Prognostic Role of Plasminogen-Activator-Inhibitor-1 Levels in Treatment with Streptokinase of Patients with Acute Myocardial Infarction

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Summary

Background: The antifibrinolytic effect of plasminogen-activator-inhibitor type 1 (PAI-1) may be responsible for delays in reperfusion and/or reinfarctions after streptokinase (STK) therapy in patients with acute myocardial infarction (AMI).

Hypothesis: This study aimed to demonstrate the prognostic role of pretreatment PAI-1 levels for the outcome of STK therapy in patients with AMI, depending on reperfusion and/or reinfarction.

Methods: The mean pretreatment PAI-1 level of 104 patients with AMI, treated with STK, determined by chromogenic method, was 5.8 ± 8.6 U/ml, range 0.3–66.2 U/ml. Streptokinase therapy was successful when reperfusion was achieved, as assessed noninvasively, without subsequent reinfarction; it failed when reperfusion was delayed and/or reinfarction developed.

Results: Fibrinolysis with STK failed significantly in patients with elevated pretreatment PAI-1 levels ($p < 0.05$), especially with levels > 4.0 U/ml ($p < 0.01$). The mean pretreatment PAI-1 level was significantly higher in unsuccessfully treated patients. Multivariate statistical testing demonstrated that among pretreatment variables, elevated PAI-1 activity was the most significant independent risk factor of failed fibrinolysis with STK.

Conclusions: Among pretreatment variables, elevated pretreatment PAI-1 activity in patients with AMI was the most significant independent risk factor of failed fibrinolysis with STK, especially at levels > 4.0 U/ml.

Key words: acute myocardial infarction, streptokinase, plasminogen-activator-inhibitor type 1

Introduction

Formation of an occlusive coronary thrombus at the site of acutely deteriorated atherosclerotic plaque is the triggering

event for acute myocardial infarction (AMI) in 90% of patients.^{1,2} Pharmacologic dissolution of the clot by fibrinolytic agents, such as streptokinase (STK), especially when combined with heparin and acetylsalicylic acid (ASA), leads to reperfusion of jeopardized myocardium in 30 to 70% of patients.² The result is reduced infarct size, preservation of left ventricular function, improved survival, and prevention of sudden cardiac death.² Currently available thrombolytic agents have some important limitations, such as resistance to fibrinolysis with subsequent delays in reperfusion in 15 to 40% of patients, acute coronary reocclusion after previous successful reperfusion with reinfarction in 5 to 25% of patients, and intracerebral bleeding in up to 0.7% of patients.^{2,3}

Several in vitro studies demonstrated the important role of platelets, mainly due to their profibrinolytic and antifibrinolytic effects, once they had been activated in the process of thrombosis. Some in vitro experiments suggest that plasminogen-activator-inhibitor-1 (PAI-1) is responsible for the antifibrinolytic effect of platelets.^{4–6} It is mainly present in platelets, but also in endothelial and smooth muscle cells of the vascular wall of the coronary arteries. Only a few clinical studies demonstrated that unsuccessful fibrinolytic therapy was associated with elevated pretreatment baseline PAI-1 levels, either due to delayed reperfusion or reinfarction.^{7–12} Data regarding the predictive role of PAI-1 on the outcome of pharmacologically induced fibrinolysis of patients with AMI, treated with STK, heparin, and ASA, are rare.^{7, 10, 12}

We studied the prognostic role of pretreatment PAI-1 levels for the clinical outcome of fibrinolysis with STK in patients with AMI, with the emphasis on reperfusion and reinfarction.

Patients and Methods

Among 340 patients with AMI admitted to the intensive care unit during 23 months, 124 patients were treated with STK and 11 with urokinase. Of these, 120 patients were admitted after 12 h of chest pain, and in 85 patients the usual exclusion criteria were met. Of 124 patients, 104 patients (78 men, 26 women), accounting for 30.6% (104/340) of all patients with AMI, were studied. Twenty patients were excluded: 4 were pretreated with heparin and/or ASA, and in 16 pretreatment PAI-1 levels were not estimated.

