



REGULAR ARTICLE

Changes in the Fibrinolytic System in Patients with Peripheral Arterial Occlusive Disease Undergoing Percutaneous Transluminal Angioplasty

Regina E. Roller^{1,2}, Sandra Janisch¹, Veronica Carroll¹, Erich Kvas³, Ernst Pilger², Bernd R. Binder¹ and Johann Wojta¹

¹Department of Vascular Biology and Thrombosis Research,

University of Vienna, Vienna, Austria; ²Division of Angiology, Department of

Internal Medicine, University of Graz; ³Department of Medical Physiology, University of Graz, Graz, Austria.

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Abstract

We have investigated fibrinolytic parameters in 33 patients with peripheral arterial occlusive disease (PAOD) before and 6, 24, and 48 hours after percutaneous transluminal angioplasty (PTA) as well as in 35 gender-matched healthy controls, whose mean age was not significantly different from the mean age of the patients. PAOD patients had significantly higher plasma levels of t-PA antigen (12.0 ± 4.9 vs. 9.2 ± 5.5 ng/ml), PAI-1 antigen (34.8 ± 22.1 vs. 27.2 ± 23.6 ng/ml), PAI-1 activity (10.0 ± 6.5 vs. 8.0 ± 8.0 U/ml), PCI (188.2 ± 55.6 vs. $134.1 \pm 75.5\%$ as compared with normal human plasma), and fibrinogen (420.2 ± 92.6 vs. 261.9 ± 32.7 mg/dl) as compared with controls. After angioplasty, fibrinolytic parameters and fibrinogen levels increased, reaching higher than preintervention levels 24 and 48 hours after the intervention. Six months after initially successful PTA, restenosis was demonstrated in 14 out of 33 patients (42%). Patients with late resteno-

sis had significantly higher levels of PAI-1 activity 24 and 48 hours after PTA, as compared with patients with late patency (24 hours: 16.1 ± 8.0 vs. 10.0 ± 7.4 ; 48 hours: 16.5 ± 7.9 vs. 12.0 ± 7.0 ; $p < 0.05$ for both time points). The results suggest that impaired fibrinolysis early after PTA might be a cause or marker of a disturbed repair process of vascular injury, leading to restenosis. © 1999 Elsevier Science Ltd. All rights reserved.

Key Words: Percutaneous transluminal angioplasty; Fibrinolysis; PAI-1

Percutaneous transluminal angioplasty (PTA) is an established treatment in patients with coronary heart disease (CHD) and peripheral arterial occlusive disease (PAOD) with increasing success rates within the last few years. The long-term benefit, however, is limited by “late” reocclusion, occurring in 30–50% of the patients within 6 months [1]. In CHD, numerous efforts have been undertaken to identify patients at risk for reocclusion. It has been shown that high levels of fibrinogen [2], Lp(a) [3], protein C inhibitor (PCI) [4], and plasminogen activator inhibitor-1 (PAI-1) [5,6] indicate an increased risk for late restenosis. Patients with PAOD are less well investigated. The aim of the present study was to analyze the fibrinolytic system in patients with PAOD before and after PTA and to correlate the findings with the individual late outcome.

Abbreviations: PTA, percutaneous transluminal angioplasty; CHD, coronary heart disease; PAOD, peripheral arterial occlusive disease; t-PA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor-1; PCI, protein C inhibitor; UH, unfractionated heparin.

Corresponding author: Johann Wojta, Department of Vascular Biology and Thrombosis Research, University of Vienna, Austria, A-1090 Vienna, Schwarzschanerstrasse 17, Austria. Tel: +43 (1) 4277 62507; Fax: +43 (1) 4277 9625; E-mail: <johann.wojta@univie.ac.at>.

1. Patients and Methods

1.1. Patients

Thirty-three patients (22 male and 11 female, mean age 70.1 ± 9.7 years) undergoing PTA of a 2–6 cm stenosis, located either in the femoral or proximal popliteal artery, were recruited. Twenty-four patients were classified to have PAOD grade I/3 (Fontain stage II) and nine to have PAOD grade II/5 (Fontain stage IV) according to the guidelines by the AHA 1993. Risk factors included diabetes (14:33), hyperlipidaemia (15:33), smoking (15:33), hypertension (18:33), and hyperuricaemia (7:33). Patients were pretreated with 300 mg acetyl-salicylic acid either orally the day before angioplasty or intravenously 1 hour before the intervention. All patients received acetyl-salicylic acid (100 mg/day) during the follow-up. For peri-interventional heparin therapy, patients were treated with either unfractionated heparin (UH) or low molecular weight heparin (LMWH, Fragmin®; Pharmacia, Uppsala, Sweden). Seventeen patients received an intra-arterial bolus of 5000 IU UH during angioplasty, followed by an intravenous infusion of initially 1000 IU per hour; thereafter, the dose was adjusted according to the aPTT value until 48 hours after PTA. Sixteen patients received an intra-arterial bolus of 2500 IU LMWH during the intervention, followed by 2500 IU twice daily subcutaneously for 48 hours [7]. The difference in anticoagulant (UH or LMWH) did not influence the fibrinolytic parameters tested (data not shown).

