Plasma Levels of Tissue Plasminogen Activator/Plasminogen Activator Inhibitor-1 Complex and von Willebrand Factor Are Significant Risk Markers for Recurrent Myocardial Infarction in the Stockholm Heart Epidemiology Program (SHEEP) Study

Björn Wiman, Tomas Andersson, Johan Hallqvist, Christina Reuterwall, Anders Ahlbom, Ulf deFaire

Abstract—An impaired fibrinolytic function due to elevated plasma levels of plasminogen activator inhibitor (PAI)-1 activity or tissue plasminogen activator (tPA) antigen is correlated with the development of myocardial infarction (MI) in patients with manifest coronary heart disease. Recently, methods for determining the specific tPA/inhibitor complexes constituting tPA antigen in plasma have become available. In the Stockholm Heart Epidemiology Program (SHEEP) study, 86 of 1212 MI patients, subjected to blood sampling in a metabolically stable period, suffered reinfarction before the end of 1996. These individuals have been compared with an approximately equal number of matched MI patients without recurrence and a group of matched healthy control subjects regarding the plasma concentrations of some hemostatic factors. The hemostatic compounds studied (fibrinogen, von Willebrand factor, tPA antigen, PAI-1, and the tPA/PAI-1 complex) were typically higher in the groups (men and women) with recurrence of MI compared with those without. The plasma concentrations were also typically higher in the pooled groups of patients compared with the groups of healthy control subjects. The largest between-group differences were found for the plasma tPA/PAI-1 complex. The crude odds ratio for reinfarction associated with higher concentration ($75th$ percentile among the control subjects) of $tPA/PAI-1$ was 1.8 (95% CI 1.1 to 3.1); the corresponding crude odds ratio for von Willebrand factor was 2.3 (1.3 to 4.0). The $tPA/PAI-1$ complex correlated strongly with PAI-1 and tPA antigen in all groups and with serum triglycerides and body mass index in all groups except for women with reinfarction. An increased plasma level of $tPA/PAI-1$ complex is a novel risk marker for recurrent MI in men and women. Most likely, increased plasma levels of $tPA/PAI-1$ complex reflect impaired fibrinolysis, because the correlation with PAI-1 is strong. Further support is obtained indicating that the plasma concentration of von Willebrand factor is also an important risk marker for recurrent MI. (*Arterioscler Thromb Vasc Biol.* 2000;20:2019-2023.)

Key Words: fibrinolysis ■ hemostasis ■ myocardial infarction ■ risk markers

A decreased fibrinolytic activity, which is either due to an increased plasma concentration of plasminogen activator inhibitor (PAI)-1$^{1-4}$ or an impaired function to release tissue plasminogen activator (tPA) on exercise,$^5$ has been demonstrated to be connected to an increased risk of myocardial infarction in studies with prospective designs. The plasma concentration of tPA antigen, which typically correlates well with PAI-1 activity rather than with tPA activity, has turned out to be an even stronger predictor of myocardial infarction.$^3,5,6$ Only a minor portion of the tPA in plasma is functionally active. The major portion involves tPA in complex with various inhibitors, such as PAI-1, anti-plasmin, and C1 inhibitor. We have recently developed 2-site ELISA methods to specifically measure these complexes in plasma.$^7$

It was found that tPA antigen correlated strongly with the $tPA/PAI-1$ complex but not with complexes involving the other 2 inhibitors. For this reason, it is important to evaluate the predictive value of the plasma concentration of the $tPA/PAI-1$ complex with respect to the development of myocardial infarction.

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In Stockholm, a large population-based case-control study of risk factors for myocardial infarction (first episode), the Stockholm Heart Epidemiology Program (SHEEP) study, has recently been carried out.$^8$ Exposure information on a wide range of environmental, lifestyle, and biological risk factors was collected by questionnaires and health examinations,

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including blood sampling. In the present study, we report on laboratory findings from a subset of cases and referents in the SHEEP study regarding PAI-1, tPA antigen, and the tPA/PAI-1 complex in relation to reinfarction during a restricted follow-up period. The fibrinolytic parameters have been compared with some other hemostatic factors, such as fibrinogen and von Willebrand factor, and also with some lipoprotein variables, which previously have been found to be correlated with the development of myocardial infarction.

