Plasma Urokinase Antigen and Plasminogen Activator Inhibitor-1 Antigen Levels Predict Angiographic Coronary Restenosis

Bradley H. Strauss, MD, PhD; Herbert K. Lau, PhD; Kimberley A. Bowman, RN; John Sparkes, MSc; Robert J. Chisholm, MD; M. Bernadette Garvey, MD; Louis L. Fenkell, BSc; Madhu K. Natarajan, MD; Inderbir Singh, MD; Jerome M. Teitel, MD

Background—The fibrinolytic system is intimately involved in several processes that contribute to restenosis, including clot dissolution, cell migration, and tissue remodeling. However, the role of the individual activators (urokinase [uPA] and tissue plasminogen [tPA] activators) and inhibitors (plasminogen activator inhibitor [PAI-1]) of the fibrinolytic system in maintaining patency after coronary artery angioplasty and stenting is unclear.

Methods and Results—We prospectively studied 159 patients with stable angina who underwent successful elective angioplasty (n=110) or stenting (n=49) of de novo native coronary artery lesions. Plasma samples were drawn at baseline (before angioplasty) and serially after angioplasty (immediately afterward and 6 hours, 24 hours, 3 days, 7 days, 1 month, 3 months, and 6 months afterward). Antigen and activity assays were performed for uPA, tPA, and PAI-1. Follow-up quantitative coronary angiography was performed in 92% of eligible patients. The overall angiographic restenosis rate (diameter stenosis >50%) was 31% (37% in PTCA patients, 17% in stented patients). At all time periods, including baseline, uPA antigen levels were significantly higher and PAI-1 antigen levels were significantly lower in patients with restenosis. Restenosis rates for patients in the upper tertile of baseline uPA antigen levels were 2-fold higher than for those in the lower 2 tertiles (46% versus 24% and 22%, respectively; P<0.004). In a stepwise regression multivariate analysis, obstruction diameter after the procedure and uPA antigen were significant predictors of follow-up diameter stenosis.

Conclusions—Plasma uPA antigen levels and PAI-1 antigen levels identify patients at increased risk for restenosis after percutaneous coronary revascularization. (Circulation. 1999;100:1616-1622.)

Key Words: angioplasty ■ restenosis ■ fibrinolysis ■ urokinase

The role of the activators, regulators, and enzymes of the fibrinolytic system in maintaining patency after coronary artery angioplasty and stenting is unclear. Active plasmin is generated from its inactive proenzyme, plasminogen, by the endogenous serine proteases tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). The plasminogen activators are in turn regulated by plasminogen activator inhibitors (PAI), most importantly PAI-1. The fibrinolytic system is intimately involved in several processes that potentially have opposing effects on restenosis. Plasmin plays a key role in clot lysis, which would be expected to limit restenosis because the formation and organization of thrombus and the presence of potent mitogenic substances such as clot-bound thrombin at the site of balloon injury may be contributing mechanisms to restenosis.1,2 However, uPA, tPA, and plasmin also are intimately involved in tissue remodeling during wound healing, such as occurs after balloon injury, which would favor the development of restenosis. Experimental models of rat carotid artery balloon injury have demonstrated that smooth muscle cells and endothelial cells express uPA, urokinase receptor (u-PAR), tPA, and PAI in the first week after injury, coinciding with migration and proliferation of smooth muscle cells and the development of a neointima.3–5 Plasmin has many substrates in addition to fibrin. It can degrade matrix components, stimulate cellular migration, and activate growth factors and matrix metalloproteinases that promote restenosis.6 Although tPA has been believed to be predominantly involved in clot dissolution, uPA and u-PAR are active in pericellular proteolysis that occurs during tissue remodeling and migration.7 Thus, the overall net effect of the fibrinolytic system or its individual components in determining restenosis after coronary interventions needs further clarification.

The objectives of this study were to determine whether angiographic restenosis could be predicted by either baseline...
plasma levels of the activators and regulators of the fibrinolytic system or by changes in these variables after angioplasty and stenting and to determine whether coronary interventions result in activation of the fibrinolytic system. The results demonstrate a strong and significant relationship between restenosis and plasma uPA and PAI-1 antigen levels before the procedure and over the subsequent 6 months.