1.2. Percutaneous Transluminal Angioplasty

Angioplasty was performed following a standardized protocol of balloon angioplasty [8]. All interventions were performed with balloon catheters (Cordis, Rhoden, Netherlands) of 20 or 40 mm in length and 3–5 mm in diameter, according to the angiographical status of the treated vessel. An inflation pressure of 10 bar was applied for 1 minute and control angiography was performed immediately after the dilatation. If necessary, dilatation was repeated once. Clinical success of angioplasty was documented by color Doppler sonography, which was performed on the day before PTA, as well as 48 hours and 6 months thereafter, measuring the total vessel diameter and the intraluminal

diameter at the site of the lesion by planimetry. Furthermore, velocities measured at the site of stenosis of less than 0.6 m/second or a loss of the early diastolic reversal was considered to be evidence of more than 75% narrowing in lumen diameter. Areas of abnormal blood flow were subjected to Doppler spectral analysis. Successful dilation was assumed when residual stenosis was less than 50% of the luminal diameter, as measured 48 hours after the intervention. After the described criteria of examination, a patient was defined to have restenosis, if the dilated segment had stenosis of 50% or more of the luminal diameter at the follow-up 6 months after PTA, as compared with the data obtained 48 hours after the intervention.

The study protocol was approved by the Ethic Committee at the University of Graz, and eligible patients provided written informed consent.

1.3. Controls

Thirty-five healthy subjects (28 male and 7 female), who did not exhibit any clinical manifestation of an arteriosclerotic disease, were recruited as controls. Subjects were not receiving any medication, and females were not taking the contraceptive pill. Mean age was 62 ± 4.1 years. Risk factor distribution in the controls was different from the patients: 6 out of 35 had hypertension, 7 out of 35 had hyperlipidaemia, 2 out of 35 had hyperuricemia, and 6 out of 35 controls were smokers. None of the controls was diabetic.

1.4. Laboratory Methods

Blood was drawn from the 33 patients at 8 a.m. before PTA and 6, 24, and 48 hours thereafter by venipuncture of an antecubital vein. Blood (9 volumes) was added to 1 volume of anticoagulant (3.8% m/volume trisodium citrate in Vacutainer® tubes; Becton-Dickinson, Cowley, Oxford, England) and centrifuged immediately at 25°C at 1000g for 5 minutes. Plasma samples were stored in aliquots at -70°C until use. Citrated plasma samples were obtained from the 35 healthy control subjects at 8 a.m. in a manner described above for the patients. t-PA antigen and PAI-1 antigen were determined by commercially available solid phase enzyme immunoassays (Technoclone, Vienna, Austria), by using horseradish peroxidase-labeled monoclonal

antibodies [9,10]. Determinations were performed in duplicate.

Active PAI-1 antigen (PAI-1 activity) was determined using a modified bio-immunoassay (Technoclone). In this assay, an anti t-PA monoclonal antibody is utilized to immobilize t-PA onto a plastic microtiter plate; the active site of t-PA remains exposed and is used to catch active PAI-1 contained in plasma samples. PAI-1 activity is then quantified by a monoclonal anti-PAI-1 antibody [9]. Active protein C inhibitor (PCI) levels were determined using a similar bioimmunoassay (Technoclone), by utilizing urokinase to catch active PCI contained in the plasma samples and a specific monoclonal anti-PCI antibody to detect bound PCI [11]. Values are expressed as percentage of a normal plasma pool. Fibrinogen levels in plasma were determined by the method of Clauss [12].