**Methods**

**Patients and Controls**

The SHEEP study design has been described in detail elsewhere. In short, the SHEEP study base was composed of all Swedish citizens residing in Stockholm county who previously had not been given the diagnosis of myocardial infarction. Male cases were identified during 2 years (1992 and 1993), and female cases were identified during 3 years (1992 through 1994). Through October 1992, the study base included individuals aged 45 to 65 years; from November 1, 1992, and onward, the age span was 45 to 70 years. Fatal as well as nonfatal cases were included. One referent per case was randomly selected from the study base, after stratification for sex, age, and hospital catchment area, at the case incidence. Altogether 2246 cases were included, of which 1485 were men and 761 were women. Approximately 26% of the male cases and ~29% of the female cases were fatal (deceased within the 28th day of disease onset). Cases were identified from 3 sources and were included at the time of disease incidence. The sources were (1) the coronary and intensive care units at the internal medicine departments at all the emergency hospitals within the Stockholm county area, (2) the hospital discharge register for the Stockholm county area, and (3) death certificates from the National Register of Cause of Death Statistics, Sweden. The criteria used for identification of myocardial infarction were those accepted by the Swedish Association of Cardiologists in 1991. Autopsy findings of myocardial necrosis of an age compatible with the time of disease onset. Informed consent was obtained from all participants. The study was approved by the regional ethics committee of the Karolinska Institute.

The 1267 cases (893 men and 374 women), who were subjected to a laboratory evaluation (before any reinfarction) ~3 months after the primary event, constituted the basis of the study. Until the end of 1996, 86 of these patients suffered a reinfarction and were included in the present study. In addition, 133 sex- and age-matched patients without a reinfarction and 261 sex- and age-matched control subjects were also included in the study.

**Blood Sampling**

Approximately 3 months after the primary event, when the patients were considered to be in a metabolically stable condition, they were subjected to blood sampling. After 10 minutes of rest in the supine position, the patients had blood drawn from an antecubital vein into evacuated tubes (containing sodium citrate [final concentration 0.129 mol/L], EDTA, or nothing for serum samples) with the use of minimal stasis. The citrated blood samples were centrifuged within 30 minutes, and plasma was immediately frozen in aliquots and stored at ~70°C until analysis.

**Analytical Procedures**

Determination of PAI-1 activity was performed continuously during the recruitment period with the use of the Spectrolyze PAI-1 kit (Biopool AB) on citrated plasma samples that typically had been stored at ~70°C for ~1 month. Determination of tPA antigen and tPA/PAI-1 complex were performed on stored citrated plasma samples (not previously thawed) by using kits from Biopool TintElize tPA and TintElize tPA/PAI-1 (both kits were a kind gift from Biopool AB, Umeå, Sweden; courtesy of Gunnar Pohl), respectively. The method for measuring the tPA/PAI-1 complex is based on a classic 2-site ELISA, with use of a polyclonal antibody toward tPA as a "catch antibody" and a horseradish peroxidase–conjugated monoclonal antibody toward PAI-1 for measuring purposes. Also, the complexes between tPA and antiplasmin or C1 inhibitor were analyzed by 2-site ELISA methods as described recently. von Willebrand factor antigen was measured by a commercially available ELISA method (Asserachrom vWF, Stago; provided by Triolab AB). Fibrinogen levels in plasma, blood glucose, serum cholesterol, and triglyceride concentrations, as well as HDL and LDL levels, were determined by conventional techniques in routine use at the different participating hospitals.