The inclusion criteria for STK therapy were precordial chest pain, lasting > 30 min but < 12 h and not responding to 2–3 sublingual nitroglycerin tablets, associated with 1–2 mm ST-segment elevations in at least two leads of the electrocardiogram (ECG).² Major exclusion criteria were recent trauma, surgery, or organ biopsy; terminal stage of a chronic or malign

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TABLE I Baseline characteristics of patients

Baseline clinical characteristics	All patients	Successful fibrinolysis (n = 65)	Failed fibrinolysis (n = 39)	p Value
Age (years)	60.12 ± 11.0 (33–81)	60.4 ± 10.8	59.62 ± 11.6	0.723
Gender (men/women)	78/26	52/13	27/12	0.255
Arterial hypertension	30 (28.8%)	15	15	0.094
Diabetes mellitus	15 (14.4%)	8	7	0.428
Previous MI	11 (10.5%)	7	4	0.934
Time to therapy (h)	3.1 ± 2.3 (0.5–12.0)	3.03 ± 2.45	3.09 ± 1.96	0.891
Admission CK (ukat/l)	2.4 ± 3.0 (0.01–22.3)	2.61 ± 3.56	2.16 ± 2.8	0.501
Mean pretreatment PAI-1 (U/ml)	5.8 ± 8.6 (0.3–66.2)	4.03 ± 4.18	8.816 ± 12.5	0.005

Abbreviations: MI = myocardial infarction, CK = creatine kinase, PAI-1 = plasminogen-activator-inhibitor type 1.

nant disease; active internal bleeding; known bleeding diathesis; stroke within last 6 months; untreated and unbalanced arterial hypertension; prolonged cardiopulmonary resuscitation > 10 min; allergy to STK, heparin, or ASA; and recent streptococcal infection.²

Before treatment, PAI-1 activity of plasma, red blood cell count, platelets, and creatine kinase (CK) were estimated in blood samples drawn from the antecubital intravenous (IV) line. Creatine kinase was repeated every 3 h during first 18 h of treatment, and ECG was recorded at the same time. Red blood cell and platelet counts were repeated 12 and 36 h from the start of therapy.

On admission, continuous monitoring of rhythm was initiated. Treatment started with an IV bolus of 5000 IU of heparin plus 300 mg of oral ASA, followed by systemic intravenous high-dose (1,500,000 IU), short-term (60 min) infusion of STK and continued by an IV infusion of 1000 IU of heparin/h during the next 24 h. Acetylsalicylic acid (300 mg/day) was given orally during the hospital stay.^{2,13}

Creatine kinase was estimated by the standard method, NAC activated, FCC 30. Normal range was 0.17–2.08 mikrokatal/l (Technicon-RA-XT, Mannheim, Germany, Boehringer-Lek).¹⁴

The PAI-1 activity of human plasma was determined by a chromogenic assay (Berichrom PAI by Behring, Marburg, Germany). Normal range was 0.3–3.55 U/ml.^{15,16}

During the first 4 to 6 days, the patients were continuously monitored for arrhythmias and conduction disturbances; non-invasive systemic arterial blood pressure was measured hourly and patients were clinically examined twice daily. When necessary, other medications [nitrates, antiarrhythmic drugs, analgesics, angiotensin-converting enzyme (ACE)-inhibitors, digitalis, dopamine, dobutamine] were prescribed at the discretion of the attending physician.

The outcome of fibrinolysis with STK was defined to be either successful (reperfusion achieved without subsequent reinfarction) or unsuccessful (reperfusion was delayed and/or reinfarction developed).

Reperfusion was defined as successful when resolution of ST-segment elevations by > 30% on the standard ECG at 3 h after the start of STK infusion¹⁷ was detected by the treating

physician, as well as by two independent nontreating physicians who were blinded to laboratory data, especially pretreatment PAI-1 levels and CK levels during first 18 h of treatment, or if such data were not yet available.

