Plasma Plasminogen Activator Inhibitor-1 in Angina Pectoris

Influence of Plasma Insulin and Acute-phase Response

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Plasminogen activator inhibitor-1 (PAI-1) is an important physiological inhibitor of fibrinolysis. It circulates in blood both in free active form and in inactive form complexed with tissue type plasminogen activator (t-PA). Control mechanisms for its synthesis and release from hepatocytes and endothelial cells are important in the pathogenesis of thrombosis. Possible risk factors for myocardial infarction include high insulin and PAI-1 levels, which correlate with one another in healthy subjects, and fibrinogen, which together with PAI-1, is an acute-phase reactant. We therefore studied the interrelationships between PAI-1, plasma insulin, and acute-phase proteins in 67 patients with angina pectoris. Plasma insulin correlated strongly \((r=0.59, \ p<0.001)\) with PAI activity, free PAI-1 antigen \((r=0.80, \ p<0.001)\), and total PAI-1 antigen \((r=0.58, \ p<0.001)\). The acute-phase proteins, fibrinogen and C-reactive protein, correlated significantly with t-PA antigen, total PAI-1 antigen, and PAI-1/t-PA complexes but not with PAI activity or free PAI-1. The results suggest that insulin stimulates synthesis and release of free PAI-1 (probably via hepatocytes as previously shown with cell cultures) and that endothelial cell synthesis and release of t-PA, together with PAI-1, reflects a nonspecific acute-phase response to chronic vascular disease. Hyperinsulinemia found in patients with angina pectoris could play a role in the development of myocardial infarction via the induction of high plasma PAI-1 activity.

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Impaired fibrinolysis may contribute to the development of coronary artery disease and myocardial infarction.\(^1,2\) The fibrinolytic activity of blood depends on the balance between the circulating level of tissue-type plasminogen activator (t-PA), which is secreted by endothelial cells, and plasminogen activator inhibitor-1 (PAI-1)\(^3\), which is secreted by endothelial cells and hepatocytes and is also released by platelets.\(^4\) Patients with coronary artery disease, either before or after myocardial infarction, have an increased plasma level of PAI activity\(^5,9\) which may predispose to infarction.\(^9,10\)

Plasma PAI activity is significantly correlated with the plasma concentration of insulin and with body mass index (BMI).\(^11,12\) Plasma insulin concentration is increased in coronary atherosclerosis and in myocardial infarction\(^13,14\) and constitutes a risk factor for fatal coronary events.\(^15-18\)

An increase in plasma fibrinogen, an acute-phase reactant, is also a risk factor for the development of cardiovascular disease.\(^19,20\) PAI-1 may also be an acute-phase protein.\(^21,22,23\)

We therefore investigated the relationships between PAI-1, plasma insulin, fibrinogen, and other acute-phase reactants in 67 patients with angina pectoris to understand the mechanisms that regulate PAI-1 production in patients at risk for myocardial infarction.

Methods

Patients

Sixty-seven consecutive patients undergoing coronary angiography (51 men, mean age [SD] 61 [6], range 43 to 77) were studied: 22 had angina on exertion, 17 had angina at rest, four had mixed angina, and 24, unstable angina. Electrocardiographic (ECG) changes at rest were noted in 40 patients (ST segment depression of at least 1 mm or T wave inversion). Seven patients had ECG changes during painful episodes only. The other 20 had a normal ECG at rest. Of 44 patients, 31 had an abnormal exercise ECG. Previous myocardial infarction (more than 3 months before blood sampling) had occurred in 13 men and two women, and three patients had previous deep venous thrombosis. Patients received Ca\(^2+\)-antagonists (40 patients), \(\beta\)-blocking agents (22 patients), nitrates (18 patients), heparin (18 patients), oral anticoagulants (three patients), or platelet aggregation inhibitors (13 patients).

Body mass index (BMI) defined as body weight (kg) divided by the square of height (m), was \((mean\pm SD): \) for men, \(25\pm 2.7,\) range 22 to 28 (normal value, 23); and for women, \(24\pm 3.6,\) range 21 to 28 (normal value, 21). The prevalence of risk factors is reported in Table 1.

