Determinants of tPA Antigen and Associations with Coronary Artery Disease and Acute Cerebrovascular Disease

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Summary

The aim of this study was to determine the association of tPA antigen levels with CAD and ischemic stroke and whether associations are independent of levels of PAI-1 antigen. In subjects with CAD (n = 247) tPA was associated with the number of coronary arteries with ≥50% stenosis, but this association was lost after adjustment for PAI-1, which was found to be the largest determinant of tPA levels in linear regression models and accounted for as much as 38% of the variation in levels. Levels of tPA were significantly higher in patients with a history of MI compared with those without, even after adjustment for covariates and PAI-1 (MI: 10.0 [9.4-10.6] ng/ml; no MI: 8.9 [8.5-9.4] ng/ml, p = 0.004). In a logistic regression model comparing patients with MI to patients without MI, the odds ratio for tPA levels in the upper quartile compared with the lowest quartile was 2.03 (1.33-3.10). Levels of tPA in subjects with ischemic stroke (n = 338) were significantly higher than age matched healthy control subjects (n = 366) and again this difference remained after adjustment (patients: 10.4 [9.9-10.9] ng/ml; controls: 9.0 [8.7-9.3] ng/ml, p <0.0001). In a logistic regression model comparing patients with ischemic stroke to healthy control subjects the odds ratio for tPA in the upper quartile compared with the lowest quartile was 4.23 (3.02-5.92). These data suggest that the associations of tPA with acute thrombosis are independent of levels of PAI-1 but the mechanisms whereby enhanced fibrinolysis may predispose to thrombosis remain unclear.

Introduction

The processes of atherosclerosis and thrombosis involve a complex interplay of environmental and genetic factors and much work has been carried out in order to identify the major components involved. The development of atherosclerosis begins relatively early in life with progression over decades eventually leading to platelet deposition and thrombus formation, manifested as coronary or cerebral arterial thrombosis. A number of established risk factors for coronary artery disease (CAD) are common to cerebrovascular disease (CVD), including smoking and hypertension (1-3). Several large prospective studies have investigated the association of various coagulation and fibrinolytic factors with the development of CAD and CVD. Results from the Northwick Park Heart Study indicate that impaired fibrinolytic capacity is associated with an increased risk of CAD in middle-aged men (4). Fibrinolytic capacity is influenced not only by levels of pro-fibrinolytic agents such as tissue type plasminogen activator (tPA), but also by inhibitors of fibrinolysis such as plasminogen activator inhibitor-1 (PAI-1), the major inhibitor of tPA in the circulation (5). Despite the association of impaired fibrinolysis with CAD a number of studies, including the Physicians’ Health Study, have determined elevated tPA antigen (tPA) levels in subjects with CAD and cardiovascular disease (6-9). In addition, in subjects with angina pectoris characterised by coronary angiography in the ECAT study prospectively followed for 2 years, levels of tPA were predictive of subsequent cardiac events whereas levels of PAI-1 were not (10).

In the majority of studies, assays used to determine tPA levels also detect tPA complexed with PAI-1 and it has been suggested that the observed associations of elevated tPA with thrombosis reflect an increased level of circulating tPA-PAI-1 complexes (8).

The aims of this study were to: (a) determine the association of tPA with the extent of coronary atheroma and myocardial infarction in subjects with CAD characterised by angiography and with ischemic stroke and stroke subtypes in subjects characterised clinically and by acute computed tomography scan (CT) and (b) to determine if these associations are independent of PAI-1 by adjusting for PAI-1 antigen levels in these subjects.

Materials and Methods

Subjects with CAD. White European subjects (n = 247) admitted for routine angiography for investigation of chest pain or suspected CAD were recruited from Leeds General Infirmary. Healthy age-matched White European control subjects (n = 258) were recruited from local Family Health Services Authority general practice registers. Results of angiography were reported by cardiologists blind to patient status. Presence of coronary artery disease was defined as stenosis of ≥50% in a major coronary artery, or a major coronary artery branch. The extent of disease was classified as the number of arteries with stenosis ≥50% as either no stenosis or one-, two- or three-vessel disease. Myocardial infarction (MI) was ascertained by reference to patients’ hospital case notes using WHO criteria (at least two of the following: ST elevation of 1mm in two or more successive leads; typical chest pain longer than 20 min duration; a rise in creatinine kinase of more than twice the baseline level) (11). Subjects with equivocal evidence of MI from case notes (n = 2), and those with equivocal angiography results (n = 2) were excluded from the relevant analyses.

