Predictive Value of Tissue Plasminogen Activator Mass Concentration on Long-term Mortality in Patients With Coronary Artery Disease

A 7-Year Follow-up

Jan-Håkan Jansson, MD; Bert-Ove Olofsson, MD; Torbjörn K. Nilsson, MD

Background. The fibrinolytic system is part of the defense against thrombotic and cardiovascular events, but so far no study has shown that clinical measurements of fibrinolytic key components such as tissue plasminogen activator (t-PA) or plasminogen activator inhibitor type 1 (PAI-1) have any predictive value beyond 3 years.

Methods and Results. In 1983 through 1985, 213 consecutive patients with angina pectoris and angiographically verified coronary artery disease were sampled, and the mass concentration of t-PA and the activity of PAI-1 were measured in citrated plasma samples. At a mean follow-up time of 7 years, the all-cause mortality was checked. No patient was lost to follow-up. The data were analyzed by Cox regression, and t-PA mass concentration was found to be the only laboratory risk factor significantly related to mortality in all patients (P < .022) and also in the major subgroup (78% of all patients) subjected to coronary bypass surgery (P < .027). In the latter subgroup, body mass index was also related to mortality.

Conclusions. An increased mass concentration of t-PA is a new risk factor of long-term mortality in patients with angina pectoris and coronary artery stenosis. This paradoxical effect probably reflects increased t-PA levels attributable to enzyme inhibitor complex formation in subjects with increased plasma levels of t-PA inhibitors. (Circulation. 1993;88[part 1]:2030-2034.)

Key Words: fibrinolysis • plasminogen activators • coronary disease • risk factors

The involvement of the fibrinolytic system in the development and progression of acute myocardial infarction and unstable angina pectoris has been confirmed on the phenomenological level by studies using coronary angiography and angioscopy and by postmortem histopathological studies of cases of acute myocardial infarction and sudden cardiac death.

It is therefore reasonable to assume that measurements of components of the fibrinolytic system, such as tissue plasminogen activator (t-PA) or plasminogen activator inhibitor type 1 (PAI-1), could give an indication of the risk of cardiovascular events and/or mortality. Actually, there are only two truly prospective studies addressing these questions. Thus, in a study of young survivors of myocardial infarction, PAI-1 was found to predict 3-year reinfarction, but in a longer follow-up (6 years) of the same patient group, the PAI-1 value could no longer predict events; and in a 4-year follow-up of angina pectoris patients with angiographically verified coronary artery disease, we found t-PA mass concentration to be related to myocardial infarction, stroke, and other cardiovascular events, but PAI-1 activity was not.

Although the results from these two studies differ in details, they show that disturbances in the fibrinolytic system do predict future events in some patient groups. Note the interrelation between plasma levels of PAI-1 and t-PA, which is such that a low t-PA activity (which promotes thromboembolic events) concurs with high mass concentrations of t-PA in plasma because of enzyme inhibitor complex formation with PAI-1.

So far, there are no data at all on the ability of t-PA or PAI-1 to predict long-term mortality. We here report the relation of t-PA, PAI-1, and traditional risk factors in relation to mortality in a 7-year follow-up study of 213 patients with severe angina pectoris and angiographically verified coronary artery disease. The results have been presented in abstract form.

Methods

Patients

This study is based on 248 consecutive patients admitted because of severe angina pectoris to the Department of Medicine, Umeå University Hospital, between September 15, 1983, and May 8, 1985. Coronary angiography was not performed in 15 patients, and in 20 patients no significant coronary artery disease (CAD) (defined as reduction of luminal area >50% in any of the great coronary arteries at selective coronary arteriography) could be found. These patients were excluded, and the remaining 213 patients, 178 men and 35 women, with severe angina pectoris and significant CAD were...
TABLE 1. Clinical Characteristics of the 180 Patients Who Survived and the 33 Who Died During the 7-Year Follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survived</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>151 (84%)</td>
<td>27 (82%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>57±7</td>
<td>59±7</td>
</tr>
<tr>
<td>Body mass index, kg·m⁻²</td>
<td>26.5±2.9</td>
<td>27.5±3.1</td>
</tr>
<tr>
<td>Tobacco smoking habits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>61 (33%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>80 (44%)</td>
<td>13 (39%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>39 (22%)</td>
<td>11 (33%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (7%)</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (19%)</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>144±18</td>
<td>144±24</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>88±10</td>
<td>88±13</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>26 (14%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>32 (18%)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>122 (68%)</td>
<td>26 (79%)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.59±0.10</td>
<td>0.48±0.15</td>
</tr>
<tr>
<td>Mean duration from angiography to bypass surgery, months</td>
<td>3.7±3.7</td>
<td>3.0±4.4</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>7.3±1.4</td>
<td>7.1±1.2</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>2.5±1.6</td>
<td>2.9±1.7</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.6±0.9</td>
<td>3.4±0.8</td>
</tr>
<tr>
<td>Tissue plasminogen activator, μg/L</td>
<td>9.3±3.9</td>
<td>10.9±3.5</td>
</tr>
</tbody>
</table>