1.5. Statistical Analysis

Statistical analysis was performed using the *STATISTICA*TM computer program. Values were expressed as mean±SD. To evaluate a possible role of each of the risk factors, a multivariate regression model was applied. Because of the nonparametric distribution of PAI-1 antigen and activity within the patient group, differences between two groups were calculated by Mann Whitney ranking procedure. Changes in the fibrinolytic system during angioplasty were calculated using Friedman ANOVA. A cutoff or threshold value for PAI-1 activity was determined by a probit plot [13]. PAI-1 values were logarithmically transformed in order to obtain normal distributions for both the patient and control groups; thereafter, the area under the curve was integrated to achieve a straight line. The patient group was integrated from right to left, while the

normal group was integrated from left to right. The point at which the two lines crossed was taken as the threshold value for PAI-1 activity (15 U/ml). Sensitivity, specificity, positive and negative predictive values were obtained using 2×2 contingency tables. Individual correlation analysis were done by Spearman correlation test. A *p*-value of less than 0.05 was considered to be significant. Finally the odds ratio for high vs. low PAI-1 levels was calculated and corrected for all other variables and risk factors.

2. Results

Laboratory parameters of controls and patients (before, 6, 24, and 48 hours after PTA) are depicted in Table 1. t-PA antigen (*p*=0.008), PAI-1 antigen (*p*=0.03), and PAI-1 activity (*p*=0.05) were significantly higher in patients than in controls. Similarly PCI (*p*=0.006) and fibrinogen levels (*p*<0.0001) were higher in patients. There was some association of risk factors with fibrinolysis parameters: t-PA antigen (*p*=0.02), PAI-1 antigen (*p*=0.004) and PAI-1 activity (*p*=0.007) were higher in smokers than in nonsmokers. PCI levels were higher in patients with hyperlipidaemia (*p*=0.008), and fibrinogen levels were increased in patients with diabetes (*p*=0.001). Otherwise no correlation of risk factors with fibrinolytic parameters was found (data not shown). Fibrinolytic parameters were not correlated to the two clinical stages of PAOD. After PTA, significant changes of the fibrinolytic parameters were observed. t-PA antigen remained unchanged at the 6-hour time point, thereafter progressively increased to reach approximately two-fold initial values 48 hours after PTA (*p*=0.001). PAI-1 antigen decreased significantly at 6 hours

Table 1. Fibrinolysis parameters, fibrinogen, and PCI levels in normal controls and in patients with PAOD

	Control	Patients before PTA	Patients 6 hours after PTA	Patients 24 hours after PTA	Patients 48 hours after PTA
t-PA Ag ng/ml	9.2±5.5	12.0±4.9	12.0±7.0	17.8±8.5	22.5±11.4
PAI-1 Ag ng/ml	27.2±23.6	34.8±22.2	25.4±17.0	36.2±18.6	36.2±20.8
PAI-1Act. U/ml	8.0±8.0	10.0±6.5	7.6±3.5	12.9±8.0	14.2±7.5
Fibrinogen mg/dl	261.9±32.7	420.2±92.6	419.1±118.5	447.9±143.3	475.7±125.5
PCI % of normal	134.1±75.5	188.2±55.6	175.2±60.8	176.7±63.0	175.3±53.4

Values are expressed as mean±SD.

($p=0.008$), to return to values slightly above pre-intervention levels 24 and 48 hours after PTA (borderline significant). PAI-1 activity dropped slightly at the 6-hour time point to significantly increase above pre-PTA values at 24 and 48 hours after angioplasty ($p<0.001$), respectively. PCI showed a significant decrease 6 hours after PTA ($p=0.01$), while fibrinogen levels were increased significantly at the 24- and 48-hour time points ($p<0.0001$), respectively (Table 1).

Six months after catheter intervention, restenosis had occurred in 14 of 33 patients (42%). Neither age nor gender or stage of the disease were predictive for the late outcome. The same held true for any of the risk factors studied (diabetes, hyperlipidaemia, smoking, hypertension, and hyperuricemia) as determined by multivariate regression analysis. When patients were categorized according to their late clinical outcome (late restenosis and late patency, Table 2) and changes in the individual parameters within the two groups were tested over all of the four time points by ANOVA, no statistically significant differences were found. In a post hoc analysis, however, high PAI-1 activity levels 24 and 48 hours after PTA were significantly associated with restenosis (printed in bold; $p<0.05$).

Individual PAI activity levels of patients with late restenosis and late patency are depicted in Figure 1. The positive and negative predictive value of the 24- and 48-hour PAI-activity level in an individual patient, however, was low. Using 15 U/ml PAI-1 activity as the threshold level, we predicted restenosis in seven out of fourteen patients reflecting a test sensitivity of 50%. Four out of nineteen patients, however, had favorable clinical outcome (late patency) despite PAI-1 activity of more than 15 U/ml 24 hours after PTA (test specificity 78%), whereas eight out of nineteen patients had favorable clinical outcome despite PAI-1 activity of more than 15 U/ml 48 hours after PTA (test specificity 58%). A corrected odds ratio of 7.1 was determined for high vs. low PAI-1 levels indicating a sevenfold higher risk of restenosis in the group of patients with high PAI-1 levels as compared with the group of patients with low PAI-1 levels.

