90-min angiogram. This difference was highly significant in univariate as well as in multivariate analysis. In patients with partial perfusion of the infarct vessel, the mortality rate was 6.6%.

Conclusions. The early perfusion status of the infarct-related artery is an independent predictor of short-term survival. However, only complete early reperfusion is associated with a reduced in-hospital mortality rate whereas patients with partial perfusion (TIMI grade 2) have a short-term prognosis similar to that of patients with persistently occluded infarct vessels. Therefore, when used as a surrogate end point for mortality, only TIMI grade 3 perfusion of the infarct vessel should be interpreted as a treatment success of thrombolysis in acute myocardial infarction.

(J Am Coll Cardiol 1993;21:1391–5)

The efficacy of thrombolytic treatment for acute myocardial infarction was evaluated in several studies by angiographic assessment of early patency of the infarct-related vessel because reperfusion was thought to be the most important mechanism of thrombolysis to improve survival. It has been shown that infarct vessel patency 90 min after the initiation of thrombolysis varies between 65% and 75% with different thrombolytic agents and dose regimens (1–11). Recently, we (12,13) demonstrated an increased early patency rate >80% with front-loaded infusion of recombinant tissue-type plasminogen activator (rt-PA). In contrast, large scale clinical trials (15–17) failed to demonstrate a difference in mortality associated with different thrombolytic treatments, raising the question whether early patency of the infarct vessel had a major influence on the outcome of myocardial infarction.

Since the Thrombolysis in Myocardial Infarction (TIMI) study (3), an infarct-related vessel has commonly been regarded as patent when complete anterograde filling has been demonstrated angiographically, even if the anterograde flow is obviously compromised (TIMI perfusion grade 2). It was recently claimed (18) that this partial perfusion may represent a mostly occluded, but not an open, infarct artery. If this is correct, the traditional definition of infarct vessel patency would significantly overestimate the efficacy of thrombolysis, and the possible impact of early infarct vessel patency on clinical outcome would be masked by an angiographic misinterpretation of functionally occluded vessels as being open.

Therefore, we retrospectively analyzed the angiographic results in >900 patients from four cooperative studies with similar protocols (11–14). The patients were treated with different thrombolytic agents and dose regimens. However, the aim of this analysis was not to assess the differences among various thrombolytic treatments, but to examine possible correlations between the perfusion status of infarct-related vessels and the short-term clinical outcome of the patients.

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Manuscript received June 3, 1992; revised manuscript received November 11, 1992, accepted November 12, 1992.

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0735-1097/93/$6.00

Methods

Study protocol and treatment. Patients aged 25 to 75 years with acute myocardial infarction diagnosed by typical clinical symptoms of >30 min and <6 h duration and by ST segment elevations in the electrocardiogram (≥3 mm in two precordial or ≥2 mm in two limb leads) were included in four multicenter studies of thrombolytic treatment (11–14). Of the 954 patients who entered the studies, 290 were treated with front-loaded rt-PA (15 mg bolus injection, 50 mg over 30 min, 35 mg over 60 min), 124 with 70 mg of rt-PA/90 min, 210 with a bolus injection of 30 mg of anisoylated plasminogen streptokinase activator complex (APSAC), 121 with urokinase (1.5-million U bolus injection and 1.5 million U over 60 min) and 194 with bolus injections of r-PA of 10 million U (n = 43), 15 million U (n = 100) or 10 million U and another 5 million U after 30 min (n = 51). Fifteen patients received no thrombolytic treatment because of withdrawal of informed consent or detection of a contraindication after study entry.

The common main end point of the four studies was the 90-min patency of the infarct-related artery as determined by angiography. Secondary end points were reocclusions as documented by control angiograms after 24 to 48 h and before hospital discharge (day 14 to 21), in-hospital clinical events (especially death and reinfarction) and adverse effects of the thrombolytic treatment.

Each coronary angiogram was evaluated centrally by at least two independent observers. The perfusion of the infarct-related artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) study criteria (3).