Methods

Patients

In this single-center prospective study, 159 patients were enrolled from January 1994 to April 1997. The study was approved by the Hospital Research Ethics Board, and subjects gave informed consent. The inclusion criteria were successful elective PTCA or stenting of a single de novo lesion in a native coronary artery. Exclusion criteria included recent (<2 weeks) unstable angina (defined as rest pain with ST-segment changes) or myocardial infarction, bypass graft lesions, total occlusions, and concurrent illnesses (cancer or chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease). Patients with an unsuccessful procedure (residual diameter stenosis [DS] >50%) or abrupt occlusion within the first 7 days were excluded from additional analyses. None of the patients had undergone recent (<1 year) interventions of other lesions except for 1 patient who had angioplasty of a different artery 2 months before the angioplasty for which he was enrolled in this study.

Coronary angioplasty and stent insertion were performed according to standard techniques by 2 of the investigators (B.H.S. and R.J.C.). The procedure was considered successful when the residual DS in the dilated segment was <50% immediately after angioplasty and no major complications ensued (in-hospital death, urgent bypass surgery, redo PTCA, or myocardial infarction). Myocardial infarction was defined as the presence of new Q waves of ≥0.04-second duration and/or an increase in serum creatine kinase to more than twice the normal value together with an elevation of creatine kinase–MB isoenzyme. Adjunctive stenting was left to the discretion of the operator.

Quantitative Angiographic Analysis

All cineangiograms were analyzed offline with the Cardiac Measurement System (Medical Imaging Systems) with techniques that have been described in detail elsewhere.8 Measurements of minimal luminal diameter, reference diameter, percent DS, and lesion length were obtained, with the guiding catheter used as a calibration factor. All cineangiograms were analyzed offline with the Cardiac Measurement System (Medical Imaging Systems) with techniques that have been described in detail elsewhere.8 Measurements of minimal luminal diameter, reference diameter, percent DS, and lesion length were obtained, with the guiding catheter used as a calibration factor.

Laboratory Measurements

Blood was drawn from the antecubital vein with minimal tourniquet pressure at the following times: baseline (preprocedure) and immediately, 6 hours, 24 hours, 3 days, 7 days, 1 month, 3 months, and 6 months after the procedure. At all time points (except 6 hours), blood sampling was done between 9 AM and 1 PM to limit the effects of diurnal variation. Plasma samples were stored at −20°C until assays were performed. The assays for tPA and PAI-1 antigens became available later in the study and were only performed on the baseline and immediately postprocedure specimens.

uPA antigen was measured by radioimmunoassay with an affinity-purified antibody against high-molecular-weight urokinase (HUK) as previously described.10 The radioimmunoassay for HUK cross-reacts with single-chain urokinase (scu-PA) equally but does not detect low-molecular-weight urokinase. It also detects HUK complexed with PAI-1. Urokinase activity was measured by an immunonotrapping method as previously described.11 Levels of tPA antigen were determined by a commercial ELISA, according to the manufacturer’s instructions (TintElize, Biopool). tPA activity was assessed by a modification of a spectrophotometric solid-phase fibrin-tPA assay (SOFIA-tPA).12 PAI-1 antigen levels were measured by a commercial ELISA, according to the manufacturer’s instructions (Imubind, American Diagnostica). This assay detects active and inactive forms of PAI-1 as well as tPA/PAI-1 and uPA/PAI-1 complexes. PAI-1 activity was measured by use of published techniques.13

Statistical Analysis

Two approaches were used to assess angiographic restenosis. First, a binary approach used the commonly used cutoff of >50% DS based on angiographic follow-up. This definition classifies the outcome in patients as either restenosis (>50% DS) or patent (≤50% DS). For each fibrinolytic variable, we calculated mean values for the patent and restenosis groups at the specific time points studied. We then assessed whether the mean values of the fibrinolytic variable of interest in the restenosis and patent groups differed over the range of time points, using a general linear model analysis for repeated measures of the same variable over time (SAS FSP version 6.10). If significant differences were present, individual time points were compared by use of a Dunnett t test. Restenosis rates were also compared by use of a Fisher exact test in the study patients who were grouped according to tertiles for the specific fibrinolytic variable of interest.

