

PREINFARCTION ANGINA AS A PREDICTOR OF MORE RAPID CORONARY THROMBOLYSIS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Abstract Background. When a myocardial infarction is preceded by angina, the infarct tends to be smaller than when there is no preinfarction angina. Prompt re-canalization of the occluded infarct-related artery is crucial in limiting the size of the infarct. We prospectively studied the relation among preinfarction unstable angina, the speed of coronary reperfusion, and the size of the infarct in patients with acute myocardial infarction receiving thrombolytic therapy.

Methods. We compared 14 patients who had unstable angina during the week before myocardial infarction with 9 patients who had no preinfarction angina. Coronary arteriograms were obtained at base line and 15, 35, 55, and 90 minutes and 24 hours after the start of thrombolytic therapy. The size of the infarct was estimated on the basis of creatine kinase and creatine kinase MB levels, which were measured every 4 hours during the first 24 hours.

Results. Complete reperfusion (a flow of grade 3 according to the Thrombolysis in Myocardial Infarction classification) was achieved at 35 minutes in 64 percent of the patients with preinfarction angina but in none of those without preinfarction angina ($P=0.006$); at 55 minutes in

86 percent and 38 percent, respectively ($P=0.05$); and at 90 minutes in 86 percent and 50 percent, respectively ($P=0.14$). The mean (\pm SD) time to reperfusion was 27 ± 16 minutes in the group with preinfarction angina and 48 ± 17 minutes in the group without preinfarction angina ($P=0.04$); the peak creatine kinase levels were 1118 ± 783 and 2395 ± 1615 U per liter, respectively ($P=0.03$); the peak creatine kinase MB levels were 102 ± 67 and 251 ± 186 U per liter, respectively ($P=0.009$); and the 24-hour integrated creatine kinase MB levels were 1716 ± 1171 and 4267 ± 3252 U \cdot liter $^{-1}\cdot$ 24 hours, respectively ($P=0.009$). The time to reperfusion was positively correlated with the indexes of infarct size ($r\geq 0.53$, $P\leq 0.02$).

Conclusions. In patients with acute myocardial infarction preceded by unstable angina, as compared with those without preinfarction angina, thrombolytic therapy resulted in more rapid reperfusion and smaller infarcts. Earlier myocardial reperfusion may thus account for the smaller infarct size in patients with preinfarction angina. (N Engl J Med 1996;334:7-12.)

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RECENT studies indicate that patients with myocardial infarction preceded by angina have smaller infarcts and a better in-hospital outcome after thrombolytic therapy than patients without preinfarction angina.^{1,2} The reason for this finding is unclear, although myocardial preconditioning by the ischemic episodes associated with angina has been proposed.³

Occlusive thrombosis in a coronary artery is the predominant cause of acute myocardial infarction.^{4,5} Prompt reperfusion of the occluded artery is crucial in limiting the size of the infarct and preserving left ventricular function.^{6,7} The susceptibility of coronary thrombi to lytic treatment is influenced by a number of related factors, including the age of the thrombus,^{8,9} its composition,¹⁰ the characteristics of the surrounding plasma,¹¹⁻¹³ the time of day when treatment is started,¹⁴ and the temporal evolution of the occluding thrombosis.

In a prospective study, we investigated the association between the pattern of chest pain and the speed of coronary reperfusion in patients with acute myocardial infarction receiving intravenous recombinant tissue plasminogen activator (t-PA). Base-line levels of

hemostatic factors and the size of the infarct were also assessed.

METHODS

Patients

Twenty-eight consecutive patients (19 men and 9 women; mean [\pm SD] age, 56 ± 9 years; range, 36 to 71) admitted to the coronary care unit at Hammersmith Hospital between September 1987 and January 1989 with a diagnosis of acute myocardial infarction who were considered candidates for thrombolytic therapy were eligible for the study. The inclusion criteria were typical chest pain lasting more than 30 minutes, an ST-segment elevation of at least 0.2 mV in at least 2 contiguous leads of the standard 12-lead electrocardiogram that was resistant to a 2-to-4-mg intravenous bolus of isosorbide dinitrate, and thrombolytic treatment started within 6 hours after the onset of continuous chest pain. Exclusion criteria were a myocardial infarction within the previous three months, an inability to describe the pattern of pain, and lack of written informed consent to participate in the study. A total of five eligible patients were excluded: one because of a recent infarct, two because they were unable to describe their symptoms, and two because they did not provide informed consent. The other 23 patients (17 men and 6 women; mean age, 58 ± 9 years; range, 36 to 71) were enrolled.

