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Early Spontaneous Intermittent Myocardial Reperfusion During Acute Myocardial Infarction Is Associated With Augmented Thrombogenic Activity and Less Myocardial Damage

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Objectives. **This study investigated the influence of early spontaneous intermittent reperfusion on the extent of myocardial damage and its relation to endogenous hemostatic activity.**

Background. **In the early phase of acute myocardial infarction coronary occlusion is often intermittent, even before thrombolytic therapy is administered. The relation between this phenomenon, myocardial damage and hemostatic activity is unknown.**

Methods. **Holter ST segment recording and pretreatment plasma tissue-type plasminogen activator (t-PA) antigen, plasminogen activator inhibitor-1 (PAI-1) antigen, prothrombin fragment F1+2 and soluble fibrin levels were measured in 57 patients with acute evolving myocardial infarction. Spontaneous intermittent myocardial reperfusion, defined as two or more episodes of transient resolution of ST segment elevation to within 0.05 mV of baseline, lasting ≥1 min, before the start of recombinant t-PA (rt-PA) treatment was present in 28 patients (group 1) and absent in 29 (group 2). Left ventriculography and coronary angiography were performed 90 min after intravenous rt-PA administration. Plasma creatine kinase-MB fraction (CK-MB) levels were measured every 6 h for 24 h, and C-reactive protein levels were measured daily for 3 days.**

Results. **Group 1 had lower peak plasma CK-MB (141.9 ± 28.3 vs. 203.8 ± 23.3 IU/liter [mean ± SEM], $p < 0.014$) and C-reactive protein levels (16 ± 4 vs. 28 ± 4 mg/liter on day 1; 26.6 ± 5.5 vs. 61.8 ± 14.4 mg/liter on day 2; 19.6 ± 4.2 vs. 40.6 ± 6.5 mg/liter on day 3, $p < 0.012$) and a higher left ventricular ejection fraction (62.9 ± 4% vs. 51.1 ± 5%, $p < 0.04$) than group 2. Group 1 had lower plasma t-PA antigen levels (15.6 vs. 27 μg/liter, $p < 0.006$) but higher prothrombin fragment F1+2 (1.8 vs. 1.1 nmol/liter, $p < 0.003$) and soluble fibrin levels (66.8 vs. 31 nmol/liter, $p < 0.01$). Coronary patency at 90 min was similar.**

Conclusions. **Early spontaneous intermittent reperfusion during acute myocardial infarction is associated with augmented thrombogenic activity and less subsequent myocardial damage. This finding is consistent with a protective effect of intermittency on the myocardium and a procoagulant effect of spontaneous lysis on blood. It may also reflect a different rate of evolution of coronary thrombosis and myocardial infarction in patients with and those without spontaneous intermittent myocardial reperfusion.**

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Thrombus formation is the main mechanism of obstruction of the coronary artery during acute myocardial infarction (1), and in the early phase, before treatment is given, spontaneous closure and reopening of the artery with its associated intermittent ischemia and reperfusion, is common (2,3). The mechanism of this spontaneous intermittent reperfusion is unknown. However, there is evidence that acute coronary reperfusion induced by thrombolytic therapy is thrombogenic (4,5). Furthermore, animal studies have shown (6–8) that short transient episodes of myocardial ischemia can "precondition" the myocardium such that it is rendered more resistant to subsequent episodes of sustained myocardial ischemia. Myocardial protection has been demonstrated (9,10) in patients subjected to brief periods of intermittent ischemia and reperfusion during percutaneous coronary angioplasty and coronary artery bypass surgery.

In the present study we investigated the hemostatic system and the extent of myocardial damage in patients with acute myocardial infarction with and without spontaneous intermittent reperfusion.