Second, a continuous approach was used that analyzed follow-up DS as a continuous variable. This avoids the somewhat artificial cutoff of the binary approach. This approach was used to determine whether there was an association between various clinical (age, sex, and presence of diabetes), angiographic (vessel type, preprocedural reference diameter, obstruction length, and obstruction diameter), procedural (PTCA versus stent and postprocedural obstruction diameter), and fibrinolytic variables (preprocedural antigen and activity levels of uPA, tPA, and PAI-1) and follow-up DS, based on Pearson correlation coefficients. A stepwise regression analysis was also done with follow-up DS used as a continuous variable. Prediction models, with the variables listed above used to predict DS, were generated for the overall group as well as the PTCA and stenting subgroups by use of the SAS stepwise regression procedure. In the final prediction model, the variables selected were those that had significant and independent correlations with DS.

To determine whether significant changes occurred in the fibrinolytic variables over time compared with the preprocedural levels, Dunnett t tests were performed. A value of P<0.05 was considered to indicate statistical significance.

Results

Clinical Results

The characteristics of the patients are shown in Table 1. The study population consisted of 159 patients, of whom 77% were male. Angioplasty alone was performed in 69% of patients; 31% underwent adjunctive stent placement. The overall clinical event rate was 25%. Early (<2 week) events occurred in 3 patients (1 death at day 7 in a stent patient and 2 myocardial infarctions at day 4 due to subacute occlusions [1 stent and 1 PTCA]). Late clinical events were documented in 36 patients, including 35 target-lesion revascularizations (33 re-PTCA, 2 CABG) and 1 nontarget-vessel revascularization (PTCA).

Angiographic Results

Angiographic follow-up was obtained in 143 (92%) of 156 eligible patients. The overall restenosis rate (DS >50%) was 31%. Restenosis occurred in 37 (37%) of 101 PTCA patients and in 7 (17%) of 42 stented patients, which was statistically significant (P<0.03 by Fisher exact test).
Restenosis and Fibrinolytic Variables

Urokinase

There was a strong and significant correlation between preprocedure uPA antigen levels and follow-up DS (Pearson correlation coefficient 0.254, \( P < 0.003 \)). When a binary definition of restenosis was used (ie, >50% DS at angiographic follow-up), uPA antigen levels were significantly higher in patients with than in those without restenosis at all time periods, including baseline (Figure 1A). As shown in Table 2, when patients were grouped according to their baseline uPA antigen levels, restenosis rates in the upper tertile were 2-fold higher than in the mid and lower tertiles (46% versus 24% and 22%, respectively; \( P < 0.004 \)). In the overall group, uPA antigen levels showed a modest increasing trend in the months after revascularization that reached significance only at 3 months (\( t = 3.54, P = 0.01 \); Figure 1B).

In contrast, uPA activity levels were not different in the groups with and without restenosis (Figure 2A). However, in the overall group, activity levels of uPA showed much greater fluctuation than uPA antigen levels (Figure 2B). There was a sharp decline immediately after the procedure (\( t = 3.25, P < 0.01 \), with a subsequent return toward baseline values by 6 hours. This was followed by a rise to significantly elevated levels, which persisted up to 3 months.

Tissue Plasminogen Activator

There were no significant correlations between either baseline tPA antigen levels or tPA activity levels and follow-up DS, nor were there any differences according to the presence or absence of restenosis (Figure 3A and 3B).