Protocol

A base-line blood sample was obtained before the intravenous administration of drugs. An intravenous infusion of nitroglycerin was then started at a rate of 1 to 10 mg per hour, titrated according to the systolic pressure, and maintained for 24 hours. The patients were taken to the cardiac catheterization laboratory, where coronary angiography was performed. An appropriate view of the infarct-related artery was selected and used for all the subsequent arteriograms.

As part of a study of two different regimens of intravenous t-PA (duteplase, Wellcome Foundation), the patients were then randomly assigned to receive either 4 boluses of 10 clot-lysis megaunits each, administered at 20-minute intervals (12 patients), or 40 clot-lysis

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megaunits administered as a continuous infusion for 90 minutes, followed by an infusion of 20 clot-lysis megaunits during a period of 5 hours (11 patients).¹⁵ Thus, at 90 minutes, each treatment group had received 40 megaunits of t-PA, corresponding to approximately 100 mg of protein.¹⁶ No significant differences in the rate of coronary reperfusion or the size of the infarct, estimated on the basis of enzyme studies, were found with these two regimens.¹⁵ All patients also received oral aspirin (150 mg per day) and an intravenous infusion of heparin during the first 24 hours, adjusted every 4 hours to achieve an activated partial-thromboplastin time between two and three times the control value.

To determine the speed of reperfusion and the perfusion status during treatment with t-PA, coronary arteriography was repeated 15, 35, 55, and 90 minutes after the start of treatment with t-PA and also if symptoms were relieved or the ST-segment elevation resolved. Additional angiography and left ventriculography were performed after a mean of 24 hours (range, 18 to 36).

The flow in the infarct-related artery was subsequently graded according to the system used in the Thrombolysis in Myocardial Infarction (TIMI) trial¹⁷; the grades were assigned by two independent cardiologists unaware of the clinical data. There was agreement on the TIMI grade in all cases. The infarct-related artery was considered patent if the TIMI grade was 3, since there is evidence that a grade of 2 during acute myocardial infarction is not associated with optimal coronary reperfusion.^{7,18,19} The time to reperfusion was defined as the time from the start of treatment with t-PA to the time when the flow in the infarct-related artery reached a grade of 3. If a grade 3 flow was not achieved within 24 hours, the reperfusion time was recorded as more than 24 hours. The minimal luminal diameter of the infarct-related artery was determined with a computer program (the Cardiovascular Angiography Analysis System).

The study protocol was reviewed and approved by the ethics committee at Hammersmith Hospital. At the time the study was performed, it was not considered unethical to perform coronary angiography before the administration of thrombolytic therapy.¹⁵

Cardiac-Enzyme Levels and Hemostatic Factors

Blood samples were obtained every 4 hours during the first 24 hours after admission to determine the values for plasma total creatine kinase and its MB isoenzyme. The size of the infarct was estimated on the basis of peak creatine kinase and creatine kinase MB values and the area under the curve of the creatine kinase MB concentration plotted against time.²⁰

For the measurement of plasma hemostatic factors, blood was obtained through puncture of an antecubital vein before the administration of intravenous drugs. The blood samples were put into chilled plastic tubes containing trisodium citrate (0.106 M) and centrifuged at 1600×g for 20 minutes at 4°C. Plasma aliquots were frozen and stored at -70°C within one hour after the samples had been obtained.