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Methods

Patients. Fifty-seven consecutive patients satisfying the inclusion criteria were enrolled in a study of three different thrombolytic treatment regimens using recombinant tissue-type plasminogen activator (rt-PA). The inclusion criteria were chest pain lasting between 30 min and 6 h and electrocardiographic (ECG) changes of early evolving acute myocardial infarction (ST segment elevation >0.2 mV in at least two contiguous leads of the 12-lead ECG) refractory to a 2-mg intravenous bolus of isosorbide dinitrate. Patients with cardiogenic shock, contraindications to thrombolytic therapy and age >75 years were excluded. The study was approved by the Hammersmith Hospital Research Ethics Committee, and all patients gave written informed consent.

Protocol. A continuous 24-h ECG recording (Marquette 8000 AM recorder) of the two leads showing the greatest ST segment elevation was started. An intravenous infusion of 1 to 10 mg/h of isosorbide dinitrate, titrated against blood pressure, was commenced and continued for 24 h. A venous blood sample was taken by direct venipuncture after minimal venostasis for assay of creatine kinase, myocardial isoenzyme fraction (CK-MB), C-reactive protein, prothrombin fragment F1+2, soluble fibrin, plasminogen activator inhibitor-1 (PAI-1) and t-PA antigen levels. An intravenous bolus of heparin (5,000 IU) was administered. Coronary angiography was performed, and double-chain rt-PA (Wellcome Foundation, Beckenham, United Kingdom) was administered intravenously within 6 h of onset of pain.

The dose of rt-PA is expressed in clot-lysis megaunits (MU) of active protein (11). As part of a study of three different rt-PA regimens, the drug was administered according to one of the following schedules: 1) as a continuous infusion of 40 MU over 90 min, followed by 4 MU/h over the next 5 h (n = 12); 2) as four rapid boluses of 10 MU each, given every 20 min over 1 h, with no subsequent infusion (n = 14); or 3) as a single rapid bolus of 0.30 to 0.6 MU/kg body weight (n = 31). Coronary angiography was repeated 90 min after the start of rt-PA administration, and single-plane left ventriculography was performed in the 30° right anterior oblique projection. Heparin infusion was then commenced, to achieve an activated partial thromboplastin time between two and three times control value, and continued for 24 h. Aspirin, 300 mg daily, and diltiazem, 60 mg every 8 h orally, were started immediately after angiography. Further blood samples for C-reactive protein were taken at precisely 24, 48 and 72 h from the time of entry to the study. Samples were taken every 6 h over the first 24 h for determination of CK-MB levels.

Data analysis. *ST segment monitoring.* The 24-h continuous ECG recordings were analyzed using the Marquette 8000 laser system. A marker indicating the start of rt-PA administration was located. Spontaneous intermittent recanalization of coronary arteries was defined as two or more episodes of transient resolution of ST segment elevation to within 0.05 mV of baseline, lasting ≥1 min and occurring before the start of rt-PA treatment. Time of resolution of maximal sustained ST elevation to 50%, measured from the onset of rt-PA treatment, was taken as an indirect assessment of recanalization time (12). The duration of persistent ischemia was measured from the point at which 50% of the ST segment elevation had resolved after rt-PA administration to baseline (onset of Holter monitoring) or to that at the last episode of ST segment reelevation in patients showing early intermittent ST segment elevation.

Blood samples and plasma assays. After discard of the first 2 ml of blood, 9 ml were transferred to cooled plastic tubes containing 1 ml of 0.109 mol/liter of trisodium citrate. Platelet-poor plasma was obtained by cold (4°C) centrifugation at 1,300*g* for 20 min. Plasma aliquots were snap-frozen within 1 h of blood collection and stored at −70°C.

The CK-MB activity level was measured kinetically after immunoinhibition (MB CK NAC-activity kit, Boehringer Mannheim, Lewes, United Kingdom) and expressed in IU/liter. The C-reactive protein concentrations were determined by immunoturbidimetric assay (RA-1000 analyzer, Bayer Diagnostics method SM4-0183B87, Basingstoke, United Kingdom) and expressed in mg/liter. Plasma concentrations of prothrombin fragment F1+2 (nmol/liter), t-PA antigen (μg/liter) and PAI-1 (μg/liter) were measured by enzyme-linked immunosorbent assays using commercially available kits (Enzygnost F1+2, Behring, Behringwerke, Marburg, Germany; Imulyse t-PA, Biopool, Umea, Sweden; and TintElize PAI-1, Biopool, Umea, Sweden). Soluble fibrin concentrations (nmol/liter) were measured using a commercially available functional assay (Coa-set fibrin monomer, KabiVitrum, Amsterdam, The Netherlands).