Plasminogen Activator Inhibitor-1

There was a strong and significant inverse correlation between baseline PAI-1 antigen levels and follow-up DS (Pearson correlation coefficient -0.228, \( P = 0.006 \)). When the binary definition of restenosis was used, PAI-1 levels were significantly lower in restenotic patients at the time periods studied, baseline and immediately after angioplasty (Figure 4A). The highest restenosis rates were found with baseline PAI-1 antigen levels in the lowest tertile (40%) compared with the 2 higher tertiles (27% and 25%, respectively). This difference was of borderline statistical significance (\( P = 0.058 \)) (Table 3). In the overall group, PAI-1 antigen levels showed a significant decrease from before angioplasty to immediately after angioplasty (35 ± 18 to 26 ± 17 ng/mL; \( P < 0.000001 \); Figure 4B). There were no significant correlations between baseline PAI-1 activity levels and follow-up DS, nor were there any differences according to the presence or absence of restenosis (Figure 5A).

Interactions Between Urokinase Antigen and PAI-1 Antigen in Predicting Restenosis

The correlation of restenosis with uPA and PAI-1 antigens reflects their opposing effects, as an activator and an inhibitor

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**TABLE 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>77%</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>18%</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>44%</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>26%</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>39%</td>
</tr>
<tr>
<td>Vessel</td>
<td></td>
</tr>
<tr>
<td>LAD/RCA/LCx</td>
<td>58%/20%/22%</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>2.80 ± 0.53</td>
</tr>
<tr>
<td>Obstruction length, mm</td>
<td>9.29 ± 3.29</td>
</tr>
<tr>
<td>Obstruction diameter, mm</td>
<td>0.84 ± 0.34</td>
</tr>
<tr>
<td>DS, %</td>
<td>70 ± 11</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending coronary artery; RCA, right coronary artery, and LCx, left circumflex artery.

Values are percentages or mean ± SD.

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**TABLE 2. Restenosis Rates According to Urokinase Antigen Levels**

<table>
<thead>
<tr>
<th>Urokinase Antigen Tertile</th>
<th>Restenosis Rate (&gt;50% DS)</th>
</tr>
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<tbody>
<tr>
<td>Low (&lt;0.92 ng/mL)</td>
<td>22%</td>
</tr>
<tr>
<td>Mid (0.92–1.12 ng/mL)</td>
<td>24%</td>
</tr>
<tr>
<td>Upper (&gt;1.12 ng/mL)</td>
<td>46%</td>
</tr>
</tbody>
</table>

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**Figure 1.** A, uPA antigen (ng/mL; mean ± SEM). There is a significant overall difference between restenosis group and nonrestenosis group (\( P < 0.01 \)). At all time points, including baseline, uPA antigen levels were higher in restenosis patients (\( P < 0.01 \), except at 1 day, where \( P = 0.04 \)). B, In the overall group, there was a significant but relatively small increase (0.06 ng/mL) in uPA antigen levels at 3 months compared with preprocedure values (\( t = −3.54 \), but not at any other time points. Pre indicates preangioplasty.**
of fibrinolysis, respectively. To determine the interaction between these 2 variables, we grouped the patients on the basis of uPA antigen (highest tertile versus lower values) and PAI-1 antigen (lowest tertile versus higher values) (Table 4). There was a significant difference in restenosis rates between the 4 groups ($P = 0.0031$, Fisher exact test). The most adverse profile consisted of patients whose uPA was in the highest tertile and whose PAI-1 was in the lowest. Patients in this group had a significantly higher restenosis rate of 67% compared with the other groups, including patients who also had uPA antigen levels in the highest tertile but had higher values of PAI-1 antigen levels ($P = 0.035$). Conversely, those who were in the lowest tertile for uPA and highest tertile for PAI-1 had the most favorable outcome, with a restenosis rate of 21%. Those in the intermediate groups had restenosis rates between these 2 extremes.

**Multivariate Analyses of Predictors of DS at Angiographic Follow-Up**

Analyses that used stepwise regression modeling were performed for the overall study population and separately for the PTCA and stent subgroups. For the overall group, we performed analyses in 2 ways: using only preprocedural variables and using both preprocedural variables and postprocedural obstruction diameter. The latter analysis incorporates a risk factor that has been consistently associated with restenosis,$^{14,15}$ whereas the former is more relevant to the clinician in assessing the potential risk of restenosis rate before the intervention.