Subjects with acute stroke. White European subjects (n = 338) with a clinical diagnosis of acute ischemic stroke, whose pathological type was confirmed by non-contrast cranial computed tomography (CT) scan within 10 days in order to exclude subarachnoid and intracerebral haemorrhage, were recruited from four hospitals in Leeds. Healthy age-matched white European control subjects (n = 366) were recruited from Family Health Services Authority (FHSA) general practice registers. We subclassified stroke according to the Oxfordshire Community Stroke Project classification (12), as having either probable small vessel disease (lacunar infarction) or probable large vessel disease (total anterior circulation infarction or partial anterior circulation infarction), as described previously (13). Those subjects with posterior circulation infarcts, which are considered to be of mixed vascular pathology, were excluded from the relevant sub-analyses.
All patients and controls gave informed consent according to protocols approved by the United Leeds Teaching Hospitals Research Ethics Committee. Patients and controls were classified as smokers if they had ever smoked more than one cigarette per day for at least one year. The presence of hypertension was defined as two pre-admission blood pressures of $160/95$ mmHg or current antihypertensive therapy. Body mass index (BMI) was calculated as the weight in kg divided by the square of the height in metres.

**Analysis of circulating factors.** Blood was taken into lithium/heparin for the determination of plasma lipids as previously described (13). Blood samples for the determination of tPA and PAI-1 antigen were taken into ice-cold 0.1 M tri-sodium citrate, centrifuged at 2500 x g at $4^\circ$C and plasma snap frozen in liquid nitrogen and stored at $-40^\circ$C until analysis. In stroke patients, samples were taken within 10 days of the acute event, and a further venous blood sample was taken from survivors at least three months after the acute event, as previously described (13). Subjects with CAD gave a single sample prior to sedation for angiography as previously described (14). All control subjects gave a single sample for determination of circulating factors. Levels of tPA were determined by ELISA (Biopool) with intra-assay and inter-assay coefficients of variation of $7.0\%$ and $10.4\%$ respectively. Circulating PAI-1 antigen levels were determined by ELISA (Biopool) (intra-assay and inter-assay coefficients of variation of $4.4\%$ and $9.8\%$ respectively) and fibrinogen levels were determined by the Clauss method as previously described (14, 15).

**Statistics.** The distributions of tPA, fibrinogen, BMI and triglycerides were positively skewed and values were log transformed to normalise the distribution and allow analysis by parametric tests. Differences in levels between groups were compared by unpaired Student’s t-test. Where results were log transformed they are expressed as geometric mean and anti-logged 95% confidence intervals. All other values are expressed as mean (95% confidence intervals). Ages were compared by Mann-Whitney U-tests and expressed as median and inter-quartile range. Multiple regression analysis was used to identify independent predictors of tPA levels in each group. General factorial ANOVA models were used to give mean levels of tPA after adjustment for covariates and to investigate the interaction of age and sex in the determination of tPA levels. Logistic regression models were used to identify determinants of stenosis, MI and stroke with odds ratios presented with 95% confidence intervals. All statistical analyses were performed using the SPSS statistical package (SPSS Inc., Chicago, USA).

**Results**

**Subjects with CAD**

The characteristics of subjects with CAD and healthy control subjects are presented in Table 1. Levels of cholesterol, triglycerides, fibrinogen and BMI were significantly higher in the patients compared with the control subjects. In addition there were more men, smokers, hypertensives and subjects with diabetes in the patient group compared with controls.