For the reason of assessing reperfusion, standard ECG was repeated every 3 h during the first 18 h of therapy.¹⁷ Reperfusion was delayed when noninvasive reperfusion criteria were not met. Reinfarction was assessed as recurring chest pain, lasting > 30 min and not responding to 2–3 sublingual nitroglycerin tablets, and if it was associated with changes in ECG and elevated values of CK.²

Statistical analysis was performed by IBM PC, SPSS for Windows. Values were expressed as means ± standard deviations, or percentages where necessary. Between-group differences were tested by chi-square test and Student's *t*-test. A *p* value < 0.05 was statistically significant. Multiple regression analysis was performed to test the relative importance of pretreatment variables, with *p* value < 0.05 statistically significant.

Results

Pretreatment baseline clinical variables are listed in Table I.

After STK therapy was completed, reperfusion was achieved in 80 patients (76.9%) and delayed in 24 patients (23.0%). Reinfarction developed in 16 patients (15.4%): in 15 after successful reperfusion and in 1 with delayed reperfusion in whom the infarction was extended (Table II). Therefore, fibrinolysis with STK was successful in 65 (62.5%) and unsuccessful in 39 (37.6%) patients (Table II). According to pretreatment PAI-1 levels, the patients were stratified into several groups, which were compared according to the outcome of fibrinolysis with STK. It was demonstrated that fibrinolysis with STK failed significantly in patients with elevated pretreatment PAI-1 levels, especially PAI-1 levels > 4.0 U/ml, mainly due to reinfarctions (Table II).

Among pretreatment variables between successfully and unsuccessfully treated patients, there was a statistically significant difference only in mean pretreatment PAI-1 levels, which were higher in patients with failed fibrinolysis with STK (Table I). The median pretreatment PAI-1 values of successfully and unsuccessfully treated patients are shown in Figure 1.

TABLE II Stratification of patients, according to pre-treatment PAI-1 levels

Pretreatment PAI-1 (U/ml)	Patients	Reperfusion	Delayed reperfusion	Reinfarction	Failed therapy (%)	Success of therapy (%)
<2.0	26	22	4	2	6 (23.0)	20 (76.9)
>2.0	78	58	20	14	33 (42.3)	45 (57.7)
<3.0	41	32	9	3	12 (29.3)	29 (70.0)
>3.0	61	48	15	13	27 (44.2)	36 (59.0)
<3.5	48	39	9	4	13 (27.0)	35 (72.9)
>3.5	56	41	15	12	26 (46.4) ^a	30 (53.5) ^a
<4.0	55	46	9	4	13 (23.6)	42 (76.4)
>4.0	49	34	15	12 ^e	26 (53.0) ^b	23 (46.9) ^b
<5.0	73	50	13	8	21 (28.8)	52 (71.2)
>5.0	31	20	11	8	18 (58.0) ^c	13 (41.9) ^c
<6.0	80	67	13	10	23 (28.8)	57 (71.3)
>6.0	24	13	11	6	16 (66.7) ^d	8 (33.3) ^d
All	104	80 (76.9%)	24 (23.0%)	16 (15.4%)	39 (37.5)	65 (62.5)

^ap=0.042, ^bp=0.002, ^cp=0.005, ^dp=0.001, ^ep=0.015.

Abbreviation as in Table I.

Multivariate statistical testing demonstrated that elevated pre-treatment PAI-1 activity was the most significant independent risk factor of failed fibrinolysis with STK (Table III).

Discussion

Among fibrinolytic agents, STK is still most widely used because it is effective, easy to administer intravenously, and mainly because it is the least expensive. Tissue-plasminogen-activator (TPA) has some advantages over streptokinase only in selected groups of patients with AMI, as demonstrated by Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO) trial: in large anterior infarctions, after bypass surgery, when streptokinase has already been used, and in patients who present within 6 h of symptoms. Besides the low cost, other advantages of STK over other fibrinolytic agents are that it offers effective treatment for up to 12 h of symptoms of AMI and in cardiogenic shock, and has the lowest incidence of disabling hemorrhagic stroke.¹⁸

Delays in reperfusion and reinfarctions reduce the rate of success of systemic IV STK therapy in about 50%.^{2,3,12,18} According to experimental and clinical data, PAI-1 with its antifibrinolytic activity may participate in treatment failure;^{7,10,15,16} it inhibits spontaneous and pharmacologically induced fibrinolysis and also promotes extension of thrombosis.^{5,9,19}