Coronary angiograms were performed with the femoral or brachial approach. The severity of coronary disease...
Table 1. Prevalence of Coronary Risk Factors

| Risk factors         | Men (n=51) | Women (n=16) |
|----------------------|------------|--------------|
| Hypertension*        | 18         | 3            |
| (S>140 mm Hg, D>90 mm Hg) |            |              |
| Hypertriglyceridemia | 21         | 5            |
| Men>1.75 mmol/l, women>1.5 mmol/l | |              |
| Hypercholesterolemia | 2          | 2            |
| >7 mmol/l            |            |              |
| Combined hyperlipidemia | 9        | 4            |
| Type II diabetes†    | 12         | 1            |
| Obesity†             | 18         | 5            |
| BMI: Men>27, women>25|            |              |

Smoking habits
- Current smoker        | 25         | 5            |
- Ex-smoker             | 8          |              |
- Non-smoker            | 20         | 11           |
- Familial history of CAD | 25        | 7            |

*WHO criteria, †National Diabetes Study Group criteria (Diabetes 1979;29:1037–1057).
S=systolic blood pressure, D=diastolic blood pressure, BMI=body mass index, CAD=coronary artery disease.

was assessed by three coding systems: 1) the number of major vessels narrowed by at least 50% (mean 1.1, range 0 to 2); 2) the extent score for coronary atherosclerosis (mean 3.0, range 0 to 6); and 3) the severity score for number and extent of stenoses (mean 6.2, range 0 to 11).

Procedures
Blood was collected from resting patients, who gave their informed consent to the study, between 8:00 and 9:00 A.M. after a 12-hour fast on the day before the coronary angiogram. Smoking was prohibited for 24 hours before blood sampling. Blood samples from an antecubital vein were obtained in accordance with institutional guidelines before (without stasis) and at the end of a 10-minute venous occlusion. The venous occlusion test was carried out by using a sphymomanometer at the midpoint between systolic and diastolic blood pressures. Blood was collected into trisodium citrate (final concentration 0.111 M) and was immediately cooled on ice. Platelet-poor plasma was obtained by centrifugation, within 30 minutes after collection, at 4°C for 15 minutes at 2500 g. PAI-1 antigen assays were performed on blood collected on an antiplatelet/anticoagulant mixture (Thrombotact, Abbott Laboratories, Chicago, IL) from which platelet-poor plasma was obtained by centrifugation at 2500 g for 45 minutes at 4°C. The plasma was shell-frozen at -70°C and was stored in aliquots until used.

Fibrinolytic activity was measured with the euglobulin clot lysis time (ECLT); the euglobulin precipitate was made according to the method of Kluit et al.[27] t-PA Ag was determined by a solid-phase double-antibody immunnoassay (Biopool AB, Umea, Sweden), which measures free t-PA as well as t-PA-inhibitor complexes.[28] PAI activity was evaluated according to the method of Verheijen et al.[29] four concentrations of t-PA were added to a fivefold diluted plasma, and residual t-PA activity was measured with a chromogenic substrate (S2251, Kabi Vitrum, Stockholm, Sweden). The results for PAI activity were expressed in arbitrary units, one unit corresponding to the amount that inhibited one international unit of t-PA as calibrated with the first International Reference Preparation for t-PA (50/517, National Institute for Biological Standards and Control, London, UK). This assay is not specific for PAI-1 activity. PAI-1 antigen levels were determined by using two-enzyme-linked immunosorbent assay (ELISA) assays based on monoclonal antibodies.[30] One detected free PAI-1, whereas the other assay measured total PAI-1 antigen, consisting of free PAI-1 as well as PAI-1 complexed with t-PA. PAI-1/t-PA complexes were evaluated by an ELISA assay by using monoclonal antibodies directed against PAI-1 and t-PA. oPA Antiplasmin and plasminogen were measured by using chromogenic substrate (S2251) assays (Kabi Vitrum, Stockholm, Sweden). Fibrinogen assays were performed according to the method of Claus.[31] C-reactive protein (CRP) antigen was evaluated with a nephelometric method (Behringwerke AG, Marburg, FRG) on citrated plasma. Von Willebrand factor antigen (vWF antigen) was quantified by electrophoresis (Behringwerke AG, Marburg, FRG). Plasma insulin was measured on citrated plasma with a radioimmunoassay (Sorin Biomedica, Soluggia, Italy). Serum triglyceride was measured by the method of Buco and David[32] and cholesterol, by the method of Seldet.[33] White blood cell (WBC) count was performed by using a Technicon H 6000 from blood collected on EDTA.