Statistics. In this retrospective analysis, the 15 patients without thrombolytic therapy were excluded. None of these patients died in the hospital and none had other serious events. Statistical tests for univariate differences between groups were performed with the chi-square test or analysis of variance (ANOVA). Multivariate analysis for predictors of death was performed with backward stepwise logistic regression analysis. The regression equation used was $\log(P/1-P)=b_0+b_1x_1+b_2x_2+\ldots b_nx_n$, where P is the probability of death, b_0 is the intercept and b_1 through b_n are the regression weights of variables x_1 to x_n. The following variables were tested for possible correlation with short-term mortality in the univariate and multivariate analyses: age, gender, thrombolytic regimen, duration of symptoms before the start of thrombolysis, perfusion status of the infarct-related vessel on the 90-min angiogram, acute coronary interventions (generally angioplasty) and early reocclusion of the infarct vessel. All statistics were computed with the CSS program by STAT-SOFT. Data are reported as mean value ± SD unless otherwise indicated.

Results

Patients and in-hospital events. The mean age of the 939 patients analyzed here was 57 ± 10 years; 163 patients (17.4%) were female. The duration of symptoms to the start of thrombolytic therapy was 163 ± 70 min. The maximal serum activity of creatine kinase was 1,062 ± 775 U/liter; 398 patients (42.4%) had an anterior myocardial infarction.

During the hospital stay (until 21 days after the acute infarction), there were 43 deaths (4.6%). Nineteen patients died in intractable cardiac failure or shock, nine as a result of reinfarction and nine of other cardiac causes (pericardial tamponade in two, ventricular rupture in two, sudden death in two, complications of coronary angioplasty in two, perioperative death in one). Six patients died of noncardiac causes (cerebral bleeding in three, ischemic stroke in two, and retroperitoneal bleeding in one). Definite reinfarction, as diagnosed by chest pain accompanied by newly developed Q waves or a significant increase in cardiac enzyme levels, or both, was encountered in 55 patients.

Angiographic results. Of 939 patients, 907 (96.6%) had a 90-min angiogram of the infarct-related vessel; 860 (91.6%) and 750 (79.9%) had control angiograms after 24 to 48 h and 14 to 21 days, respectively. The infarct-related artery was the left anterior descending coronary artery in 395 patients (42.1%), the right coronary artery in 396 (42.2%) and the left circumflex coronary artery in 124 (13.2%). In 12 patients, the infarct vessel could not be determined angiographically. The overall patency rate of the infarct arteries (TIMI perfusion grade 2 or 3) was 75.4% at 90 min, 87% at 24 to 48 h and 85.6% after 14 to 21 days.

One hundred thirty-eight patients underwent angioplasty of the infarct-related vessel immediately after the 90-min angiogram; no additional interventions were performed before. In the later studies (12–14), the investigators were requested to perform angioplasty only in patients with a persistently occluded infarct vessel (TIMI grade 0 or 1) or if clinical signs of ischemia were present. In these studies, therefore, only 86 (12.4%) of 694 patients had acute angioplasty. Twenty-three of these interventions were performed in open infarct vessels (10 TIMI grade 3 and 13 TIMI grade 2). In the earlier German Activator Urokinase Study (GAUS) (11), acute angioplasty was used more frequently (52 [21.2%] of 245 patients) and in 17 of these patients, the infarct vessel was already open before angioplasty (TIMI grade 3 perfusion in 10 patients and TIMI grade 2 perfusion in 7 on the 90-min angiogram). Overall, the success rate of these acute angioplasty procedures was 79%. Thirty-seven patients had other interventions immediately after the 90-min angiogram (guide wire manipulation or additional thrombolysis); 22 of these interventions were successful.

Angiographically documented reocclusion of the infarct-related vessel was seen within the 1st 48 h in 54 patients; this group comprises 6% of 907 patients with a 90-min angiogram and 7% of 775 patients with an open artery (by thrombolysis or additional interventions) at the end of the 90-min angiogram. Fourteen of these early reocclusions occurred after coronary angioplasty. Late reocclusion (after the second angiogram) was documented angiographically in 52 patients; this group comprises 5.7% of 907 patients with a 90-min

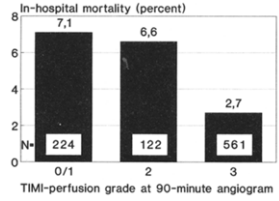

Figure 1. In-hospital mortality in patients with an occluded infarct-related vessel on the 90-min angiogram (0/1) and with partial (2) and complete (3) reperfusion. The group differences are significant by multivariate analysis ($p < 0.01$). N denotes the number of patients in either group. TIMI = Thrombolysis in Myocardial Infarction.

angiogram and 7% of 748 patients with an open artery on the control angiogram after 24 to 48 h. In the total group of 106 patients with early or late angiographically documented reocclusion, 26 patients had definite reinfarction and 2 patients died.