**Other Risk Factors**

Body mass index (BMI=weight/length²) and the waist/hip circumference (W/H) ratio were calculated from measurements obtained at the health examination. The W/H ratio was calculated as the circumference midway between the lower rib margin and the iliac crest divided by the circumference at the widest point between hip and buttock. Subjects fulfilling ≥1 of the following criteria were defined as hypertensives: treatment with, or a history of, regular treatment with antihypertensive drugs at inclusion, a systolic blood pressure ≥170 mm Hg, or a diastolic blood pressure ≥95 mm Hg. Individuals on treatment with insulin or other antidiabetic agents or on diet control at the time of inclusion in the study were defined as diabetics. Subjects who smoked at the time of inclusion or had stopped within the last 2 years were defined as smokers. Individuals who had stopped smoking ≥2 years before inclusion were classified as exsmokers.

**Statistical Methods**

Comparisons between groups were performed by Student t test. The relationship between combinations of the continuous variables was quantified by the Spearman rank-order correlation coefficient. The influence of the different risk indicators was evaluated from odds ratios calculated by logistic regression. SAS version 6.12 for Windows '95/NT (SAS Institute) was used for all epidemiological and statistical computations.

**Results**

**Basic Characteristics of the Study Groups**

Because many of the parameters differ between the sexes, we divided all the groups into men and women. A statistical comparison of the results in the different groups was made, but the data are not shown in detail. As can be seen from Table 1, the men were, on average, 5 years younger than the women. A higher BMI (statistically significant) was observed in the male infarction patients compared with control subjects. Also, reinfarction patients had a higher BMI than did patients with only 1 infarction. In contrast, no difference was found between the female groups. Small, but significantly increased, W/H ratios were observed in the reinfarction groups for men and women. Hypertension was more common in the male compared with the female reinfarction group. Smoking was more common in male patients compared with control subjects, especially for those patients with a reinfarction. However, regarding diabetes, this was much more common in female and in male patients compared with healthy control subjects. In the female reinfarction group, as many as 38% suffered from diabetes. Compared with the male groups, the female groups had higher HDL cholesterol levels, but female and male control subjects had higher levels compared with the patient groups, respectively. Slightly elevated LDL cholesterol levels were found among the male reinfarction patients and all female patients compared with the respective control groups. The triglyceride concentrations were elevated in all patient groups compared with the control groups. Basic characteristics of the SHEEP study group have recently been reported.
levels of the different hemostatic factors were dichotomized when calculating the odds ratio for recurrence, the plasma concentration of tPA/antiplasmin or tPA/C1 inhibitor complexes did not differ between any of the patient groups and the healthy control groups (data not shown).

Prediction of Reinfarction
When calculating the odds ratio for recurrence, the plasma concentrations of the tPA/PAI-1 complex than for tPA antigen when the different groups were compared. The plasma concentration of tPA/PAI-1 complex for the different subgroups. All 5 parameters were significantly higher in male patients (groups with or without recurrence combined) compared with healthy male controls. Except for PAI-1 activity, this was also true for the female groups but not between the male groups. The plasma fibrinogen levels were statistically different between any of the patient groups and the healthy control groups (data not shown). However, the differences were not statistically significant. In addition, significant correlations were observed with the W/H ratio, BMI, and serum triglycerides, but mainly in the groups of healthy control subjects or in patients with only 1 myocardial infarction. Only weak correlations were found between the tPA/PAI-1 complex and von Willebrand factor (plasma concentration over the 75th percentile) had a 3.2-fold higher risk of reinfarction. Patients who had increased tPA/PAI-1 complex and increased von Willebrand factor gave the highest crude odds ratio, 2.3 (95% CI 1.3 to 4.0), compared with the odds ratio for the tPA/PAI-1 complex, 1.8 (95% CI 1.1 to 3.1). For the other factors (tPA antigen, PAI-1, and fibrinogen), lower odds ratios were found. Adjustment for smoking and LDL cholesterol changed the odds ratios only slightly but caused the CI to overlap 1.0. Patients who had increased tPA/PAI-1 complex and increased von Willebrand factor (plasma concentration over the 75th percentile) had a 3.2-fold higher risk of reinfarction.