In both the patients and controls, levels of tPA were significantly positively correlated with PAI-1, cholesterol, BMI, fibrinogen and triglycerides and with age in control subjects with a trend to an association with age in patients, as shown in Table 2. In the patients, levels of tPA were significantly higher in hypertensives (10.4 [9.6-11.2] ng/ml) compared with non-hypertensives (8.9 [8.3-9.6] ng/ml, $p = 0.003$), smokers (10.2 [9.5-11.0] ng/ml) compared with non-smokers (8.7 [8.1-9.3] ng/ml, $p = 0.003$) and men (10.1 [9.6-10.7] ng/ml) compared with women (8.0 [7.2-8.8] ng/ml, $p < 0.0001$). In the controls, levels of tPA were significantly higher in men (7.7 [7.2-8.3] ng/ml) compared with women (6.6 [6.1-7.1] ng/ml, $p = 0.005$), but there was no significant difference in levels by hypertensive or smoking status in these subjects. In stepwise linear regression models including all factors associated with tPA levels in univariate analyses; in the patients PAI-1, sex, age, triglycerides and fibrinogen were independent predictors of tPA levels accounting for 36%, 5%, 6%, 5% and 1% of the variation in levels respectively. Similarly in control subjects PAI-1 accounted for 38% of the variation in tPA levels, with age and sex together accounting for a further 11%.

Fig. 1A and Fig. 1B show levels of tPA by history of MI and extent of coronary stenosis respectively. Levels of tPA were significantly higher in subjects with one-, two-, or three-vessel stenosis compared with those with no vessel stenosed, however this association was lost after adjustment for PAI-1, sex, age, triglycerides and fibrinogen (data not shown). Similarly, levels of tPA were significantly higher in patients with MI (10.6 [9.7-11.4] ng/ml) compared with patients without MI (8.7 [8.1-9.3] ng/ml, $p < 0.0001$), and this association remained after adjustment (MI: 10.0 [9.4-10.6] ng/ml; no MI; 8.9 [8.5-9.4] ng/ml, $p = 0.004$). In a logistic regression model comparing patients with MI to those without including PAI-1, tPA, age, sex and smoking, hypertension and cholesterol as covariates, only tPA was an independent predictor of MI ($p$ value for trend = 0.008) with an odds ratio for the upper quartile of tPA compared with the lowest quartile of 2.03 (1.33-3.10). When patients with MI were compared with control subjects, in univariate analyses levels were significantly higher in patients compared with controls however this association was lost after adjustment for confounding factors.

**Subjects with Acute Ischaemic Stroke**

The characteristics of subjects with acute stroke and healthy control subjects are presented in Table 3. There were more hypertensives, smokers, men and subjects with diabetes in the patient group compared with the controls. Patients had higher fibrinogen and lower cholesterol levels compared with the controls.

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**Table 1** Characteristics of subjects with CAD and healthy age-matched controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=247)</th>
<th>Controls (n=258)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.4 (52.0-65.2)</td>
<td>58.4 (47.0-66.0)</td>
<td>na</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 (26.3-27.3)</td>
<td>25.7 (25.2-26.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>6.3 (6.1-6.4)</td>
<td>5.9 (5.7-6.0)</td>
<td>$&lt;$0.0001</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.9 (1.8-2.0)</td>
<td>1.5 (1.4-1.7)</td>
<td>$&lt;$0.0001</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.32 (3.23-3.41)</td>
<td>3.00 (2.93-3.08)</td>
<td>$&lt;$0.0001</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>165/82</td>
<td>132/126</td>
<td>$&lt;$0.0001</td>
</tr>
<tr>
<td>Hypertensive (y/n)</td>
<td>171/76</td>
<td>225/33</td>
<td>$&lt;$0.0001</td>
</tr>
<tr>
<td>Smoker (y/n)</td>
<td>133/114</td>
<td>224/34</td>
<td>$&lt;$0.0001</td>
</tr>
<tr>
<td>Diabetes (y/n)</td>
<td>228/19</td>
<td>257/1</td>
<td>$&lt;$0.0001</td>
</tr>
</tbody>
</table>