Figures indicate the number of subjects (and %) or mean±SD as appropriate.

included in this study. The mean age (SD) was 56.9 (7.0) years (range, 37 to 77 years). Three-vessel disease was found in 70%, and 46% had a history of at least one myocardial infarction. Coronary bypass surgery was subsequently performed in 167 patients (78.4%), and the mean duration from angiography to surgery was 4.6±3.7 months. Of these, 4 died within 1 month of the operation. Coronary bypass surgery was not performed in 31 patients because these were considered to be too little disabled and there was no survival indication for surgery. In this group, 3 died during follow-up. In 14 patients, coronary bypass was considered to be too risky; these were subsequently not operated on (9 patients in this group died during follow-up). One patient died soon after angiography and thus did not have a coronary bypass. The clinical and laboratory characteristics of the patients, grouped according to outcome in terms of mortality, are shown in Table 1. The prevalence of drug treatment with β-blockers, calcium channel blockers, and nitrates was the same (Fisher exact test) in those who survived and those who died (79% versus 79%, 54% versus 45%, and 93% versus 88%, respectively).

Sampling

Before coronary arteriography, blood samples were obtained in the early morning after an overnight fast for preparation of citrated plasma, which was assayed for mass concentration of t-PA with an ELISA method and for PAI-1 activity with a chromogenic substrate assay. The reagents for these assays (Imulys t-PA and Spectrolyse/Fibrin, respectively) were purchased from Biopool, Umeå, Sweden. The details of these and other assays performed were given by Olofsson et al.

Follow-up Study Protocol

In March 1992, the patients’ records were searched for death occurring after the day of coronary angiography. Death certificates were obtained for all who had died. No patient was lost to follow-up.

Statistical Analysis

Statistical analyses were performed by use of the SAS program. To illustrate the relation between a possible prognostic factor and the incidence of mortality, baseline variables were divided into quartiles, and the incidence of cardiovascular events in each quartile (Q₁ through Q₄) was calculated per 1000 patient-months. These quartiles were not used to test relations: for this, a Cox regression analysis was performed. Two-tailed tests were performed, and a value of P≤.05 was regarded as statistically significant. Relative risk (RR) was calculated as incidence of events in Q₁ per incidence of events in Q₄. Expert statistical advice was given by Kjell Pennert, Gothenburg.

Results

The mean follow-up time was 7 years. During this follow-up period, 33 patients died (15%). The life table for the proportion of subjects remaining alive is shown in Fig 1. Four patients died of malignancies, one of pneumonia, and 28 of cardiovascular disease.

In univariate Cox analyses with death as the response variable, t-PA mass concentration and ejection fraction were related to death (Table 2). To check whether the same risk relations also held true in a shorter time span after angiography, we performed the Cox regressions with 4 years as the maximum follow-up time, when only 19 patients had died (Table 2). As seen, t-PA mass concentration, ejection fraction, and age were related to death even over this shorter time span.

The subgroup that was subjected to coronary bypass surgery showed a pattern at 7-year follow-up similar to the total patient group, except that body mass index was also associated with the outcome. In this subgroup, only t-PA mass concentration and sex were related to mortality at the 4-year follow-up. Thus, only t-PA mass concentration consistently showed associations with mortality, both at 4- and 7-year follow-up, both in the total patient group and in the subgroup that was treated with coronary bypass. The number of deaths in quartiles 1 through 4 of t-PA mass concentration is shown in Fig 2.

In multivariable Cox regression analyses, only t-PA mass concentration was significantly related to death at 7 years of follow-up when clinical and laboratory risk factors were entered as independent variables; continuous variables were age, body mass index, fibrinogen, cholesterol, and triglycerides, and discrete variables
were treatment for hypertension, sex, and smoking habits (never smoked, ex-smoker, current smoker).

The RR (incidence of events in Qj per incidence of events in Q\) for 7-year mortality in the total patient group was 3.85 with t-PA as the marker (Fig 2). The RR to die within 7 years for a person who had been subjected to coronary bypass surgery because of severe angina pectoris was 9.9 times if the t-PA mass concentration was \(>11.5\) \(\mu g/L\) (the lower limit of Q\) compared with those having a t-PA mass concentration \(\leq7.1\) \(\mu g/L\) (the upper limit of Q\); see Fig 2.

