

Predictive Value of PAI-1 Plasma Activity and Thallium Perfusion Imaging for Restenosis after Percutaneous Transluminal Angioplasty in Clinically Asymptomatic Patients

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Summary

Background. The main long-term complication of percutaneous transluminal coronary angioplasty (PTCA) is restenosis that occurs in 30-50 percent of all primary successful cases. The purpose of this study was to evaluate the predictive value of changes in plasminogen activator inhibitor-1 (PAI-1) activity and of thallium dipyridamole perfusion imaging performed 3 months after successful angioplasty. All patients were asymptomatic at evaluation. The results of these two noninvasive tests were compared with the angiographic outcome after 6 months.

Methods and Patients. Twenty-five patients were included in this prospective study. All patients had single vessel disease, successful angioplasty and were free of clinical symptoms 3 months after angioplasty that would suggest late restenosis. In 12/25 patients (48%) angiographic restenosis (percent diameter stenosis >50%) was determined by follow-up angiography 6 months after angioplasty. PAI-1 plasma activity was determined by a functional titration assay and increase or decrease of PAI-1 plasma activity was evaluated between values obtained before and 3 months after angioplasty. In 7/25 (28%) patients PAI-1 plasma activity increased to more than 90% of pre-angioplasty values. This increase correlated with angiographic restenosis evaluated 6 months after angioplasty (sensitivity 42%, specificity 85%, positive predictive value 71%, and negative predictive value 61%). TI-201-perfusion imaging was performed 3 months after angioplasty. This test was indicative for subsequent restenosis in 5/25 patients (sensitivity 33%, specificity 100%, positive predictive value 62%, and negative predictive value 100%). In 10/25 (40%) patients at least one of the two non-invasive tests performed 3 months after angioplasty predicted angiographic restenosis at 6 months; the combined use of PAI-1 and TI-201-perfusion imaging resulted in increased sensitivity (67%) and high specificity (85%).

Conclusion. The results of this study indicate that an increase of PAI-1 plasma activity may improve the predictive value for restenosis of TI-201-scintigraphy performed 3 months after angioplasty even in asymptomatic patients.

Introduction

Long-term clinical outcome of percutaneous transluminal coronary angioplasty (PTCA) introduced in 1977 (1) is hampered by the occur-

rence of restenosis (2). Clinical restenosis is seen in 20-30% (3, 4) of the patients and in addition 15-20% exhibit asymptomatic restenosis (4, 5). Therefore, in a total of 40-50% of the patients restenosis occurs within 6 months after angioplasty (6). It is assumed that injury of the vessel wall followed by platelet deposition and activation of the coagulation cascade contributes to neointimal proliferation that is thought to play a key-role in the development of restenosis (7-9). For this process thrombin formation seems to be important not only because of its mitogenic activity towards smooth muscle cells but also because of thrombin triggered fibrin formation and platelet activation (10). Persistence of fibrin caused by impaired function of the thrombolytic system in turn has been demonstrated to promote atherosclerosis (11). Consistently, plasminogen activator inhibitor-1 (PAI-1), the main inhibitor of the fibrinolytic system, was found to be elevated in patients with stable and unstable coronary artery disease (12-15).

Early prediction of late restenosis in asymptomatic individuals would be beneficial because a decision of a more aggressive approach for follow-up angiography could be made at a much earlier time point. Currently TI-201-perfusion imaging is routinely performed to assess or even predict restenosis in many centers (16-19). Whereas TI-201-perfusion imaging 6 months after angioplasty is quite accurate in determining the presence of restenosis as made evident by a positive correlation with follow-up angiography in 80-100% (16, 17), the predictive value of TI-201-perfusion imaging is only 50-60% when performed 3 months after angioplasty (18, 19).

Also determination of PAI-1 after angioplasty was shown to predict late restenosis. We could show that a decrease in PAI-1 plasma activity from pre-PTCA to values determined 3 months after PTCA was a highly significant predictor for the absence of late restenosis (7). Others have shown that PAI-1 plasma activities after PTCA are persistently elevated as compared to baseline levels in patients who exhibit late angiographic restenosis (20, 21).

In addition, several risk factors as well as the type of lesion have been identified as indicator for restenosis 6 months after successful PTCA (22). In this study it was the aim to evaluate whether the combination of two currently used predictive parameters, namely TI-201 perfusion imaging and changes in PAI-1 plasma activity, increases the predictive value for restenosis in asymptomatic patients.