Plasma Levels of Fibrinogen, von Willebrand Factor Antigen, tPA Antigen, PAI-1 Activity, and tPA/PAI-1 Complex
Table 2 shows plasma concentrations of fibrinogen, von Willebrand factor, PAI-1 activity, tPA antigen, and tPA/PAI-1 complex for the different subgroups. All 5 parameters were significantly higher in male patients (groups with or without recurrence combined) compared with healthy male controls. Except for PAI-1 activity, this was also true for the women. Comparing the groups with and without recurrence, the plasma fibrinogen levels were statistically different between the female groups but not between the male groups. The PAI-1 activity concentrations differed neither among the male groups nor among the female groups. However, von Willebrand factor, tPA antigen, and tPA/PAI-1 complex were all significantly higher in the male reinfarction patients compared with patients without reinfarction. A tendency in the same direction was observed between the female groups, although the differences were not statistically significant. In all cases, the probability values (not shown) were lower for the plasma concentrations of the tPA/PAI-1 complex than for tPA antigen when the different groups were compared. The plasma concentration of tPA/antiplasmin or tPA/C1 inhibitor complexes did not differ between any of the patient groups and the healthy control groups (data not shown).

Prediction of Reinfarction
When calculating the odds ratio for recurrence, the plasma levels of the different hemostatic factors were dichotomized at the value corresponding to the 75th percentile among the control subjects. The cutoff values are shown in Table 3, together with the odds ratios. When calculated for the whole group of infarction patients (men and women together), von Willebrand factor gave the highest crude odds ratio, 2.3 (95% CI 1.3 to 4.0), compared with the odds ratio for the tPA/PAI-1 complex, 1.8 (95% CI 1.1 to 3.1). For the other factors (tPA antigen, PAI-1, and fibrinogen), lower odds ratios were found. Adjustment for smoking and LDL cholesterol changed the odds ratios only slightly but caused the CI to overlap 1.0. Patients who had increased tPA/PAI-1 complex and increased von Willebrand factor (plasma concentration over the 75th percentile) had a 3.2-fold higher risk of reinfarction.

Correlation Between tPA/PAI-1 Complex and tPA Antigen, PAI-1 Activity, and Other Factors
The correlation between the tPA/PAI-1 complex and other possible risk factors is demonstrated in Table 4. As can be seen, by use of the Spearman rank method, a good correlation with tPA antigen and PAI-1 was found in all groups. In addition, significant correlations were observed with the W/H ratio, BMI, and serum triglycerides, but mainly in the groups of healthy control subjects or in patients with only 1 myocardial infarction. Only weak correlations were found between the tPA/PAI-1 complex and von Willebrand factor in the patient groups.

Discussion
An impaired fibrinolytic function, as measured by elevated plasma PAI-1 or tPA antigen levels, has previously been
TABLE 2. Plasma Concentrations of Fibrinogen, vWF, PAI-1 Activity, tPA Antigen, and tPA/PAI-1 Complex in the Different Study Groups