When only preprocedural variables were considered, procedure type (ie, stent versus PTCA) ($F = 10.9, P = 0.001$) and uPA antigen ($F = 8.6, P = 0.004$) were significantly associated with follow-up DS. This model had a regression $R^2$ of 0.17 ($F = 9.2, P = 0.0001$).

When postprocedural obstruction diameter was included, obstruction diameter after the procedure ($F = 30.3, P = 0.0001$) and uPA antigen ($F = 8.9, P = 0.003$) were significantly associated with follow-up DS. Obstruction length ($F = 3.5, P = 0.06$) and reference diameter ($F = 3.3, P = 0.07$) were of borderline significance. This model had a regression $R^2$ of 0.26 ($F = 12.31, P = 0.0001$). This analysis was also repeated separately for patients who underwent PTCA or stenting. For the PTCA group, the significant variable was obstruction diameter after the procedure ($F = 14.6, P = 0.0002$), whereas uPA antigen was of borderline significance ($F = 2.8,$
For the stent subgroup, only uPA antigen was significant ($F = 4.9, P = 0.033$).

Discussion

Our study has demonstrated that the plasma levels of uPA and PAI-1 antigens are significantly associated with restenosis after percutaneous coronary intervention. The differences in uPA levels between patients with and without restenosis were consistent at all time points, from the preprocedure baseline sampling through the final sampling at 6 months. The baseline concentration of uPA correlated with follow-up DS after both PTCA and stenting. Furthermore, the data also suggest a threshold level of plasma uPA antigen ($\geq 1.12$ ng/mL). Restenosis rates were almost identical in patients in the lower 2 tertiles of uPA concentration (ie, $<1.12$ ng/mL) but were twice as high among those in the upper tertile. A similar but inverse relationship to restenosis was found for PAI-1 antigen levels, with a threshold level of PAI-1 antigen of $\approx 25$ ng/mL. Moreover, there appears to be an interaction between uPA and PAI-1 antigen levels that enables identification of even higher-risk groups for angiographic restenosis than either antigen predicts alone. Those with the most adverse combination of values for the 2 variables had a restenosis rate $\approx 3$-fold greater than those with the least adverse combination of values (67% versus 21%). Because PAI-1 is the main plasma inhibitor of urokinase, it is not surprising that the combination of high urokinase levels and low PAI-1 levels would most favor a profibrinolytic state, which appears to be a critical factor in the development of restenosis.

uPA and its cellular receptor, u-PAR, are active in the pericellular proteolysis that occurs during tissue remodeling and migration. uPA promotes smooth muscle cell migration directly, via its proteolytic activity either alone or in a complex with uPAR (uPAR/uPA), or indirectly by activating latent growth factors, such as hepatocyte growth factor/scatter factor. uPA/uPAR complex also transduces intracellular signals that can trigger events leading to cell migration. For example, the amino-terminal fragment of uPA, which constitutes the nonenzymatic portion of the enzyme, can induce epidermal cell motility. uPA may interact with

<table>
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<th>TABLE 3. Restenosis Rates According to PAI-1 Antigen Levels</th>
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<tr>
<td>PAI-1 Antigen Tertile</td>
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<tr>
<td>------------------------</td>
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<tr>
<td>Low (&lt;25 ng/mL)</td>
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<tr>
<td>Mid (25–41 ng/mL)</td>
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<tr>
<td>Upper (≥41 ng/mL)</td>
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Figure 4. A, Plasma PAI-1 antigen levels (ng/mL; mean±SEM). The assay was only performed at preangioplasty (Pre) and immediately postangioplasty time points. There is a significant overall difference between restenosis and nonrestenosis groups at both time points ($t=2.2, P=0.03$ preangioplasty; $t=3.4, P=0.001$ postangioplasty). B, In overall group, there was a significant decrease after angioplasty compared with preprocedure values ($P<0.00001$).

Figure 5. Plasma PAI-1 activity (IU/mL; mean±SEM). No significant differences were present between the 2 groups, nor were there significant differences over time.