The following hemostatic factors were measured: fibrinogen by the clot-rate method²¹; plasminogen and α_2 -antiplasmin by chromogenic-substrate assays (Coatest Plasminogen kit, KabiVitrum, and Coatest Antiplasmin, Flow Laboratories); t-PA antigen and plasminogen-activator inhibitor type 1 antigen by enzyme-linked immunosorbent assays (Imulyse t-PA kit and TintElize PAI-1 kit, Biopool); plasmin-antiplasmin complexes and thrombin-antithrombin III complexes by enzyme-linked immunosorbent assays (EIA APP Micro and Enzygnost-TAT, Behring); the fibrin fragment D-dimer by a latex-agglutination test (Mabco Dimertest, Porton Products), and von Willebrand factor antigen by a modified version of a specific enzyme-linked immunosorbent assay.²²

Pattern of Chest Pain

Within 48 hours after admission, the patients were questioned by one interviewer about the timing of their recent chest pain and their symptoms during the seven days before admission. The patients were classified as having either intermittent pain related to infarction or unstable angina (or both) in the week preceding the infarction (preinfarction angina) or a single episode of chest pain

without unstable symptoms in the preceding week (no preinfarction angina).

Intermittent pain was defined as one or more episodes of chest pain in the six hours preceding the final episode of pain. Unstable angina was defined as one or more attacks of new-onset angina, angina at rest, or worsening angina during the preceding week, lasting less than 30 minutes and occurring in the same location as the pain associated with infarction at the time of admission. We selected a period of seven days because most unstable symptoms culminating in myocardial infarction occur in the preceding week.²³

Statistical Analysis

Hemostatic factors are expressed as median values and interquartile ranges; other continuous variables are expressed as means \pm SD unless otherwise specified. Values for creatine kinase, creatine kinase MB, reperfusion time, and hemostatic factors in the group of patients with preinfarction angina and the group without preinfarction angina were compared by the Mann-Whitney U test; other continuous variables were compared by the unpaired two-tailed t-test. Proportions were compared with a two-tailed Fisher's exact probability test. Correlations were determined with Spearman's rank-correlation test.²⁴

RESULTS

Characteristics of the Patients

Of the 23 patients enrolled in the study, 14 reported preinfarction angina: 10 had recent unstable angina, 3 intermittent pain from infarction, and 1 both intermittent pain and recent unstable angina. The other nine patients reported a single episode of chest pain and no unstable angina in the week before admission. The two groups did not differ significantly in terms of other base-line characteristics (Table 1). Two patients (one from each group) had had a previous myocardial infarction in a different anatomical location from the present one. Two patients without preinfarction angina died in the first week after admission: one from cardiogenic shock and the other from ventricular arrhythmia.

Coronary Arteriography

Arteriography before thrombolysis showed an occluded infarct-related artery (TIMI grade, ≤ 2) in 22 of the 23 patients. One patient without preinfarction angina had a TIMI grade of 3 at base line; since a filling defect highly suggestive of an intraluminal thrombus was seen, this patient also received t-PA according to the protocol but was excluded from the analysis of coronary reperfusion. At base line, a TIMI grade of 2 was observed in four patients with preinfarction angina and in none of those without preinfarction angina.

Reperfusion occurred within 35 minutes after the start of treatment with t-PA in 9 of the 14 patients with preinfarction angina (64 percent) but in none of the 8 patients without preinfarction angina ($P=0.006$). Reperfusion rates at 55 and 90 minutes were also higher in the group with recent unstable angina (Fig. 1). Among the 16 patients in whom coronary reperfusion occurred within 90 minutes, the time to reperfusion was 27 ± 16 minutes in the group with preinfarction angina and 48 ± 17 minutes in the group without preinfarction angina ($P=0.04$). Inclusion of the patient with a base-

Table 1. Clinical Characteristics of 23 Patients with Myocardial Infarction, According to the Presence or Absence of Preinfarction Angina.*