<table>
<thead>
<tr>
<th>Component</th>
<th>Men Reinfarction (n=61)</th>
<th>No Reinfarction (n=95)</th>
<th>Healthy Controls (n=189)</th>
<th>Women Reinfarction (n=25)</th>
<th>No Reinfarction (n=38)</th>
<th>Healthy Controls (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.83±0.74</td>
<td>3.69±0.93</td>
<td>3.43±0.70</td>
<td>4.50±1.29</td>
<td>3.72±0.83</td>
<td>3.65±0.78</td>
</tr>
<tr>
<td>Median</td>
<td>3.80</td>
<td>3.50</td>
<td>3.30</td>
<td>3.95</td>
<td>3.60</td>
<td>3.50</td>
</tr>
<tr>
<td>vWF, IU/mL</td>
<td>1.69±0.77</td>
<td>1.44±0.52</td>
<td>1.34±0.54</td>
<td>1.66±0.43</td>
<td>1.57±0.72</td>
<td>1.36±0.48</td>
</tr>
<tr>
<td>Median</td>
<td>1.60</td>
<td>1.35</td>
<td>1.22</td>
<td>1.60</td>
<td>1.39</td>
<td>1.25</td>
</tr>
<tr>
<td>PAI-1, U/mL</td>
<td>22.1±17.5</td>
<td>18.2±16.5</td>
<td>15.7±11.7</td>
<td>15.4±13.6</td>
<td>17.8±12.4</td>
<td>15.4±11.0</td>
</tr>
<tr>
<td>Median</td>
<td>17.5</td>
<td>16.5</td>
<td>11.7</td>
<td>13.6</td>
<td>12.4</td>
<td>11.0</td>
</tr>
<tr>
<td>tPA antigen, µg/L</td>
<td>12.3±4.3</td>
<td>11.0±3.6</td>
<td>10.3±3.7</td>
<td>11.0±3.3</td>
<td>10.3±3.2</td>
<td>9.4±3.3</td>
</tr>
<tr>
<td>Median</td>
<td>12.9</td>
<td>11.3</td>
<td>10.0</td>
<td>10.7</td>
<td>9.7</td>
<td>8.8</td>
</tr>
<tr>
<td>tPA/PAI-1, µg/L</td>
<td>8.02±3.67</td>
<td>6.59±2.96</td>
<td>5.77±3.07</td>
<td>7.15±3.44</td>
<td>5.89±2.48</td>
<td>5.23±2.85</td>
</tr>
<tr>
<td>Median</td>
<td>7.30</td>
<td>6.25</td>
<td>5.60</td>
<td>6.40</td>
<td>5.45</td>
<td>4.85</td>
</tr>
</tbody>
</table>

Values are mean±SD and median for all compounds studied. vWF indicates von Willebrand factor.

found to be correlated with the development of myocardial infarction.1–6,9 In the present study, we have investigated the plasma concentration of a specifically determined tPA/PAI-1 complex in a nested case-control study based on patients and control subjects drawn from the SHEEP study. The data obtained showed that the plasma concentrations of the hemostatic factors studied (fibrinogen, von Willebrand factor, PAI-1, tPA antigen, and the tPA/PAI-1 complex) were higher in the patients with myocardial infarction than in the healthy control subjects. In most cases, the concentrations measured were higher for individuals with recurrence of MI than for the patients without recurrence. However, it is clear that the plasma concentration of the tPA/PAI-1 complex (Table 2) has the edge over PAI-1 and tPA antigen regarding differences between patients and healthy subjects and also regarding differences between patients with reinfarction compared with those without. This is true for the groups of men and for the groups of women. The tPA/PAI-1 complex typically constitutes ≈60% of the tPA antigen in plasma, whereas the remaining 40% mainly consists of tPA/antiplasmin and tPA/C1 inhibitor complexes, respectively. These latter compounds did not differ between any of the studied groups (data not shown) and are therefore not diagnostically important, at least not in connection with myocardial infarction. From the data demonstrated in Table 2, it is also evident that the interindividual variation is somewhat larger for the tPA/PAI-1 complex compared with tPA antigen, most likely because of a lesser variation in the plasma concentrations of tPA/antiplasmin and tPA/C1 inhibitor complexes. The intra-individual concentration regarding the tPA/PAI-1 complex has not yet been studied. This is of course important, especially if the plasma concentration of tPA/PAI-1 complex eventually can be of practical use for evaluation of the risk of myocardial infarction in individual patients.

The tPA/PAI-1 complex in plasma correlates strongly with PAI-1 activity and with tPA antigen. Thus, it is quite evident that increased plasma tPA/PAI-1 levels reflect a decreased fibrinolytic activity, but further data are needed to exactly pinpoint the mechanisms responsible for having increased plasma levels of this complex. The tPA/PAI-1 complex is also correlated with serum triglyceride levels, W/H ratio, and BMI, in a manner similar to that for PAI-1,10–15 suggesting a connection with the insulin resistance syndrome. Further work is also needed to correctly understand the exact mechanisms behind this connection. In the present study, too few individuals are included to allow separation into subgroups.