<table>
<thead>
<tr>
<th>TABLE 4. Interaction Between Urokinase Antigen and PAI-1 Antigen on Restenosis Rates</th>
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<tr>
<td>Urokinase Antigen, ng/mL</td>
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<tr>
<td>&gt;1.12</td>
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<tr>
<td>&gt;1.12</td>
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<tr>
<td>≤1.12</td>
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<td>≤1.12</td>
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integrin receptors such as the vitronectin receptors $\alpha_v\beta_3$ and $\alpha_v\beta_{3*}$, which are required for cell movement. The interactive site of vitronectin with $\alpha_v\beta_3$ involves the RGD amino-acid sequence, which is common to many adhesive macromolecules. PAI-1 binds to a region of vitronectin that overlaps with this sequence, thereby antagonizing the function of vitronectin in cell migration. By competing for the binding of PAI-1, uPA indirectly promotes cell migration. There is also evidence that the uPA/uPAR complex enhances cell migration mediated by vitronectin and $\alpha_v\beta_3$.

Other evidence suggests that uPA may have additional plasmin-independent actions relevant to restenosis. Receptor-mediated signaling pathways have been implicated in uPA-mediated increases in monocyte adhesion in the presence of cytokines. The amino-terminal fragment of prourokinase (scu-PA) does not activate plasmin but can stimulate smooth muscle adhesion to vitronectin.

One of the interesting findings in the present study was the lack of relationship between plasma tPA antigen levels and restenosis. This may reflect underlying differences in the roles of the various plasminogen activators in that tPA appears to be primarily involved in clot dissolution, perhaps due to its specificity for fibrin. As discussed above, uPA serves an important role as a pericellular protease that is an integral part of vessel wall repair. Although this provides a potential mechanism for the effect of uPA on restenosis, our results do not allow us to exclude the possibility that plasma uPA antigen is a marker for an undetermined influence. Additional experimental evidence in support of a causal role is provided by transgenic knockout mice studies. In 2 separate models of vessel wall injury, Carmeliet and colleagues demonstrated that neointima formation and neointimal cell accumulation were decreased in uPA-deficient mice but not in tPA-deficient mice, with evidence of decreased smooth muscle cell migration in the uPA knockout mice. Moreover, in a separate study, Carmeliet et al. showed increased neointimal area in PAI-1−deficient mice that were subjected to vascular trauma, which could be inhibited by intravenous injection of replication-defective adenovirus expressing human PAI-1. These animal data, which are entirely consistent with the results of our human coronary intervention study, suggest that uPA and PAI-1 are indeed causative.

Our data also reveal a discrepancy between antigen and activity levels for urokinase and PAI-1 as predictors of angiographic restenosis. There are several potential explanations for this discrepancy. The uPA activity assay is an in vitro plasmin-based assay that has several limitations in assessing in vivo events. For example, this assay is insensitive to the plasmin-independent effects of uPA described above. Furthermore, the uPA antigen assay also detects the urokinase precursor scu-PA as well as uPA/PAI-1 complexes, both of which may have plasmin-independent roles in mediating smooth muscle cell adhesion to vitronectin and cellular migration. Discrepancies between antigen and activity levels of plasminogen activators and adverse coronary events in patients with coronary disease have previously been reported.

We found that transient reductions in plasma uPA activity occurred immediately after the procedure, followed by a significant elevation in uPA activity up to 3 months, with a subsequent return to baseline levels at 6 months. This period of plasma uPA activation after coronary intervention is very consistent with the timing of restenosis, which typically occurs within the first 3 months after the procedure. A significant decline in PAI-1 antigen levels occurred as a result of the procedure, but later time points for PAI-1 antigen were not assessed. The clinical significance of this early decline is unclear, particularly because the corresponding decrease in PAI-1 activity was only a transient event.

In summary, our results suggest that plasma uPA and PAI-1 antigen levels identify patients at increased risk for restenosis after coronary interventions. Patients with the most-profibronolytic state (ie, high uPA antigen and low PAI-1 antigen) appear to be at particularly high risk for restenosis. Selective inhibition of uPA may be an effective therapeutic strategy to limit restenosis.

Acknowledgments

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