Data presented as mean or geometric mean and 95% confidence intervals

**Table 2** Correlations of tPA in patients with CAD and age-matched healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=247)</th>
<th>Controls (n=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p value</td>
</tr>
<tr>
<td>PAI-1</td>
<td>0.62</td>
<td>$&lt;$0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.12</td>
<td>0.06</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.14</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI</td>
<td>0.19</td>
<td>0.003</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.16</td>
<td>0.02</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.42</td>
<td>$&lt;$0.0001</td>
</tr>
</tbody>
</table>
In patients both initially and after 3 months and control subjects, levels of tPA were significantly positively correlated with age, PAI-1 and fibrinogen levels. In the patients, initial tPA levels were also positively correlated with cholesterol and triglyceride levels; and control levels were also positively correlated with BMI and triglycerides. In the patients, initial but not follow-up levels of tPA were significantly higher in smokers (12.6 [11.8-13.4] ng/ml, p = 0.02) compared with non-smokers (11.2 [10.2-12.1] ng/ml), and in women (12.8 [12.0-13.7] ng/ml) compared with men (11.2 [10.5-12.1] ng/ml, p = 0.01). In addition, those patients administered heparin during hospitalisation (n = 21) had significantly higher levels of tPA (18.2 [15.1-22.0] ng/ml) than those without heparin (11.6 [11.1-12.2] ng/ml, p <0.0001). Initial levels of tPA were strongly correlated with follow-up levels (r = 0.63, p <0.0001). In control subjects, levels of tPA were significantly higher in subjects with diabetes (13.0 [8.9-18.9] ng/ml) compared with those without (8.4 [8.1-8.8] ng/ml, p = 0.009), in hypertensives (9.7 [8.9-10.6] ng/ml) compared with non-hypertensives (8.2 [7.9-8.6] ng/ml, p = 0.02) and in women (8.9 [8.4-9.4] ng/ml) compared with men (8.0 [7.5-8.5] ng/ml, p = 0.01), which is in contrast to the observation in subjects with CAD. A scatter plot of tPA levels by age in male and female control subjects is presented in Fig. 2 which indicates a difference in the regression slopes of tPA on age by sex. This difference was found to be significant (p <0.0001) as indicated by the interaction term age*sex included in a general factorial ANOVA model with tPA as the dependent variable. In linear regression models including all factors associated with tPA levels in univariate analyses, in the patients initially, PAI-1 accounted for 25% of the variation in levels with fibrinogen, age, heparin and triglycerides accounting for 7%, 2.5%, 1.5% and 1.5% respectively. In patients followed up after 3 months levels of tPA were independently associated with PAI-1, age and fibrinogen accounting for 14%, 5% and 2% of the variation respectively. In control subjects, PAI-1 accounted for 27% of the variation in levels, with age, triglycerides and fibrinogen explaining a further 14% of the variation.

In the patients, initial levels of tPA were significantly higher than in control subjects and this remained after adjustment for PAI-1, age, fibrinogen, heparin treatment and triglycerides, as shown in Table 4. Similarly levels of tPA in patients followed up after 3 months were significantly higher than in control subjects after adjustment for PAI-1,
Table 5  Levels of tPA in control subjects and in patients by stroke subtype

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Small-vessel infarction</th>
<th>Large-vessel infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial tPA (ng/ml)</td>
<td>8.5 (6.2-8.9)</td>
<td>11.0 (10.0-14.7) *</td>
<td>12.7 (11.7-14.6) *</td>
</tr>
<tr>
<td>Adjusted initial tPA (ng/ml)</td>
<td>8.9 (8.6-6.3)</td>
<td>10.0 (8.2-10.8) *</td>
<td>10.5 (9.7-11.3) *</td>
</tr>
<tr>
<td>3 month tPA (ng/ml)</td>
<td>8.5 (8.2-8.9)</td>
<td>10.3 (9.5-11.2) *</td>
<td>11.9 (10.2-11.9) *</td>
</tr>
<tr>
<td>Adjusted 3 months tPA (ng/ml)</td>
<td>8.9 (8.6-6.3)</td>
<td>10.1 (9.5-10.8) *</td>
<td>10.3 (9.7-10.9) *</td>
</tr>
</tbody>
</table>

Levels are adjusted for PAI-1, age, fibrinogen and also triglycerides and heparin for initial levels only.

p<0.0001 for controls vs. stroke subtype. * p<0.05 for small vs. large vessel infarction when compared by one way ANOVA with Scheffe post-hoc analysis.

age and fibrinogen (Table 4). 241 patients had both an initial and a follow-up determination of tPA. In these subjects levels of tPA at follow-up (10.7 [10.1-11.2] ng/ml) were significantly lower than initial levels (11.7 [11.1-12.4] ng/ml, p < 0.0001).