Patients and Methods

Patients

Criteria for inclusion into this study were: stable angina pectoris at admission; angiographically successful PTCA; and no clinical symptoms for restenosis three months after PTCA. Twenty-five consecutive patients fulfilling these criteria were included in the study. The degree of stenosis was measured from

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cine-film as mean of two orthogonal projections with a digital caliper. Percent diameter stenosis (%DS) was defined as the ratio between the diameter of the non-diseased vessel proximal of the stenosis and the minimal lumen diameter at the site of stenosis. Initial success after angioplasty was defined as less than 30% stenosis. During follow-up all patients were treated using the same drug regimen (isosorbiddinitrate 40 mg/day, nifedipin 30 mg/day, dipyridamole 225 mg/day, and acetylsalicyl acid 100 mg/day). In all patients follow-up angiography was performed about 6 months (217 ± 88 days) after angioplasty or earlier in case of a positive nuclear stress test and/or clinical signs of angina, indicating a possible restenosis. Restenosis was defined angiographically by a %DS of more than 50%.

Blood Sampling

Blood was collected one day before angioplasty as well as 12 weeks thereafter. In all patients blood samples were withdrawn between 8.00 and 10.00 a.m. to exclude possible influences of circadian variations on the result of the fibrinolytic parameters (23, 24). Blood was drawn from resting patients after a 12 h fast from an antecubital vein using a 1.2 mm siliconized needle with minimal venous occlusion. After discarding the first 2 ml, 7 ml of blood were drawn directly into plastic tubes prepared with EDTA (final concentration 5×10^{-2} M). Blood was centrifuged immediately (15° C, 3000 RPM, 10 min) and plasma was stored at -70° C until use.

PAI-1 Determination

PAI-1 activity was determined according to a functional titration assay (25), as modified by us (26). This assay is specific for PAI-1 because of the use of single-chain t-PA and exhibits an intra-assay variation of 7% and an inter-assay variation of 12%. Values are given as t-PA inhibiting units (U/ml). A decrease of PAI-1 activity in the follow-up plasma sample 3 months after PTCA of more than 10% was used as the cut-off value for a reduced risk for coronary restenosis (7). Accordingly, PAI-1 activity in the follow-up evaluation of more than 90% of the pre-PTCA activity was used as indicative for late restenosis (7).

Table 1 Clinical characteristics

	All	No Restenosis	Restenosis	P
N	25	13	12	
Male (%)	19	8 (62%)	11 (92%)	.16
Age (a)	55 ± 7	54 ± 8	56 ± 7	.48
PTCA: LAD/CX/RCA	19/5/1	8/1/4	11/0/1	.20
% DS pre PTCA	91 ± 7	90 ± 6	92 ± 7	.56
% DS post PTCA	7 ± 13	9 ± 14	5 ± 10	.38
% DS 6-month post PTCA	48 ± 42	12 ± 19	88 ± 10	.0001
Triglycerides (mg/100mL)	114 ± 28	112 ± 29	116 ± 29	0.72
PAI-1 (U/ml) before PTCA	7.0 ± 3.3	6.6 ± 3.4	7.2 ± 3.2	.77
PAI-1 (U/ml) 3 months after PTCA	5.2 ± 3.4	5.0 ± 3.9	5.4 ± 3.0	.82
PAI-1 positive	7	2	5	
TI-210 perfusion imaging positive	4	0	4	

PTCA: percutaneous transluminal coronary angioplasty; LAD: left anterior descending artery; CX: circumflex artery; RCA: right coronary artery; % DS: percent diameter stenosis; TI-210 perfusion imaging: single photon emission computer tomography (SPECT) thallium dipyridamole perfusion imaging; PAI-1: plasminogen activator inhibitor-1 plasma activity; PAI-1 positive: increase in PAI-1 plasma activity 3 months after angioplasty to a value of more than 90% of PAI-1 plasma activity before PTCA; TI-210 perfusion imaging positive: reversible defect in the vessel territory where PTCA was performed

TI-201 Dipyridamole Myocardial Perfusion Imaging

Dipyridamole was infused via a peripheral venous canula at the rate of $0.142 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 4 min as suggested by Gould et al. (27). Thallium-201 injection was given 3-4 min after the end of the dipyridamole infusion. In patients whose heart rate increased by less than 15% after dipyridamole infusion an isometric hand-grip test was additionally performed. If a patient developed pain and/or significant (>2 mm) ST segment depression during the procedure, 0.24 g aminophylline was administered. Aminophylline was always given at least 1 min after thallium-201 administration to ensure sufficient extraction time of the tracer. Single photon emission computerized tomography (SPECT) imaging was started 3-5 min after thallium-201 injection. Images were obtained over 180° rotation (continuous rotation, 30 frames). Redistribution images were taken 3.0-3.5 h after the thallium-201 injection. Perfusion images were evaluated in a semiquantitative way by 3 observers unaware of the clinical history and the results of the other tests. The final judgment was made by consent. Negative images, probably negative, or equivocal images were grouped as normal (negative for restenosis) and probably positive images, and definitive positive images as abnormal (positive for restenosis) to achieve a dichotomous classification of perfusion results.