Impact of early perfusion status on outcome. Of the 43 patients who died in the hospital, 4 died in cardiogenic shock without a 90-min angiogram of the infarct-related vessel. However, three of these four patients had an angiogram obtained 60 min after the start of thrombolysis that showed an occluded infarct artery. The fourth patient died within 50 min after the start of thrombolytic therapy without any angiogram.

In the remaining patients, the perfusion grade on the 90-min angiogram proved to be a significant predictor of in-hospital mortality (Fig. 1). Complete early reperfusion of the infarct-related artery was associated with ≈60% lower in-hospital mortality rate than that observed in patients with an occluded vessel. In patients with only partial perfusion of the infarct vessel (TIMI perfusion grade 2 at 90 min), the mortality rate was similar to that in patients with complete occlusion.

In univariate analysis, age and gender were also significant predictors of mortality. Mortality was 1.3% in patients <50 years of age, 2.4% in those aged 50 to 60 years and 8.3% in patients >60 years old ($p < 0.001$, ANOVA). The mortality rate was 8.6% in women compared with 3.7% in men ($p = 0.013$, chi-square analysis). However, gender was not a significant predictor of mortality in multivariate analysis. The reason may be that the female patients were significantly older than the male patients (61.4 ± 9.6 years vs. 56.5 ± 9.9 years, $p < 0.001$). In multivariate analysis, age, early perfusion grade and infarct-related vessel were significant independent predictors of mortality. Patients with the left anterior descending coronary artery as infarct vessel had a mortality rate of 5.8% versus 3.8% and 3.2%, respectively, in patients with the right and left circumflex coronary artery as the infarct vessel. These differences were not significant in the univariate chi-square test, presumably because the patency rate of the left anterior descending artery was higher than that of the left circumflex or right coronary artery (80.3% vs. 71.2% and 70.6%, respectively, $p < 0.01$), an effect that could have partially masked the otherwise negative impact of the left anterior descending artery as the infarct vessel.

Table 1. Mortality and Cause of Death by Early Perfusion Status of the Infarct-Related Artery in 39 of 907 Patients

	TIMI Perfusion Grade		
Cause of Death	0/1 (n = 224)	2 (n = 122)	3 (n = 561)
Reinfarction	1	2	6
Shock or heart failure	5	5	5
Other cardiac	6	1	2
Noncardiac	4	0	2
Total causes (%)	16 (7.1)	8 (6.6)	15 (2.7)

In patients with complete early reperfusion, the cause of death was more commonly reinfarction, whereas patients with an occluded or an only partially perfused infarct-related vessel died more often from intractable heart failure without reinfarction or from other cardiac causes (Table 1). No differences were seen in the arterial blood pressure or heart rate in patients with occluded or partially or completely perfused infarct vessels on the 90-min angiogram.

Reinfarction was encountered in 35 (6.2%) of 561 patients with complete reperfusion on the 90-min angiogram, 10 (4.5%) of 224 patients with an occluded artery and 8 (6.6%) of 122 patients with partial perfusion (p = NS for all).

Discussion

Homogeneity of study group. In this retrospective analysis, we included patients from four multicenter studies (11–14), which leads to the question, do these patients form a homogeneous group? The most important difference among the studies was the thrombolytic treatment. The four studies used five different treatment regimens and four different drugs; however, the differences in mortality among these treatment groups were not statistically significant in univariate or multivariate analyses. The protocols of the four studies were similar with respect to inclusion criteria and the main study end point, namely, perfusion status of the infarct-related artery 90 min after the initiation of thrombolytic therapy. The central evaluation of the angiograms was performed by the same group of only three investigators, and only 3.4% of the 90-min angiograms of the infarct vessel were missing. The patient groups in the four studies did not differ significantly with respect to age, gender distribution, incidence of anterior myocardial infarction, maximal serum creatine kinase activity or in-hospital mortality. The earlier GAUS study (11) differed from the more recent rt-PA–APSAC Patency Study (TAPS) (13) and German Recombi-