| CHARACTERISTIC | PREINFARCTION ANGINA (N=14) | NO PREINFARCTION ANGINA (N=9) | P VALUE |
|---|-----------------------------|-------------------------------|---------|
| Age — yr | 59±10 | 58±8 | 0.80 |
| Male sex — no. of patients (%) | 10 (71) | 7 (78) | 0.88 |
| Infarct-related artery — no. of patients (%) | | | 0.41 |
| Left anterior descending | 5 (36) | 3 (33) | |
| Circumflex | 0 | 2 (22) | |
| Right | 9 (64) | 4 (44) | |
| No. of leads with ST elevation | 3.9±1.1 | 3.8±1.0 | 0.81 |
| Sum of ST elevations — mm | 11.5±3.9 | 13±5.2 | 0.48 |
| Anterior acute infarction — no. of patients (%) | 5 (36) | 4 (44) | 0.98 |
| Time from onset of continuous chest pain to thrombolytic therapy — hr | 3.0±1.2 | 3.8±1.4 | 0.24 |
| Time of treatment — no. of patients (%) | | | 0.79 |
| a.m. | 7 (50) | 5 (56) | |
| p.m. | 7 (50) | 4 (44) | |
| t-PA regimen — no. of patients (%) | | | 0.87 |
| Bolus | 7 (50) | 5 (56) | |
| Infusion | 7 (50) | 4 (44) | |
| Current smokers — no. of patients (%) | 6 (43) | 5 (56) | 0.68 |
| History of ischemic heart disease — no. of patients (%) | 6 (43) | 2 (22) | 0.39 |
| Chronic stable angina | 2 (14) | 1 (11) | 0.68 |
| Unstable angina | 3 (21) | 0 | 0.25 |
| Previous infarction | 1 (7) | 1 (11) | 0.67 |
| Postinfarction angina — no. of patients (%) | 2 (14) | 1 (11) | 0.83 |

*Plus-minus values are means ±SD.

line TIMI grade of 3 did not substantially change the results (rate of coronary perfusion at 35 minutes, 64 and 11 percent, respectively; $P=0.03$). The strikingly higher early-reperfusion rate among the patients with preinfarction unstable angina persisted even after the exclusion of the four patients with a base-line TIMI grade of 2 (reperfusion rate at 35 minutes, 60 percent among the 10 patients with preinfarction angina and 0 among the 8 without preinfarction angina; $P=0.01$).

Coronary arteriography at 24 hours showed two further reperfusions and two late occlusions in the group with preinfarction angina and one reperfusion in the group without preinfarction angina; the patency rates at 24 hours were 86 and 62 percent, respectively ($P=0.31$) (Fig. 1). The time to reperfusion in the first 24 hours after thrombolytic treatment was significantly shorter in the patients with preinfarction angina ($P=0.007$ by the Mann-Whitney U test) (Fig. 2). Within the first 24 hours, all 14 patients with preinfarction angina had at least transient coronary reperfusion, whereas 3 of the 9 patients without preinfarction angina had persistent occlusion ($P=0.05$). The time from the onset of continuous chest pain to the start of thrombolytic therapy was not correlated with the time to reperfusion ($r=0.23$ and $P=0.33$ by Spearman's rank correlation).

Among the patients with coronary reperfusion, the minimal luminal diameter of the infarct-related artery did not differ significantly between the group with preinfarction angina and the group without preinfarction angina: 1.26 ± 0.41 and 1.15 ± 0.42 mm, respectively, at 90 minutes ($P=0.92$) and 1.36 ± 0.48 and 1.57 ± 0.42 mm, respectively, at 24 hours ($P=0.29$). Similarly, there was no significant difference in the percentage of stenosis in the infarct-related artery at 90 minutes (57 ± 18 percent in the group with preinfarction angina and 59 ± 20 percent in the group without preinfarction angina, $P=0.92$), although the percentage of stenosis at 24 hours tended to be higher in the patients with preinfarction angina (58 ± 13 percent vs. 46 ± 15 percent, $P=0.06$). The global left ventricular ejection fraction at 24 hours (with the two patients with previous infarcts excluded) was 69 ± 12 percent in the group with preinfarction angina and 60 ± 10 percent in the group without preinfarction angina ($P=0.42$).

Hemostatic Factors

The base-line values for hemostatic factors in peripheral venous blood did not differ significantly between the two groups of patients (Table 2).