Statistical Analysis

Analysis of variance was employed to describe differences in clinical characteristics between patients with/without restenosis at follow-up. The McNemar test was used to compare changes in PAI-1 plasma activities and TI-201 perfusion imaging determining restenosis. Data are expressed as means \pm SD. A value of $p < 0.05$ was considered significant. The "Primer of Biostatistics" Version 3.02 and "Statview" Version 4.5 were the statistical programs used.

Results

Patient-specific data are summarized in Table 1. Twelve of 25 (48%) patients developed angiographic restenosis. Patients developing restenosis did not differ from patients without restenosis in baseline characteristics. The left anterior descending artery (LAD) was the most frequently treated vessel in both groups of patients, with and without restenosis (92% vs. 62%; $p = 0.20$). The percent diameter stenosis before PTCA ($92 \pm 7\%$ vs. $90 \pm 6\%$; $p = 0.56$) and after PTCA ($5 \pm 10\%$ vs. $9 \pm 14\%$; $p = 0.38$) were similar in both groups.

Evaluation of Restenosis by TI-201-Perfusion Imaging

TI-201-perfusion imaging was performed in all patients after dipyridamole administration to obtain maximum vasodilatation and 3 to 3.5 h later. Four of 25 (16%) patients showed a filling defect after dipyridamole that was reversible 3-3.5 h later. This pattern indicated a local stenosis in the supplying vessel. Such a TI-201 perfusion pattern was indicative for an angiographic restenosis determined 3 months later in all 4 cases (specificity 100%; positive predictive value 100%). In 8 patients TI-201-perfusion imagings were normal despite restenosis in the follow-up angiogram (sensitivity 33%; negative predictive value 62%).

Prediction of Restenosis by Changes in PAI-1 Plasma Activity

In this study 7/25 (28%) patients showed unchanged or increased PAI-1 plasma activity compared to the values before angioplasty (Fig. 1). Five of these 7 (71%) patients revealed restenosis in the follow-up angiogram 6 months after angioplasty (sensitivity 42%). Thus, the positive predictive value of changes in PAI-1 plasma activity determined 3 months after angioplasty was 71% for late angiographic restenosis.

Table 2 Sensitivity and specificity of changes in plasminogen activator inhibitor-1 (PAI-1) and TI-201 perfusion imaging

	PAI-1	TI-201-perfusion imaging	PAI-1 and/or TI-201-perfusion imaging
Sensitivity (%)	42	33	67
Specificity (%)	85	100	85
NPV (%)	61	62	73
PPV (%)	71	100	80

PAI-1: plasminogen activator inhibitor-1; TI-201-perfusion imaging: single photon emission computer tomography (SPECT) thallium dipyridamole perfusion imaging; NPV: negative predictive value; PPV: positive predictive value; PAI-1 and/or TI-201-perfusion imaging: positive PAI-1 and/or TI-201-perfusion imaging for restenosis

The negative predictive value of decreasing PAI-1 plasma activities was 61% for the absence of late angiographic restenosis and the specificity of this parameter was 85% (Table 2).

Prediction of Restenosis by a Combination of TI-201-perfusion Imaging and Changes in PAI-1 Plasma Activity

Both, TI-201-perfusion imaging and changes in PAI-1 plasma activity were not significantly different with respect to the prediction of restenosis 6 months after angioplasty ($p = 0.51$). However, the combination of both tests (at least one of the two positive) was superior in predicting restenosis as compared to each test used alone with respect to sensitivity and negative predictive value (Table 2). Eight of 10 patients scored abnormal in at least one out of the two tests. Only one of these 8 patients scored positive in both tests.

Discussion

Cardiovascular disease morbidity is high in the Western world and contributes about 50% to overall mortality. Angioplasty became increasingly popular over the last decade in managing patients with coronary artery disease (28), however, the major long-term limitation still

remains restenosis. Angiographic restenosis is known to develop mainly between 2 and 4 months after initially successful angioplasty (29).