nant Plasminogen Activator (GRECO) study (14) with respect to the duration of symptoms until the start of thrombolysis (180 ± 70 vs. 157 ± 69 min) and there were more acute coronary interventions. The duration of symptoms, however, was not significantly related to short-term outcome in these studies; it was 172 ± 51 min for patients who died in the hospital and 162 ± 71 min for survivors ($p = 0.385$). In GAUS study (11), 21.2% of the patients underwent angioplasty immediately after the 90-min angiogram compared with only 12.4% of patients in the more recent studies. This higher incidence of early interventions may affect the incidence of reocclusion, but there was no significant association between early angioplasty and survival in these studies. Thus, the patients in the four studies form a sufficiently homogeneous group, although not ideal or prospectively defined, with respect to the factors analyzed in this report.

Early perfusion as a predictor of mortality. The main result of our analysis is that early complete reperfusion of the infarct-related vessel is associated with a significantly lower in-hospital mortality rate than that of patients with an occluded infarct vessel on the 90-min angiogram. This association is statistically highly significant even after correction for age, gender and the infarct vessel involved. We conclude, therefore, that the early perfusion status of the infarct vessel is an independent predictor of short-term outcome of myocardial infarction. Of the four patients who died without a 90-min angiogram, three had an occluded infarct vessel 60 min after the start of thrombolysis. Thus, even these excluded patients more than confirm the main result of the analysis.

Lack of effect of reocclusion on mortality. In contrast to early patency, angiographically documented reocclusion of infarct-related vessels had no influence on mortality. The reason may be that most of the patients with angiographically documented reocclusion had no definite reinfarction. None of the patients with clinically asymptomatic reocclusion died. In an earlier study of reperfusion as a determinant of survival, Sheehan et al. (19) demonstrated a significantly improved long-term survival in 134 patients with sustained reperfusion compared with that in 31 patients with unsuccessful thrombolysis or reocclusion. In their study, however, the early perfusion status alone was not a significant predictor of survival. Recently, Brodie et al. (20) reported that infarct vessel patency was the most important predictor of in-hospital survival after direct coronary angioplasty for acute myocardial infarction. In contrast to our observation, Ohman et al. (21) in a compilation of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) experience reported a significantly increased in-hospital mortality rate of 11% in patients with versus 4.5% in those without reocclusion of the infarct vessel after initially successful thrombolysis. One major difference between their study and ours is that a much larger proportion of patients in the TAMI studies underwent angioplasty in the acute period, a factor that might influence the incidence as well as the clinical consequences of reocclusion. Moreover, early reocclusion in our studies was restricted to the time interval between the first and second angiogram, which was performed after 2 days at the latest, whereas in the TAMI studies control angiography was performed at a median of 7 days. Therefore, the patients with reocclusion from the TAMI compilation (21) cannot easily be compared with the patients with reocclusion in our studies.

Lack of relation of in-hospital reinfarction to early perfusion The incidence of in-hospital reinfarction was not significantly related to the early perfusion status; there was only a trend to more reinfarction in patients with early reperfusion in our studies. Six of 10 reinfarctions in patients with failed thrombolysis occurred after rescue angioplasty; in the remaining 4 cases it is likely that spontaneous reperfusion occurred after >90 min and reocclusion followed later.

TIMI grade 2 versus TIMI grade 3 perfusion. An important observation derived from this analysis is that patients with only partially perfused infarct vessels (TIMI grade 2) did not fare better than those with an occluded vessel. This finding confirms the suggestion that TIMI grade 2 perfusion represents a mostly occluded infarct-related vessel (18). Therefore, the traditional interpretation of TIMI grade 2 perfusion as successful treatment significantly overestimates the efficacy of thrombolysis for acute myocardial infarction. Because the in-hospital mortality rate is reduced only in patients with complete early reperfusion, only TIMI grade 3 perfusion of the infarct vessel should be regarded as successful thrombolysis. Using this criterion, the early perfusion status of the infarct artery might be used as a surrogate end point for short-term mortality data in future studies of thrombolysis in myocardial infarction.

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