3. Discussion

Ample evidence points towards the involvement of the fibrinolytic system in the process of arterio-

Table 2. Fibrinolysis parameters, fibrinogen, and PCI levels before and after PTA

Age±SD	Restenotic patients (n=14) (70.1±7.4)				Nonrestenotic patients (n=19) (68.1±8.4)			
	Before	6 hours	24 hours	48 hours	Before	6 hours	24 hours	48 hours
t-PA Ag ng/ml	11.2±3.1	10.9±4.0	17.1±5.6	21.9±9.7	11.1±5.1	11.4±8.1	16.9±10.5	20.8±11.5
PAI-1 Ag ng/ml	36.1±17.1	28.1±18.6	41.9±13.1	42.1±23.4	33.7±27.2	23.6±16.4	32.3±21.9	31.2±18.1
PAI-1 Act. U/ml	10.6±5.6	8.3±3.2	16.1±8.0	16.5±7.9	9.3±7.6	6.8±3.8	10.0±7.4	12.0±6.9
Fibrinogen mg/l	410.4±94.1	400.2±123.6	457.7±155.3	477.0±117.5	424.3±94.9	412.4±76.6	416.3±100.0	461.7±130.1
PCI% from normal	191.6±37.6	196.8±57.2	188.0±35.6	186.4±47.5	187.6±71.4	159.4±61.1	168.8±82.0	164.3±58.4

Boldface type indicates levels significantly associated with restenosis ($p<0.05$).