Statistical Analysis
Goodness-of-fit $\chi^2$ was used to test deviations from a normal distribution, and logarithmic transformation was performed on the individual data before statistical computations and significance testing. When logarithmic transformation was necessary, the calculation of the mean was first performed on the logarithmic values, and then the antilog was calculated. In the cases of variables not normally distributed even after logarithmic transformation, the median was used, and a nonparametric (Mann-Whitney U) test was performed. In all cases, the range distribution was described in the 15th through 85th percentiles. Group differences were determined by two-tailed t test for normally distributed variables.
A correlation matrix was used to assess the relationship between parameters. When data were not normally distributed even after log transformation, the Spearman rank correlation coefficient was used.
To evaluate the independent relationships of studied variables, partial correlation coefficients were calculated.

Results
The data from patients with or without previous myocardial infarction are summarized in Table 2. PAI activity, free PAI-1 antigen, insulin, serum triglycerides, and angiographic severity score were significantly higher in patients with previous myocardial infarction.
The following tests showed no significant differences between patients with or without previous infarction: the mean or median (range) values for both groups combined
were: fibrinogen 3.3 (2.3 to 4.2) g/l, CRP 1.5 (1 to 10) 10⁻³ g/l, vWF antigen 1.64 (0.99 to 2.75) U/ml, WBC 6.5 (5 to 7.9) 10⁹/l, α² antiplasmin 90% (75% to 106%), and plasminogen 123.9% (99% to 148%).

The correlation matrix between fibrinolytic parameters revealed that PAI activity correlated significantly with free (r=0.68, p<0.001) and total (r=0.71, p<0.001) PAI-1 antigen, indicating that the PAI activity assay mainly reflects PAI-1. The ECLT both before and after venous occlusion was significantly correlated with plasma PAI activity (r=0.52 and 0.55, p<0.001); free PAI-1 antigen (r=0.53 and 0.56, p<0.001); and with total PAI-1 antigen (r=0.60 and 0.63, p<0.001), indicating that PAI-1 is an important determinant of fibrinolytic activity in the globulin fraction before and after stimulation of the release of PAI.

Before venous occlusion, t-PA antigen strongly correlated with total PAI-1 antigen (r=0.75, p<0.001). This is not surprising because assays for t-PA antigen and total PAI-1 antigen recognize PAI-1/PA complexes. The correlation of PAI-1/PA antigen with total PAI-1 antigen was 0.59 (p<0.001), and with t-PA antigen, 0.87 (p<0.001).

Total PAI-1 antigen, t-PA antigen, and PAI-1/PA antigen were significantly correlated with the acute phase markers: fibrinogen (r=0.27, p<0.05; r=0.44, p<0.001; and r=0.45, p<0.001, respectively), CRP (r=0.29, p<0.05; r=0.48, p<0.001; and r=0.48, p<0.001); and vWF (r=0.30, p<0.05; r=0.38, p<0.01; and r=0.35, p<0.01). No correlation was found between PAI activity or free PAI-1 antigen and acute-phase markers, suggesting that it is the PAI-1/PA complex that is influenced by the inflammatory response.

Plasma insulin was significantly correlated with triglyceride (r=0.44, p<0.001); BMI (r=0.31, p<0.05); age (r=0.33, p<0.01); systolic blood pressure (r=0.32, p<0.01); and angiographic severity score (r=0.31, p<0.05).

The correlations between fibrinolytic parameters, risk factors of atherosclerosis, and markers of inflammation are summarized in Table 3. A strong correlation (r=0.59) was observed between insulin and PAI activity (r=0.59) (Figure 1) and between insulin and free (r=0.60) or total (r=0.58) PAI-1 antigen. Insulin levels were also significantly correlated with ECLT (r=0.49, p<0.001), t-PA antigen (r=0.48, p<0.001), and PAI-1/PA antigen (r=0.51, p<0.001). Insulin was weakly correlated with fibrinogen (r=0.27, p<0.05); CR protein (r=0.28, p<0.05); and plasminogen (r=0.26, p<0.05).