### Discussion

This study shows for the first time that the fibrinolytic system is a major determinant of the long-term risk of dying among patients with severe angina pectoris. The mortality increased progressively through the quartiles of t-PA mass concentration (Fig 2), but PAI-1 was unrelated in this study. Our findings are logical, considering that we have previously shown that a high t-PA mass concentration is predictive of the softer end points of myocardial infarction and stroke in this type of patient.\(^3\) The same predictive value of t-PA mass concentration was seen in the 78% of the subjects who were treated with coronary bypass surgery. These findings thus harmonize well with our previous study documenting the relation of t-PA mass concentration to cardiovascular events.\(^3\)

It is true that intuitively one would like to believe that higher levels of the "good" enzyme, t-PA, were related

### Table 2. Relation Between Risk Indicators and Mortality (Univariate Cox Regression Analysis)

<table>
<thead>
<tr>
<th>Variables</th>
<th>All 7-Year Mortality</th>
<th>Coronary Bypass 7-Year Mortality</th>
<th>All 4-Year Mortality</th>
<th>Coronary Bypass 4-Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>(&gt;.40)</td>
<td>(&gt;.40)</td>
<td>(&gt;.001)</td>
<td>(&gt;.40)</td>
</tr>
<tr>
<td>Age</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.034)</td>
<td>(&gt;.087)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>(&gt;.067)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Smoking</td>
<td>(&gt;.097)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Number of stenotic vessels (1 to 3)</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>(&gt;.016)</td>
<td>(&gt;.40)</td>
<td>(&gt;.016)</td>
<td>(&gt;.083)</td>
</tr>
</tbody>
</table>

\(P\) indicates value of regression coefficient and \(r\), regression coefficient.
Fig 2. Bar graphs showing incidence of mortality after 7 years of follow-up in relation to tissue plasminogen activator (t-PA) mass concentration in all subjects (A) and in the subgroup treated with coronary bypass (B). The incidence of deaths per 1000 patient-months is shown for the quartiles Q₁ through Q₄ of t-PA mass concentration.

to a reduced, not to an increased, risk; throughout the 1970s it was common to speak of “a deficiency of fibrinolytic activity” as one of the causes for early-onset thrombosis (see, for example, the review by Hedner and Nilsson). However, at that time it was not yet known that there is a complicated interplay between fibrinolytic activators and several plasma inhibitors (see Fig 3). When in 1983 we reported for the first time on t-PA mass concentration measurements (at that time called “t-PA antigen concentration” by us and others) in thrombotic patients who had reduced t-PA activity, we found that, paradoxically, the mass concentration of the t-PA enzyme was normal or increased in these subjects. About the same time, several groups actually identified a new plasma protein with specific t-PA-inhibitory effect, called PAI-1, which was later found to be identical with a t-PA inhibitor described earlier by cell biologists. This offered an explanation for the discrepancy between t-PA activity and mass concentration measurements described by us and the higher t-PA mass concentration that is found in subjects with high PAI-1 levels. There is therefore actually a negative correlation between t-PA mass concentration and t-PA activity in human plasma samples. As Folsom and colleagues wrote recently, “succinctly put, an increase in t-PA antigen [ie, t-PA mass concentration] reflects an inhibitory effect of PAI-1 on t-PA activity.” Fig 3 may be helpful in illustrating this circumstance. Although it is known that many lifestyle and endocrine/metabolic factors may affect the activity of the fibrinolytic system in the individual, it has proved to be quite difficult to manipulate this system by nonpharmacological methods or by drugs, although recent studies on, for instance, oral antidiabetics, cholestyramine, and doxazosin showed some encouraging results. In the subset of obese patients with the “metabolic syndrome” and hypofibrinolysis caused by high PAI-1 levels, jejunoileal bypass surgery was shown to have a PAI-1-lowering effect that persists for more than one decade after surgery. Therefore, it may be possible in the future to actually improve the t-PA and/or PAI-1 levels in patients with unfavorable levels of these factors.

To conclude, we found that the levels of factors of the endogenous fibrinolytic system can predict not only soft end points but also mortality. If this can be confirmed in other clinical studies, we will have an increased incentive to go a step further and test whether treatment modalities that manipulate the regulation of these factors can actually improve long-term mortality. These are important areas for future studies.

Note added in proof. After completion of this paper, two large-scale studies confirmed a predictive power of t-PA mass concentration on soft end points (reinfarction, occlusive events) in angina pectoris patients and in previously healthy persons.

Acknowledgments

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References

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Predictive value of tissue plasminogen activator mass concentration on long-term mortality in patients with coronary artery disease. A 7-year follow-up.

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