Coronary angiography and left ventriculography. Patency of the infarct-related artery was assessed by two independent observers according to Thrombolysis in Myocardial Infarction (TIMI) perfusion criteria (13). *Coronary occlusion* was defined as TIMI grade 0 or 1 and *patency* as TIMI grade 2 or 3. *Subtotal occlusion* was defined as the presence of arteriographic filling defects suggestive of intraluminal thrombus despite TIMI grade 2 or 3. For each patient collateral filling of the occluded infarct-related artery was also noted.

End-diastolic volume (EDVI) and end-systolic volume indexes (ESVI) were calculated by computer from automated traced silhouettes of the left ventriculogram according to the regional contribution to ejection fraction method (Computerized analysis with Pie Medical Analysis System) (14,15). Ejection fraction was determined as 100 × (EDVI − ESVI)/EDVI.

Statistical analysis. Data are expressed as mean value ± SEM, unless otherwise stated. The Wilcoxon signed rank test and Mann-Whitney test were used to compare paired or unpaired data as appropriate. Discrete data were analyzed by the chi-square test. Significance was defined as $p < 0.05$. A mixed-model analysis of variance was used to compare CK-MB and C-reactive protein values between groups and postthrombolysis time points. The presence of an interaction effect between group and time was also tested for. The data were log transformed so that the assumptions of analysis of variance were valid.

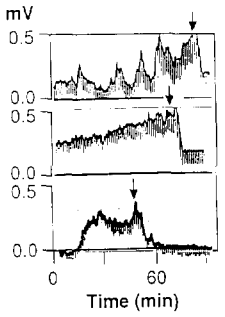

Figure 1. Examples of the pattern of ST segment change from a patient in group 1 (**top**) and two patients in group 2 (**middle and bottom**). A continuous plot of ST segment level (60 ms after the J point [mean 3 ± 1 min]) against time from admission to hospital is shown. **Top**, Three episodes of ST segment elevation, followed by resolution to baseline (indicating intermittent closure and reopening of the infarct-related coronary artery), precede a period of sustained ST segment elevation of ~30 min. The sustained ST segment elevation resolves almost to baseline after thrombolytic therapy (**arrow**). **Middle**, Continuous ST segment elevation for ~1 h from admission (indicating persistent infarct-related artery occlusion) that resolves after thrombolytic therapy has been administered (**arrow**). **Bottom**, Retrospective analysis reveals a period of sustained ST segment elevation, beginning after hospital admission (indicating the development of persistent occlusion of the infarct-related artery) and lasting ~40 min. It is not preceded by intermittent occlusion and reperfusion and resolves to baseline after the start of thrombolytic therapy.

Results

Patient characteristics. Fifty-seven consecutive patients satisfying the inclusion criteria completed the study. A mean of 24 ± 2 h/patient of continuous ST segment monitoring was available for analysis. Twenty-eight patients (49%) showed intermittent ST segment elevation and resolution before sustained, continuous ST segment elevation (group 1) before initiation of thrombolytic treatment, indicating spontaneous intermittent reperfusion; and 29 patients (51%) exhibited continuous ST segment elevation with no such preceding intermittent ST segment elevation (group 2) (Fig. 1). Duration of Holter monitoring before the start of lytic therapy was 150 ± 56 min in group 1 and 160 ± 75 min in group 2 ($p < 0.5$). Duration of continuous persistent ST segment elevation/patient was 323 ± 54 min in group 1 and 454 ± 98 min in group 2 ($p < 0.3$). Maximal ST segment elevation was less in group 1 (0.37 ± 0.05 mV) than in group 2 (0.6 ± 0.11 mV) ($p < 0.03$). In group 1, there were 4 ± 0.6 episodes (range 2 to 7) of transient ST segment elevation before rt-PA administration (duration 9.6 ± 1.3 min, range 2 to 33), and the interval between episodes was 8 ± 2 min (range 2 to 52). In both groups combined, intermittent episodes occurred after rt-PA administration in only 10 patients: 4 received the infusion regimen (2.5 ± 0.3/patient), 6 the multiple-bolus regimen (2.3 ± 0.2/patient) and none the single-bolus regimen. Table 1 shows selected baseline and short-term follow-up characteristics of the two groups.