As PAI-1 is a specific and fast-acting inhibitor of TPA, the efficacy of TPA in relation to the pretreatment PAI-1 levels was even more extensively studied than that of STK. As with STK, some animal and clinical studies revealed the importance of elevated pretreatment PAI-1 levels for unsuccessful outcome of fibrinolysis with TPA, suggesting that elevated PAI-1 levels may interfere with the natural fibrinolytic process and make pharmacologic fibrinolysis less effective.^{6-8,10-12}

Streptokinase activates the fibrinolytic system indirectly by forming a complex with plasminogen, which converts the remaining circulating and thrombus-bound plasminogen into effective plasmin. Plasmin is not directly affected by PAI-1.^{7,19} Therefore, the antifibrinolytic action of PAI-1 upon STK is most likely achieved locally, after PAI molecules are incorporated in thrombi that become resistant to lysis.⁷ The PAI-1 is

FIG. 1 Median values of successfully and unsuccessfully treated patients.

TABLE III Multivariate analysis of baseline clinical characteristics for the success of streptokinase therapy

Baseline clinical characteristics	β	p Value
Age (years)	+0.164	0.1493
Gender	-4.292	0.9695
Arterial hypertension	-0.285	0.015
Diabetes mellitus	+0.141	0.2172
Previous MI	+0.151	0.1917
Time from onset of chest pain to therapy	+0.016	0.8835
Admission CK	+0.078	0.4555
Pretreatment PAI-1	-0.266	0.0130

Abbreviations as in Table I.

released at the site of the vessel injury and/or thrombus formation by endothelial and muscle cells. The most important source of PAI-1 are thrombi rich in platelets, which are most resistant to lysis. It is suggested that both platelets and vascular wall contribute to the increased local PAI-1 activity, and that circulating PAI-1 activity represents only the marker for the local effects of PAI-1.⁵⁻⁷

More frequent reinfarctions in our patients with pretreatment PAI-1 levels >4.0 U/ml, in whom fibrinolysis with STK failed significantly (Table II), could reflect the possible predominance of thrombosis over fibrinolysis as well as partial or intermittent resolution of the clot by STK after an unstable reperfusion in these patients. The speculated mechanism could be the resistance to lysis, followed by further extension of the coronary thrombus.^{7,8,10,11}

When pretreatment variables of successfully and unsuccessfully treated patients were compared, it was shown that only the mean pretreatment PAI-1 level was significantly elevated in patients with failed fibrinolysis with STK. Multivariate regression statistical testing even demonstrated that the elevated pretreatment PAI-1 level was the most significant independent risk factor of failed fibrinolysis with STK. Therefore, when PAI-1 activity of patients with AMI was estimated before the start of fibrinolytic therapy, we could distinguish in advance between patients with high and low risk for unsuccessful outcome of therapy. Patients with normal pretreatment PAI-1 levels could be treated with STK combined with ASA and heparin, and the success rate for these patients was 70–80%. Patients with elevated pretreatment PAI-1 levels, especially >4.0 U/ml, required another therapeutic strategy, for instance angioplasty or a combination of pharmacologic agents that would be successful.¹³ Unfortunately, bedside testing of PAI-1 activity before the start of fibrinolytic therapy is not used at present. Once in the laboratory, it takes at least 20 min to assay PAI-1 activity of the blood sample. After sodium citrate solution is mixed with the venous blood, the blood sample is centrifugated for at least 10 min to get the supernatant plasma, which is then assayed for PAI-1 activity by commercially available kits in the next few minutes. In future, faster bedside testing of PAI-1 activity is necessary to confirm our data and to select patients in whom treatment with pharmacologically induced fibrinolysis, compared with primary angioplasty, will be successful. This would be of great importance.

Conclusion

Among pretreatment variables, elevated pretreatment PAI-1 level, especially >4.0 U/ml, was the most significant independent predictor of failed fibrinolysis with streptokinase in patients with acute myocardial infarction.

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