Partial correlation analysis showed that, when adjusted for the effect of insulin, t-PA antigen and PAI-1/PA antigen were significantly correlated with inflammatory markers (fibrinogen, CRP, plasminogen, and vWF antigen). Thus, PAI-1/PA complexes were independently correlated with insulin and inflammatory proteins, whereas free active PAI was significantly correlated only with insulin.

As expected,11–15 the triglyceride level significantly correlated with PAI activity, free and total PAI-1 antigen, t-PA antigen, PAI-1/PA complexes, and BMI, as previously shown.11,12 was also significantly correlated with PAI activity. Systolic blood pressure correlated with PAI activity. No relationship between age or coronary score and fibrinolytic parameters or inflammatory markers was observed.

Partial correlation analysis showed that, independently of other risk factors of atherosclerosis, insulin was significantly correlated (r>0.50) with PAI activity, free PAI-1 antigen, and total PAI-1 antigen. Triglyceride level, BMI, and systolic blood pressure were no longer correlated with the three PAI-1 assays after adjustment for insulin.

Discussion

The present study revealed a significant correlation between insulin and PAI-1 in patients with angina pectoris.
and extends previous data obtained from other patient groups. It now appears that an increased level of insulin, independent of triglyceride level or BMI, is linked with increased free PAI-1 (increased levels of PAI activity and free PAI-1 antigen assay) and with increased PAI-1/ t-PA complexes (increased levels of total PAI-1 antigen, increased t-PA antigen, and increased PAI-1/t-PA antigen).

The highly significant correlation \( r = 0.60, p < 0.001 \) between plasma insulin and PAI-1 suggests a direct effect of insulin on the synthesis of PAI-1, the secretion of PAI-1, or both. Because insulin increases in a dose-dependent manner the synthesis of PAI-1 by hepatocytes (but not by cultured umbilical vein endothelial cells), it is probable that hyperinsulinemia increases the liver synthesis of PAI-1. The correlation between insulinemia and PAI-1 on the one hand, and between insulinemia and triglyceride and BMI on the other, explains the observed correlation between PAI-1 and triglycerides and between PAI-1 and BMI.

A high PAI-1 may increase the risk of coronary artery thrombosis. Reduction of the plasma insulin level by biguanide or by fasting results in a decrease in PAI activity. Attempts to reduce plasma insulin (by antidiabetic drugs, diet, or exercise) in order to normalize PAI-1 and fibrinolytic activity could be effective in preventing acute myocardial infarction; however, this would have to be proved by a prospective study.

Recent epidemiological studies have shown that the plasma fibrinogen level is also a risk factor for the development of cardiovascular disease. Therefore, we studied the relationship between fibrinogen and fibrinolytic parameters. Fibrinogen correlated independently of insulin with the level of PAI-1 complex but not with free PAI-1. We assume that an acute-phase increase in plasma fibrinogen concentration is associated with increased production of t-PA, and perhaps of PAI-1 by endothelial cells, causing an increase in circulating PAI-1/t-PA complexes. Plasma fibrinogen correlated with other acute-phase proteins, including CRP \( r = 0.72, p < 0.001 \); plasminogen \( r = 0.58, p < 0.001 \); and vWF \( r = 0.27, p < 0.05 \). It is likely that all these proteins increased as a nonspecific acute-phase response to atherosclerosis.

The mediators of this response, possibly including interleukin 1, presumably caused an increase in the hepatic synthesis of fibrinogen, CRP, and plasminogen and an increase in endothelial cell production of vWF, t-PA, and PAI-1. The latter responses would result in the formation of inactive complexes of PAI-1/t-PA.

We conclude that the plasma concentration of PAI-1 is regulated by at least two processes—insulinemia and acute-phase protein response—the latter giving rise to inactive complexes of PAI-1/t-PA. By increasing the hepatic synthesis of free PAI-1, hyperinsulinemia would increase the tendency to thrombosis. Thus, hyperinsulinemia found in patients with angina pectoris could play a pathogenic role in the development of myocardial infarction via the induction of a high plasma PAI-1 level, and normalization of plasma insulin could have a preventive effect.
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