Left ventricular function. Left ventricular ejection fraction at 90 min after rt-PA administration was 62.9 ± 4% in group 1 and 51.1 ± 5% in group 2 ($p < 0.04$).

Table 1. Clinical Characteristics of the Two Study Groups

	Group 1 (n = 28)	Group 2 (n = 29)	p Value
Age (yr)	57 ± 2	59 ± 2	0.2
Gender (M/F)	19/9	24/5	0.16
Previous myocardial infarction	3	1	0.1
First blood sample collection (AM/PM)	15/13	13/16	0.77
Time from onset of pain to thrombolysis (min)	197 ± 16	186 ± 15	0.63
Mode of rt-PA administration (bolus/infusion)	23/5	22/7	0.2
IRCA (LCA or LCx/RCA)	13/15	13/16	0.54
Collateral filling of IRCA at the 90-min angiogram	4	5	0.4
Patency of IRCA at 90 min (patent/occluded)	19/9	18/11	0.55
TIMI status of IRCA at 90 min (3/2, 1, 0)	18/10	16/13	0.23
Time to 50% resolution of ST segment elevation (recanalization time) (min)	273 ± 85	399 ± 588	0.39

Data presented are mean value ± SEM or number of patients. AM = midnight to 11:59 AM; F = female; Group 1 (Group 2) = patients with intermittent (persistent) infarct-related coronary artery (IRCA) occlusion; LCA or LCx = left anterior descending or circumflex coronary artery; M = male; occluded = Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow; patent = TIMI grade 2 or 3 flow; PM = noon to 11:59 PM; RCA = right coronary artery; rt-PA = recombinant tissue-type plasminogen activator.

Plasma CK-MB levels. Plasma CK-MB level averaged over the first 24 h, integrated over the first 24 h, peak level and time to peak level were 83.5 ± 16.8 and 125.5 ± 12.7 IU/liter ($p < 0.003$), 2436 ± 538 and 3436 ± 380 IU/liter × 24 h ($p = 0.43$), 141.9 ± 28.3 and 203.8 ± 23.3 IU/liter ($p < 0.014$) and 10.6 ± 1.0 and 9.6 ± 1.0 h ($p < 0.52$) in groups 1 and 2, respectively. The plasma CK-MB levels measured every 6 h over the first 24 h in the two groups are shown in Figure 2.

Plasma C-reactive protein levels. The plasma levels of C-reactive protein on admission and at 1, 2 and 3 days in groups 1 and 2 were, respectively, 5.1 ± 2 and 5.5 ± 3, 16 ± 4

Figure 2. Plasma creatine kinase, MB isoenzyme fraction (CK MB) activity measured every 6 h over the first 24 h in the two study groups. Values shown are medians and confidence intervals (group comparison by repeated measures analysis of variance, $p = 0.011$).