When patients were classified into small or large vessel infarction and compared with control subjects by one way ANOVA with Scheffe post hoc analysis, initial and follow-up levels of tPA were significantly higher than those in patients with small vessel and large vessel infarction and, initially, levels in those with large vessel infarction were significantly higher than those with small vessel infarction (p = 0.025), as shown in Table 5. After adjustment initial and follow-up levels of tPA remained significantly higher than controls in both stroke subtypes, however, the difference in levels between subtypes was lost (Table 5).

In a logistic regression model comparing patients with ischaemic stroke to control subjects, including sex, smoking, diabetes, hypertension, atrial fibrillation, tPA and PAI-1 as covariates, tPA remained as an independent predictor of stroke (p value for trend 0.0001) with an odds ratio for tPA in the upper quartile compared with the lowest quartile of 4.23 (3.02-5.92). Odds ratios for other factors independently associated with stroke in this model were as follows: 1.44 (1.21-1.73) for men compared with women, 2.94 (1.85-4.66) for diabetic subjects compared with non-diabetic subjects, 1.44 (1.18-1.75) for hypertensives compared with non-hypertensives and 3.27 (2.66-5.19) for subjects with atrial fibrillation compared with those in sinus rhythm.

Discussion

Vascular haemostasis depends on the delicate balance between coagulation and fibrinolysis. The rate of plasmin production depends on the relative amounts of plasminogen activators and their inhibitors and the Northwick Park Heart Study demonstrated reduced global fibrinolytic capacity in subjects with CAD (4). This finding has been supported by a number of studies which have found increased levels of PAI-1 in subjects with CAD and stroke (13, 14, 16-18). In contrast to this a number of case control and prospective studies have found elevated levels of tPA antigen in subjects with MI and stroke (6-9, 18). In the Physicians’ Health Study, tPA was related to the development of MI in univariate analyses but after controlling for classical risk factors this association was lost (7); tPA was also related to the development of stroke in both univariate and multivariate analyses (6). The authors suggested that activation of the fibrinolytic system occurs many years before the manifestation of acute occlusive events (6). An alternative explanation for these observations is that the majority of assays for tPA antigen levels detect both active tPA and tPA bound to PAI-1 and are therefore reflecting elevated PAI-1 levels and thus inhibition of fibrinolysis (8). In the present study we have also used an ELISA for determining tPA levels which also detects tPA complexed with PAI-1, the ELISA for PAI-1 only weakly detects these complexes. However, we have found strong correlations of tPA/PAI-1 complexes with both tPA (r = 0.78, p < 0.0001) and PAI-1 (r = 0.77, p < 0.0001) antigens when measured by these methods (Mansfield MW, Carter AM, Grant PJ, unpublished observation 1997). Therefore, since there is a strong correlation between free PAI-1 and complexes we have adjusted for levels of PAI-1 as a surrogate for tPA/PAI-1 complexes in multivariate analyses in order to determine if the observed associations of tPA with CAD and CVD are independent of PAI-1. We have found a strong correlation between tPA and PAI-1 antigen levels. PAI-1 was the strongest independent predictor of tPA levels in all groups studied and accounted for as much as 38% of the inter-individual variation in tPA. This may reflect detection of tPA/PAI-1 complexes in the assay used, as has been previously suggested (8), but it may similarly reflect the fact that endothelial cells release both tPA and PAI-1 (19) and they may therefore both be acting as markers of endothelial cell dysfunction.

In the present study, sex was an independent predictor of tPA levels in each group although paradoxically levels were lower in female patients with CAD and their controls compared with the men but higher in females with ischaemic stroke and their controls when compared with men. The subjects in the stroke group were considerably older than those with CAD and there was an apparent difference in the association of tPA levels with age in men and women observed in both groups: the regression slope of tPA levels on age was much steeper for women than men with a significant age*sex interaction term in a general factorial ANOVA model with tPA as the dependent variable. Thus, in younger subjects tPA levels were higher in men than in women, but with advancing age the increase in levels of tPA was greater in women such that in the elderly subjects the levels in women became higher than those in men. In addition to PAI-1 and sex, levels of tPA were also independently associated with age, triglycerides and fibrinogen.