One group of factors determining the development of late restenosis seems to be patient-related, in so far as patients with diabetes (30) or unstable angina (31) develop late restenosis more frequently. A second important group of parameters lies in the procedure and lesion-related factors. Lesion localization, baseline percentage diameter stenosis, stenosis length, and severity of post-angioplasty stenosis are strongly linked to the development of restenosis (32). In fact, lesion morphology can be used as a predictor for late restenosis. However, from the available data it is clear that none of the patient- and procedure-related parameters predicts late restenosis reliably. As far as procedure-related factors are concerned, most of these reflect vessel wall damage. Among those, platelet-released products are good indicators because inhibition of platelet-derived growth factor (33) or blocking GP IIb/IIIa to inhibit platelet aggregation (34) were shown to effectively reduce late restenosis. However, while these factors might be locally causative for restenosis, their plasma levels are not high enough or only short-lived to allow their use for prediction of late restenosis. The same might hold true for activation markers of the coagulation system such as thrombin/anti-thrombin-III complexes and the prothrombin fragments F(1+2) (35). Nevertheless, markers of thrombin generation were shown to increase in plasma after angioplasty in animal models (36, 37).

A further factor in the development of restenosis seems to be a local inflammatory response reflected by NF- κ B activation within the injured arterial wall (38). Local injury and generated oxygen radicals cause NF- κ B activation which in turn leads to upregulation of cell adhesion molecules, tissue factor, and PAI-1 (38, 39). While expression of adhesion molecules induces local leukocyte accumulation, tissue factor expression, and local thrombus formation, PAI-1 causes persistence of the formed thrombus and reaches the general circulation. PAI-1 plasma activity measured before angioplasty correlates with late restenosis (40). According to this concept an increase in PAI-1 plasma activity 3 months after angioplasty might indicate persistent inflammatory activation of the vessel wall. Inflammatory activation can cause smooth muscle cell proliferation and migration and finally neointima formation and angiographic restenosis (41).

In our study we measured changes in PAI-1 plasma activity and in fact found that 7/25 patients showed an increase of PAI-1 plasma activity; within that group 5/7 patients developed angiographic restenosis. However, only 5/12 patients with late restenosis showed an increase in PAI-1 plasma activity. Three of seven PAI-1-negative patients revealed already impaired perfusion measured by TI-201 perfusion imaging. Only 1 patient exhibited both, impaired perfusion as measured by TI-201 perfusion imaging and elevated PAI-1 plasma activity 3 months after angioplasty. It can be assumed that in the 3 patients showing impaired perfusion without PAI-1 plasma activity elevation the triggering mechanism for restenosis was not active anymore and the restenotic process proceeded without any further inflammatory stimulation. However, 4 patients were negative by TI-201 perfusion imaging as well as by PAI-1; these patients still developed restenosis as detected by angiography 3 months later. False negative TI-201 perfusion images can be caused by the fact that restenosis developed after the noninvasive test had been performed. In these patients an inflammatory silent restenotic process may have been responsible for late restenosis with no PAI-1 increase at measurement.

TI-201 perfusion imaging detects late restenosis in patients with mild to severe coronary stenosis 3 months after angioplasty. Increase in PAI-1 plasma activity detects patients with an ongoing inflammatory process leading to significant late restenosis. However, borderline

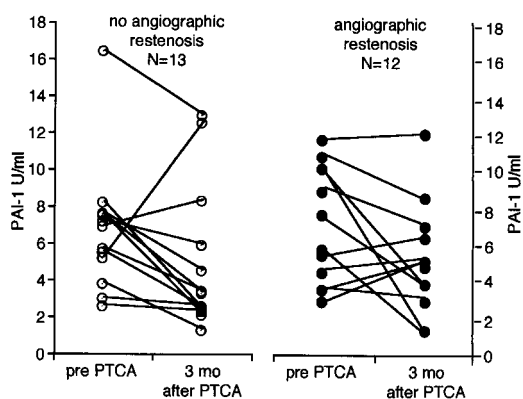


Fig. 1 Changes in plasminogen activator inhibitor-1 (PAI-1) plasma activity before angioplasty and 3 months after angioplasty in asymptomatic patients with (N =12) and without (N =13) angiographic restenosis (= 50 percent diameter stenosis) 6 months after angioplasty

changes of the above mentioned parameters may lead to late restenosis, but cannot be detected by the test system employed.

Limitations and Clinical Implications

The present study represents a relatively small sample size of 25 patients. However, the relatively high restenosis rate reflects realistically the outcome of angioplasty in patients with single vessel disease in many institutions. The value of changes in PAI-1 plasma activity as a marker of disease activity may be limited in patients with multi vessel disease, where despite the absence of a restenotic process, disease activity in other vessels may cause elevated PAI-1 levels. Nevertheless, this study is one of the few combining information from noninvasive testing with parameters of fibrinolytic/inflammatory activity in a population with well defined morpho-anatomical descriptors by angiography in patients without clinical symptoms.

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