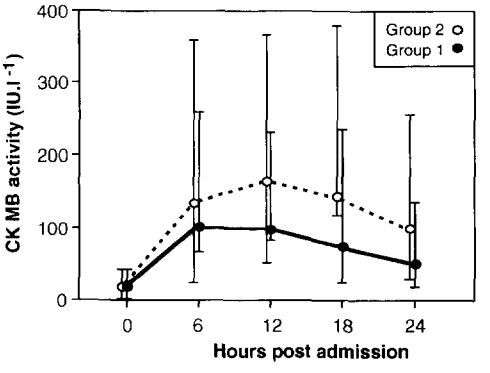

Table 2. Hemostatic Factor Levels Before Thrombolytic and Anticoagulant Treatment

	Group 1 (n = 28)	Group 2 (n = 29)	p Value
Prothrombin fragment F1+2 (nmol/liter)	1.86 (1.37–2.32)	1.1 (0.75–1.46)	0.003
Soluble fibrin (nmol/liter)	66.8 (32.6–86.7)	31 (23.9–41.8)	0.01
Plasminogen activator inhibitor-1 antigen (μg/liter)	25.2 (13.2–31)	24 (16.1–33.1)	0.54
Tissue-type plasminogen activator antigen (μg/liter)	15.6 (6.3–24.1)	27 (15.2–38.3)	0.006

Data presented are median value (95% confidence interval). Group comparison by Mann-Whitney U test.

and 28 ± 4, 26.6 ± 5.5 and 61.8 ± 14.4, and 19.6 ± 4.2 and 40.6 ± 6.5 mg/liter ($p < 0.012$).

Hemostatic factor levels before fibrinolytic and anticoagulant treatment. Pretreatment plasma levels of prothrombin fragment F1+2 and plasma soluble fibrin were significantly higher in group 1 than in group 2 (Table 2). Plasma PAI-1 antigen levels were similar in the two groups, but the t-PA antigen level was significantly lower in group 1 than in group 2 (Table 2).

Discussion

The results of the present study show that spontaneous intermittent reperfusion in patients with evolving myocardial infarction leads to lower plasma t-PA antigen levels and a lesser degree of myocardial damage than in patients with persistent infarct-related artery occlusion and causes greater thrombogenic activity. This augmented thrombogenic activity is probably a direct consequence of the intermittency.

Early spontaneous intermittent reperfusion and myocardial protection. Spontaneous intermittent reperfusion was assessed by computerized ST segment analysis of continuous ECG recordings. It has previously been demonstrated (2,3) that in the early hours of infarct evolution, ST segment elevation indicates complete occlusion of the infarct-related artery and resolution of ST segment elevation to baseline indicates patency with a variable degree of stenosis. The extent of myocardial infarction was assessed by three independent methods: myocardial enzyme release, magnitude of the acute phase response and left ventricular ejection fraction.

Enzyme levels. Serial measurements of enzymes released by necrotic myocardium, particularly CK (16) and its MB isoenzyme (17), are helpful in determining myocardial infarct size. In the present study the peak level, 24-h mean and plasma CK-MB activity measured every 6 h were lower in the intermittent than the persistent coronary occlusion group, indicating less extensive myocardial damage (Fig. 2). Measurements of plasma CK-MB levels between 1 and 2 h were used in the original validation of this method of estimating (16) infarct size. However, peak CK-MB levels have also been found (18) to reflect the amount of myocardial damage. Although peak CK-MB levels could have been increased in our group of patients with intermittent occlusion by spontaneous reperfusion with increased washout of the enzyme, any adjustment of the results to compensate for this effect would accentuate the already significant difference between the two groups. We compared the mean of the 6-hourly CK-MB levels in the two groups, and the result was also significantly lower in the group with early intermittent occlusion. The integral of the CK-MB curve shows a lower value in the intermittent occlusion group, but the difference was not statistically significant.

C-reactive protein levels. The generation and release of C-reactive protein is a systemic response to myocardial injury (19). The relation of C-reactive protein to infarct size has been reported previously (20), and a larger infarct results in a greater increase in plasma C-reactive protein. Elevation of C-reactive protein levels could have been due to factors other than infarction, including pericarditis, but these were not found in our patients. Furthermore, the increase in C-reactive protein correlated positively with changes in the other indexes of myocardial damage. Measurement of left ventricular ejection fraction is a sensitive method of estimating the extent of myocardial necrosis (14). Patients with spontaneous intermittent reperfusion had a higher ejection fraction at 90 min after thrombolysis than those with persistent coronary occlusion.