Infarct Size

The three enzymatic indexes of infarct size were all significantly lower in the patients with preinfarction angina than in those without preinfarction angina: peak total creatine kinase level, 1118 ± 783 as compared with 2395 ± 1615 U per liter ($P=0.03$); peak

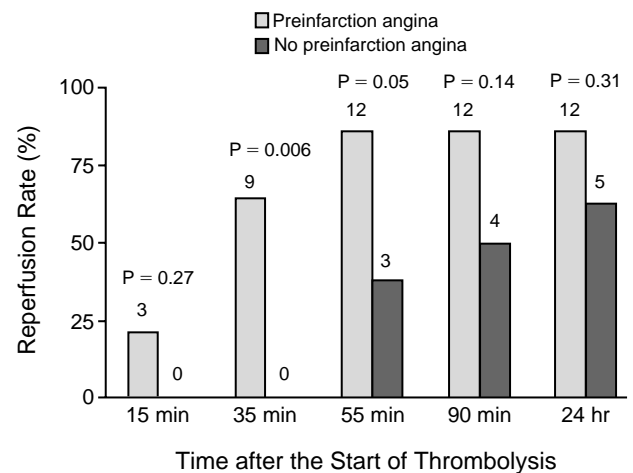


Figure 1. Rates of Coronary Reperfusion among 14 Patients with Preinfarction Angina and 8 without Preinfarction Angina.

Coronary arteriography was performed at predetermined times after the start of thrombolytic therapy. Reperfusion was defined as a TIMI grade of 3 in a previously occluded artery. Reperfusion occurred very early (within the first 35 minutes) in most of the patients with preinfarction angina but in none of those without preinfarction angina. The difference in the reperfusion rates between the two groups subsequently decreased with time. The numbers above the bars denote the numbers of patients with reperfusion.

creatine kinase MB level, 102 ± 67 as compared with 251 ± 186 U per liter ($P=0.009$); and area under the 24-hour creatine kinase MB curve, 1716 ± 1171 as compared with 4267 ± 3252 U·liter⁻¹·24 hours ($P=0.009$). The creatine kinase MB values at four-hour intervals in the two groups are shown in Figure 3. The time to the peak creatine kinase MB value tended to be shorter in the patients with preinfarction angina than in those without preinfarction angina (10.1 ± 5.5 hours vs. 13.7 ± 5.0 hours; $P=0.17$). The time to reperfusion in the first 24 hours was positively correlated with all three indexes of infarct size ($r=0.56$ and $P=0.01$ for the peak total creatine kinase value, $r=0.54$ and $P=0.02$ for the peak creatine kinase MB value, and $r=0.53$ and $P=0.02$ for the integrated 24-hour value of creatine kinase MB).

DISCUSSION

This study shows that patients with acute myocardial infarction who have intermittent infarct-related pain or unstable angina in the seven days preceding the infarction have faster coronary-artery reperfusion and smaller infarcts after thrombolytic therapy than patients without preinfarction angina. The two different patterns of pain were not associated with significant differences in the hemostatic factors measured on admission.

Occlusive coronary thrombosis in the early phases of myocardial infarction is a dynamic process, with repeated episodes of spontaneous reperfusion and occlusion occurring during a period of hours and perhaps days. This has been demonstrated by serial coronary arteriography²⁵ and may be inferred from intermittent

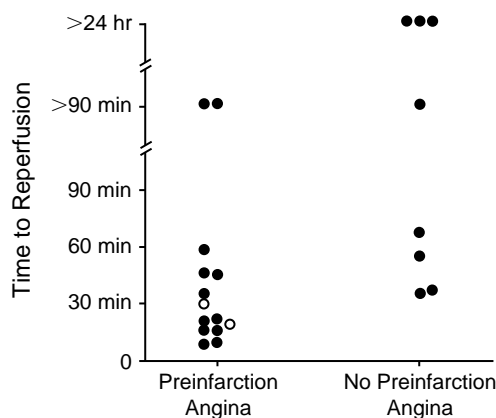


Figure 2. Time to Coronary Reperfusion According to the Presence or Absence of Preinfarction Angina.

For each patient, the circle indicates the time, after the start of thrombolytic therapy, when a TIMI grade of 3 was achieved in the previously occluded artery. All the patients with preinfarction angina had at least transient coronary reperfusion within 24 hours after the start of thrombolysis. Two patients with early reperfusion (open circles) had subsequent reocclusion. The time to reperfusion differed significantly between the two groups ($P=0.007$ by the Mann-Whitney U test).