We have found elevated levels of tPA in subjects with MI and acute ischaemic stroke. The association of tPA with the extent of coronary artery stenosis observed in univariate analyses was lost after adjustment for factors independently related to tPA levels, in particular PAI-1 antigen levels. In addition, levels were significantly higher in the patients with MI compared with patients without MI and control subjects in univariate analyses, after adjustment for confounding factors tPA levels remained significantly higher only in patients with MI when compared with those without MI and in this group tPA was the only factor independently associated with MI in a logistic regression model accounting for classical risk factors. In subjects with acute stroke, tPA was associated with both small and large vessel disease and these associations remained after adjustment for classical risk factors as well as for PAI-1 levels. It must be considered that in the present study the subjects with stroke were recruited acutely and thus the results may reflect an acute phase response due to the event itself, although levels in those followed-up 3 months later were also significantly higher than healthy control subjects suggesting that this is less likely. For the subjects with CAD, this was a retrospective study of MI and these subjects represent survivors of MI; of these only 5 had an MI less than 3 months prior to study, thus it is unlikely that the results reflect an acute rise in levels as a result of the MI. Although the results of the present study must be interpreted in light of these limitations, these data are in keeping with those of prospective studies (4, 6, 7).

We have previously reported no association of levels of PAI-1 antigen with MI and a trend (p = 0.06) towards an association with extent of stenosis in the subjects with CAD (14). Levels of PAI-1 were, however, significantly higher in subjects with acute ischaemic stroke (both...
small and large vessel) compared with control subjects (13). In the present study we adjusted results for levels of PAI-1 and we observed that the association of PAI-1 with ischaemic stroke was lost after accounting for tPA in the logistic regression model. Therefore, it is unlikely that the observed associations of tPA with MI and ischaemic stroke are merely a reflection of PAI-1 levels but rather are independent of PAI-1.

Most studies have concentrated on explaining their observations in terms of intravascular fibrinolysis despite evidence that extravascular fibrinolysis may play a role in the processes involved in the progression of atherosclerosis. Fibrinogen, fibrin and their degradation products have been identified as components of atherosclerotic plaques (20) suggesting that there is ongoing extravascular fibrinolysis. In support of this, a number of studies have identified both tPA and PAI-1 within atherosclerotic lesions (5, 21-23). Plasmin production may be involved in the modulation of the extravascular environment in several ways. TGFβ is a potent inhibitor of cell migration released in an inactive form by a large variety of cell types and, number of studies have demonstrated that plasmin is capable of cleaving this inactive peptide to release the active molecule (24, 25) which itself induces PAI-1 synthesis ultimately leading to regulation of its own activity (22). Plasmin causes enhanced breakdown of extracellular matrix proteins which, in conjunction with its role in cellular inhibition, may serve to weaken the extracellular matrix in regions of plaque formation (22). Thus it is possible that elevated levels of tPA within atherosclerotic plaques lead to increased plasmin formation resulting in the breakdown of extracellular matrix proteins and inhibition of cellular infiltration, ultimately resulting in a weakening of the developing plaque making it more susceptible to rupture. Conversely elevated levels of PAI-1 within the atherosclerotic plaque would inhibit matrix breakdown and this may explain the observation that PAI-1 levels are correlated with the extent of atherosclerosis in arterial plaque specimens (23).

This hypothesis would, therefore, predict that in vivo elevated levels of PAI-1 would be associated with enhanced plaque stability and, therefore, the extent of atherosclerosis whilst elevated tPA would be associated with reduced plaque stability and subsequent thrombosis, and there is some support from clinical studies to support this suggestion. The ECAT study prospectively followed subjects characterised by coronary angiography for 2 years for the development of fatal or non-fatal MI. At baseline, subjects identified as having one or more coronary arteries with ≥50% stenosis or occlusion had significantly higher levels of PAI-1 but there was no independent association of PAI-1 with subsequent coronary events (10, 16). In contrast, levels of tPA were higher in those with significant stenosis or occlusion and levels were also found to be independently predictive of future coronary events (10, 16). These results are largely supported by the present study. Further studies, both in vivo and in vitro are required in order to clarify the mechanisms whereby an apparent increase in fibrinolysis results in an increased risk of thrombosis.

Acknowledgements

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References


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