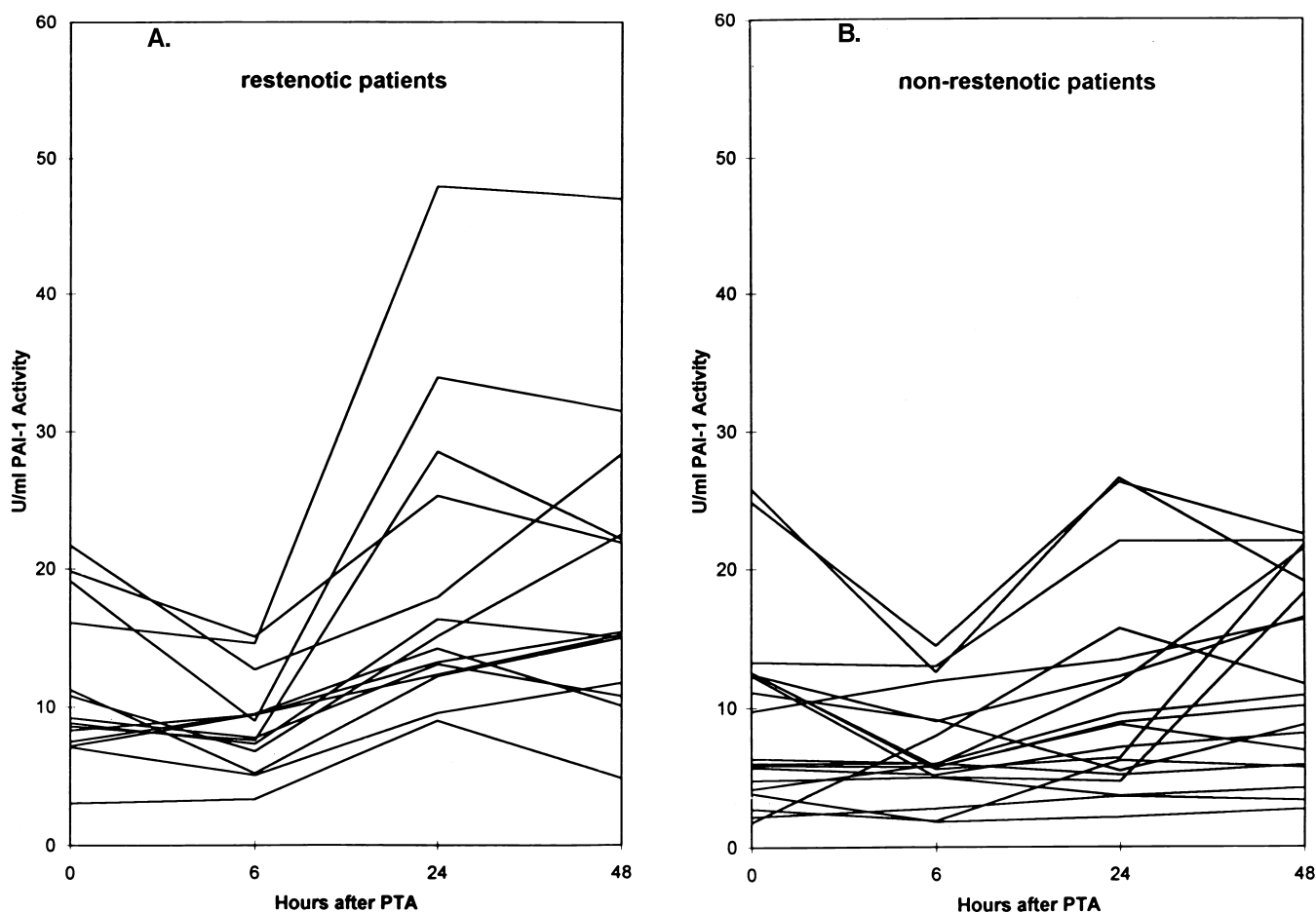


Fig. 1. PAI activity levels before PTA and 6, 24, and 48 hours thereafter in 14 patients with late restenosis (A) and 19 patients with late patency (B) Values are given in t-PA inhibiting units per ml plasma.

sclerosis. It has been shown that PAI-1 plasma levels are elevated in patients with myocardial infarction [14], angina pectoris [15–17], and in patients with PAOD [18–20]. In accordance with these data, we found increased levels of fibrinolytic factors t-PA antigen, PAI-1 antigen, and PAI-1 activity in our cohort of patients with PAOD. As in patients with acute myocardial infarction [4], PCI levels were elevated, which might contribute to the impairment of fibrinolysis, since PCI is known to be an inhibitor of t-PA and u-PA. Furthermore fibrinogen levels were increased as in other diseases caused by arteriosclerosis [21,22].

To our knowledge the time course of fibrinolysis parameters after PTA has not yet been studied in detail. Six hours after the catheter intervention, we found a decrease of PAI-antigen and PAI-activity. This possibly reflects consumption of fibrinolytic factors as a consequence of coagulation activation

[23]. From 24 hours on, an increase of t-PA antigen, PAI-antigen, and PAI-activity was observed, probably due to increased synthesis and/or release. Fibrinogen levels also increased, whereas PCI remained unchanged. Similar patterns of fibrinolysis parameters have been published in patients with CHD undergoing PTCA [24]. Similar to other studies, the fibrinolytic parameters were not differently influenced by UH and LMWH [25].

In more than 40% of the initially successfully dilated patients, restenosis was demonstrated after 6 months. This late type of postangioplasty restenosis is a complex process caused by tissue reaction in response to vascular injury. Contributing mechanisms are elastic recoil, smooth muscle cell migration and proliferation, synthesis of extracellular matrix, vessel wall remodeling, and the incorporation and organization of thrombi [26]. There is now increasing evidence for the involvement of

the fibrinolytic system in this process: experimental balloon angioplasty induces intramural expression of PAI-1 [27], PAI-1 has been shown to stimulate smooth muscle cell migration on fibrin layers [28], PAI-1 “knockout” mice are resistant to restenosis [29], and the extent of PAI-1 expression in the vascular wall is well correlated to the extent of late restenosis [27].

In accordance with these data, we found that elevated levels of PAI-1 activity 24 and 48 hours after PTA were significantly correlated with unfavorable clinical outcome (restenosis). There was, however, no association of late outcome with preintervention PAI-1 activity. It is noteworthy, that similar observations have been published by two independent groups for coronary angioplasty [5,6]. In contrast to data presented in our article, elevated PAI-1 levels in these studies were found not earlier than 1 week and up to 3 months after the intervention. These results indicate that elevated PAI-1 activity levels are a consequence of catheter intervention and are somewhat linked to the pathogenesis of restenosis. Whether they are just a marker for increased tissue reaction, leading to restenosis, or rather a cause, as suggested by experimental data, cannot be answered conclusively. Although the association of high PAI-activity values (24 and 48 hours after PTA) with restenosis was clearly significant, the predictive value in the individual patient was too low to be clinically useful. Our results are in accordance with data obtained in patients with CHD but seem to be in contrast to a recent study, in which patients with PAOD were investigated [30]. The observed differences might be explained by different patient selection, differences in PTA protocol or periinterventional anticoagulation, or, most probable, by the different test systems used for the determination of PAI-1 activity.

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