Table 2. Base-Line Hemostatic Factors According to the Presence or Absence of Preinfarction Angina.

| HEMOSTATIC FACTOR* | PREINFARCTION | NO PREINFARCTION | P VALUE |
|--|-------------------------------------|------------------|---------|
| | ANGINA (N = 14) | ANGINA (N = 9) | |
| | <i>median (interquartile range)</i> | | |
| Fibrinogen (g/liter) | 3.3 (2.5–3.8) | 3.4 (3.2–3.5) | 0.75 |
| Thrombin–antithrombin III complex (μ g/liter) | 7.4 (4.3–12.4) | 8.0 (6.4–24.2) | 0.43 |
| von Willebrand factor (%) | 107 (93–179) | 134 (113–192) | 0.32 |
| PAI-1 antigen (μ g/liter) | 17.1 (12.3–27.5) | 12.4 (10.1–28.7) | 0.59 |
| t-PA antigen (μ g/liter) | 20.7 (7.6–26.1) | 32.4 (15.6–45.4) | 0.13 |
| α_2 -Antiplasmin (%) | 91 (73–118) | 110 (68–156) | 0.43 |
| Plasminogen (%) | 91 (84–107) | 95 (90–100) | 0.57 |
| Plasmin–antiplasmin complex (μ g/liter) | 532 (352–824) | 432 (260–779) | 0.54 |
| D-Dimer (μ g/liter) | 170 (86–216) | 183 (145–356) | 0.27 |

*Percentages denote the percentage of the value in normal plasma. PAI-1 denotes plasminogen-activator inhibitor type 1.

ST-segment elevations during continuous electrocardiographic monitoring,^{25,26} multiple peaks in serum myoglobin values,²⁷ and the multilayered structure of most coronary thrombi observed at autopsy in patients with unstable angina.²⁸ Continuous electrocardiographic monitoring or repeated coronary arteriography and biochemical assays, however, can be used to assess the intermittent occurrence of coronary occlusions only after admission, whereas the pattern of chest pain described by the patient may indicate the state of coronary blood flow in the hours and days preceding hospitalization. Thus, an infarction preceded by unstable symptoms may reflect the episodic growth and resolution of coronary thrombi. In contrast, an infarction not preceded by such symptoms may reflect a sudden and often irreversible coronary occlusion, such as that observed in animal models when a copper coil is introduced into a coronary artery.²⁹ The present study suggests that these two distinct patterns of chest pain represent two different types of thrombus growth — recurrent, transient growth and isolated, persistent growth — and are associated with different responses to thrombolytic therapy.

In another series of patients, we recently found significantly higher levels of plasma C-reactive protein in the patients with myocardial infarction preceded by unstable angina than in those without preinfarction angina,³⁰ suggesting possible differences in the pathogenesis of these two clinical presentations of chest pain. In the present study, however, none of the hemostatic factors measured in peripheral venous blood at base line differed significantly between the two groups of patients. Although these negative results may be due to the small number of patients and the associated low statistical power of the study, the data at least allow us to rule out striking differences in hemostatic factors between the two groups,³¹ with the possible exception of the concentration of t-PA antigen, which tended to be higher in the patients without preinfarction angina ($P=0.13$). This

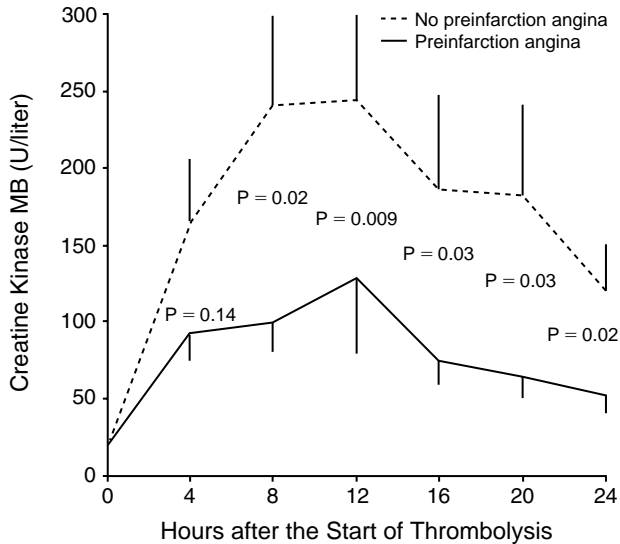


Figure 3. Mean (\pm SE) Plasma Creatine Kinase MB Values According to the Presence or Absence of Preinfarction Angina.