TABLE 3. Odds Ratios of Hemostatic Compounds Analyzed Regarding Risk of Reinfarction

<table>
<thead>
<tr>
<th>Component</th>
<th>Men Crude</th>
<th>Women Crude</th>
<th>All Crude</th>
<th>Adjusted Men</th>
<th>Adjusted Women</th>
<th>Adjusted All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, 4 g/L</td>
<td>1.23 (0.64–2.60)</td>
<td>1.74 (0.57–5.26)</td>
<td>1.41 (0.78–2.54)</td>
<td>1.40 (0.67–2.95)</td>
<td>2.16 (0.65–7.19)</td>
<td>1.68 (0.90–3.12)</td>
</tr>
<tr>
<td>vWF, 1.5 IU/mL</td>
<td>2.09 (1.09–4.04)</td>
<td>2.91 (1.05–8.10)</td>
<td>2.32 (1.33–4.02)</td>
<td>2.14 (1.07–4.28)</td>
<td>4.41 (1.33–14.7)</td>
<td>2.41 (1.35–4.30)</td>
</tr>
<tr>
<td>PAI-1, 20 U/mL</td>
<td>1.74 (0.91–3.33)</td>
<td>0.67 (0.23–2.00)</td>
<td>1.33 (0.77–2.31)</td>
<td>1.64 (0.81–3.30)</td>
<td>0.61 (0.19–1.99)</td>
<td>1.27 (0.70–2.29)</td>
</tr>
<tr>
<td>tPA antigen, 12 µg/L</td>
<td>1.83 (0.95–3.52)</td>
<td>1.32 (0.48–3.66)</td>
<td>1.64 (0.95–2.84)</td>
<td>1.56 (0.78–3.12)</td>
<td>1.37 (0.42–4.42)</td>
<td>1.52 (0.85–2.73)</td>
</tr>
<tr>
<td>tPA/PAI-1, 7 µg/L</td>
<td>1.71 (0.89–3.29)</td>
<td>2.24 (0.79–6.39)</td>
<td>1.81 (1.05–3.14)</td>
<td>1.49 (0.75–2.96)</td>
<td>2.55 (0.81–8.01)</td>
<td>1.73 (0.97–3.08)</td>
</tr>
</tbody>
</table>

The cutoff levels used were the concentrations at the 75th percentile of the various compounds. Within parentheses, the 95% CI is indicated. Values are calculated as crude and as adjusted for smoking and LDL cholesterol.
However, the tPA/PAI-1 complex is presently being investigated in all individuals included in the SHEEP study who have been subjected to blood sampling. It is hoped that we will then be able to investigate these relations and get closer to an understanding of the connection between plasma concentrations of the tPA/PAI-1 complex and insulin resistance syndrome. Nevertheless, the concentration of the tPA/PAI-1 complex in plasma seems to be a good biochemical marker predicting recurrent myocardial infarction. It would be very important to analyze this factor in a prospective study of healthy individuals eventually suffering myocardial infarction.

In addition, and in agreement with previously published data,16,17 the plasma concentration of von Willebrand factor seems to be a very good predictor of recurrence in the present study. In fact, von Willebrand factor seems to be much better in this respect than the plasma fibrinogen concentration. This is quite interesting, but the mechanisms or reasons for this is at present not known. A procoagulant activity, a reflection of endothelial cell damage, a part of an acute phase reaction, or any combinations of these phenomena might be involved. Further studies are needed to correctly evaluate and understand this finding.

Because the plasma concentrations of tPA/PAI-1 complex and von Willebrand factor are quite poorly correlated with each other (Table 4), especially in the groups of patients, the possibility of combining the 2 compounds is presented. In the present study, we found that myocardial infarction patients with an elevation of these 2 markers combined have a >3-fold increased risk of recurrence within a few years of the primary event.

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