ST segment elevation. There was a trend toward less duration of persistent ST segment elevation in the intermittent compared with the nonintermittent group, but the difference was not statistically significant. Therefore, although, it is possible that the ischemia of lesser duration contributed to the difference in myocardial infarct size, a protective effect of intermittency is a more likely explanation. Indeed, evidence of a protective effect of anterograde flow has been provided by a recent study (21) that found that anterograde flow before early angioplasty in patients with acute myocardial infarction was associated with a smaller subsequent infarct size. However, the mechanism of this protective effect on the myocardium is unclear. The intermittency may have salvaged myocardium by providing intermittent spontaneous reperfusion of the ischemic myocardium early in the evolution of the infarct by promoting earlier persistent reperfusion in response to thrombolytic therapy or by the protective effect of transient ischemia known as ischemic preconditioning (6–8). Furthermore, collateral supply, known to have protective effect (22), might have been better in the intermittent group. Earlier or more frequent reperfusion in response to thrombolytic therapy is unlikely because the recanalization time (time to 50% resolution of ST elevation and time to peak CK-MB levels) and 90-min patency rates in both groups were comparable. There was no difference in the presence of collateral vessels in the infarct region in the two groups at 90 min, although the absence of angiography before rt-PA administration represents a limitation in this respect and prevents a clear evaluation of the possible role of collateral vessels. The most likely explanation for a lesser degree of myocardial damage in the group with spontaneous

intermittent reperfusion is that the spontaneous early reperfusion provided oxygen to the jeopardized ischemic myocardium, precluding necrosis of the tissue, or that the associated spontaneous intermittent episodes of ischemia due to coronary reocclusion preconditioned the myocardium, making it less susceptible to the effects of prolonged coronary occlusion. This phenomenon may underlie the association between late patency of an infarct-related artery and a more favorable prognosis (23), with late patency identifying a subset of patients in which early intermittency was present. It remains possible that those patients with persistent occlusion were in this state for a period of unknown duration before hospital admission, reflecting different rates of evolution of acute infarction.

With regard to ischemic preconditioning, previous studies (6–8) have shown that animals subjected to episodes of myocardial ischemia separated by reperfusion develop less necrosis after continuous ischemia than control animals. One 5-min period of ischemia was sufficient to induce this protective state in dogs and rabbits (7), but periods of ischemia <90 s in duration were insufficient (8). The average duration of intermittent episodes of ST segment elevation, indicating myocardial ischemia and coronary occlusion, before continuous ST segment elevation was 9.6 min in the present study and would therefore have been sufficient to induce ischemic preconditioning in these patients. For obvious reasons the optimal duration of preconditioning ischemia is unknown in the setting of myocardial infarction in humans, but a recent study (10) demonstrated that two 3-min episodes of ischemia were sufficient to induce preconditioning during coronary artery bypass surgery.

More extensive myocardial damage has been reported in patients showing intermittent occlusion after thrombolysis (24,25). However, these studies did not investigate intermittency before treatment. Intermittency was less frequent after than before thrombolytic treatment in our study and probably had less impact on infarct size because it occurred later and was less frequent. The different significance of early and late coronary recanalization with respect to infarct size, particularly the lesser but definite impact of late patency has been discussed in detail by Tiefenbrunn and Sobel (23).