Throughout the 24-hour period, the patients with preinfarction angina had lower creatine kinase MB values than the patients without preinfarction angina.

finding is consistent with the increased cardiovascular risk associated with elevated concentrations of t-PA antigen.³²

Our findings confirm and extend the recent work of Kloner et al.,¹ who reported that angina occurring within 48 hours before infarction had a beneficial effect on the size of the infarct and the hospital outcome, with a trend toward higher rates of coronary perfusion after 90 minutes of thrombolytic therapy in the patients with preinfarction angina than in those without preinfarction angina (81 percent vs. 74 percent, $P=0.11$). Kloner et al. defined coronary patency as a TIMI grade of 2 or higher and preinfarction angina as any anginal pain; their results may therefore reflect the inclusion of patients with suboptimal myocardial reperfusion or chronic stable angina. In a study of 25 patients, Ottani et al.² also found a trend toward shorter reperfusion times, as assessed by ST-segment monitoring, after thrombolytic therapy in patients with unstable angina during the 24 hours before myocardial infarction than in those without preinfarction angina (46 ± 24 minutes vs. 58 ± 34 minutes, $P=0.32$), despite the exclusion of patients with persistent coronary occlusion or preinfarction angina of more than 24 hours' duration.

In the present study, the reperfusion rate 35 minutes after the start of thrombolytic therapy was strikingly higher in the patients with preinfarction angina than in those without preinfarction angina (64 percent vs. 0 percent, $P=0.006$), but the difference between the two groups was attenuated at 55 and 90 minutes, probably because of a "catch-up" phenomenon.⁶ We also found a clear association between prodromal unstable

angina and a smaller infarct. It has been suggested that the benefit of preinfarction angina with respect to infarct size is determined by ischemic preconditioning.¹⁻³ We propose that this benefit may depend on faster coronary thrombolysis, in addition to or instead of myocardial preconditioning.

The size of the thrombus may have influenced the speed of coronary reperfusion. However, the minimal luminal diameter and the percentage of stenosis in the infarct-related artery 90 minutes after the start of treatment with t-PA were similar in the two groups of patients, suggesting that the thrombus volume did not differ significantly between the two groups. The interval from the onset of continuous chest pain to the start of thrombolytic therapy, which may be used as a rough estimate of the age of the occlusive thrombus, also did not differ significantly between the two groups and was unrelated to the speed of coronary reperfusion; it is therefore unlikely that the age of the thrombus influenced the response to thrombolytic therapy in our patients.

Myocardial stunning may significantly influence left ventricular function in the early period after an acute ischemic episode.³³ Therefore, within the first 24 hours after admission, the left ventricular ejection fraction in patients with acute myocardial infarction may not be related only to irreversible myocardial damage. This possibility may explain the similar ejection fractions in the two groups of patients in the present study, despite the large differences in the estimated size of the infarct.

Several previous investigators have assessed the relation between preinfarction angina and the extent of myocardial damage or the short-term outcome. The results have been contradictory, with some studies finding a clearly positive effect of previous angina on the clinical outcome^{1,2,34-37} and others finding no effect²³ or even a detrimental effect.³⁸⁻⁴⁰ The discrepancies may be explained partly by the different definitions of preinfarction angina, since many of the studies did not distinguish between angina of recent onset and chronic angina.^{1,34-36} Moreover, the definition of angina of recent onset often included symptoms that preceded the infarction by as long as three months, a period that hardly seems related to the acute pathogenesis of the subsequent infarction.^{23,38,40} None of these studies used serial angiography to determine the relation between preinfarction angina and the speed of coronary thrombolysis.

In conclusion, the present study shows that among patients with acute myocardial infarction, those with prodromal unstable angina or intermittent infarct-related pain have remarkably faster responses to treatment with t-PA than those without such symptoms. Earlier myocardial reperfusion may thus explain, at least in part, the reduced infarct size in patients with previous angina receiving thrombolytic therapy.^{1,2} The absence of preinfarction angina in patients with myo-

cardial infarction may also help identify a subgroup of patients with relatively slow responses to thrombolytic drugs who may benefit the most from primary coronary angioplasty for early and complete myocardial reperfusion.

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