Early spontaneous intermittent reperfusion and hemostatic changes. The F1+2 fragment of prothrombin is cleaved during the conversion of prothrombin to thrombin, and therefore its plasma level indicates the amount of thrombin generated (26). Similarly, soluble fibrin is the product of the action of thrombin on fibrinogen, and its plasma level is an indicator of thrombin activity and the amount of fibrinogen conversion (27). Taken together these plasma levels can be used to measure the activity of the final stages of the coagulation mechanism. The results of the present study show that patients with spontaneous intermittent coronary occlusion have a higher pretreatment level of coagulation activity. This finding suggests that intermittent reperfusion is thrombogenic. The procoagulant stimulus could be located in the infarct-related epicardial artery, at the site of the occluding thrombus and atheromatous plaque or downstream in the coronary microvasculature and ischemic myocardium. In the epicardial arterial segment, the interaction between reflowing blood and the residual thrombus (28) or the subendothelial collagen exposed by the disrupted atheroma could trigger local platelet activation (29) and release prothrombotic compounds, such as thromboxane A_2 (4) or thrombin (5). Furthermore, the increased thrombogenic activity may be a result of spontaneous lysis underlying the intermittency. Downstream, in the infarct-related coronary vascular bed, microvascular or myocardial damage induced by ischemia or reperfusion, or both, might also activate coagulation within the reperfusing blood.

In the presence of greater coagulation activity, the group of patients with spontaneous intermittent myocardial reperfusion had lower t-PA antigen levels. Higher fibrinolytic activity might have been expected in this group to explain the spontaneous early reopening of the occluded arteries. However, although increase in PAI-1 activity due to platelet activation during thrombosis and thrombolysis has been reported in experimental animals (30), there was no difference in PAI-1 antigen levels between the groups, and therefore, although the activities of t-PA and PAI-1 were not measured, it is unlikely that fibrinolytic activity was higher in the intermittent group. Tissue-type plasminogen activator antigen is constitutively produced by endothelial cells. Its plasma concentrations are subject to a circadian variation (31), are age related (32) and can increase rapidly in response to catecholamines (33) or to a reduction in liver blood flow and hepatic clearance (34). The time of day of the pretreatment blood samples and age were not significantly different in the two patient groups (Table 1). It is possible that the lower t-PA antigen levels in the intermittent coronary occlusion group reflect a better hemodynamic state with less sympathetic activation, consistent with less extensive myocardial damage. The results of the present study do not exclude higher local fibrinolytic activity at the site of the epicardial coronary thrombus in patients with early intermittent occlusion. It is possible that more t-PA is bound to fibrin in freshly generated clots or to newly exposed binding sites in this group, leading to increased plasmin generation and local fibrinolysis and possibly resulting in a reduction in circulating t-PA antigen levels. Furthermore, it has been shown (5,35–38) that plasmin can activate coagulation factors and platelets, causing an augmentation of the procoagulant state. Therefore, the greater coagulant activity may be a consequence of the reopening of the artery, intensifying the possibility of reocclusion.

Although the present results suggest that patients with intermittent coronary occlusion have more active thrombin formation, the fundamental difference between the two groups may lie only in the phase of infarct evolution in which the measurements were taken. There was no significant difference in the interval between the onset of symptoms and blood sampling between the two groups. It is therefore possible that intermittency of coronary occlusion identifies a group of patients in whom the evolution of infarction is relatively slow so that the initial thrombogenic stimulus persists into the early hours of hospital admission. Conversely, persistent ST segment elevation may indicate rapid evolution of the process of

coronary thrombosis and myocardial infarction so that by the time of hospital admission the process is advanced or complete, and the thrombogenic stimulus has waned. Alternatively, patients with intermittency may be those in whom initial endogenous fibrinolytic activity is sufficient to produce spontaneous lysis and set the stage for additional spontaneous thrombosis.

Conclusions. Spontaneous intermittent myocardial reperfusion before thrombolytic treatment in the early phase of myocardial infarction in patients is associated with greater thrombogenic activity and a smaller subsequent infarct size than those with early persistent coronary occlusion. These findings may reflect different rates of evolution of coronary thrombosis and myocardial infarction. They also provide evidence that intermittent ischemia and reperfusion stimulate thrombin generation and confer myocardial protection. A better understanding of mechanisms responsible for spontaneous coronary reperfusion will help to improve thrombolytic therapy and patient prognosis.

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