Relationship of Plasmin Generation to Cardiovascular Disease Risk Factors in Elderly Men and Women

Pamela A. Sakkinen, Mary Cushman, Bruce M. Psaty, Beatriz Rodriguez, Robin Boineau, Lewis H. Kuller, Russell P. Tracy

Abstract—Plasmin–α2-antiplasmin complex (PAP) marks plasmin generation and fibrinolytic balance. We recently observed that elevated levels of PAP predict acute myocardial infarction in the elderly, yet little is known about the correlates of PAP. We measured PAP in 800 elderly subjects who were free of clinical cardiovascular disease in 2 cohort studies: the Cardiovascular Health Study and the Honolulu Heart Program. Median PAP levels did not differ between the Cardiovascular Health Study (6.05±1.46 nmol/L) and the Honolulu Heart Program (6.11±1.44 nmol/L), and correlates of PAP were similar in both cohorts. In CHS, PAP levels increased with age (r=0.30), procoagulant factors (eg, factor VIIc, r=0.15), thrombin activity (prothrombin fragment F1+2, r=0.29), and inflammation-sensitive proteins (eg, fibrinogen, r=0.44; factor VIIIc, r=0.37). PAP was associated with increased atherosclerosis as measured by the ankle-arm index (AAI) (P for trend, ≤0.001). PAP was negatively related to factors associated with the insulin resistance syndrome (IRS) (eg, fasting insulin, r=−0.26; body mass index, r=−0.26), possibly reflecting an association with plasminogen activator inhibitor-1 (r=−0.29). Although our study did not have sufficient power to detect a significant interaction, PAP and AAI appeared to be more weakly associated in subjects with more manifestations of the IRS: PAP appeared more strongly associated with AAI in the subgroup with 0 or 1 metabolic disorders (P≤0.001; slope estimate, −0.14) compared with the subgroup with 2 or more metabolic disorders (P=0.10; slope estimate, −0.08) and in those with non–insulin-dependent diabetes mellitus (P=0.46; slope estimate, −0.04). Although PAP reflects reactive fibrinolysis and is associated with subclinical atherosclerosis, this relationship may be weaker in populations with characteristics of the IRS, possibly reflecting the inhibitory effects of plasminogen activator inhibitor-1 on PAP. Decreased fibrinolysis in the presence of subclinical disease in subjects with hyperinsulinemia or glucose intolerance is consistent with the premise that depressed plasmin generation may enhance the progression of atherosclerosis in these people. (Arterioscler Thromb Vasc Biol. 1999;19:499-504.)

Key Words: blood coagulation ■ fibrinolysis ■ myocardial infarction ■ elderly ■ diabetes

Markers of both increased and decreased fibrinolytic activity1-3 have been associated with an increased risk of cardiovascular disease (CVD). Plasminogen activator inhibitor-1 (PAI-1), the major negative regulator of fibrinolysis, is a risk factor for recurrent myocardial infarction (MI)4 and may mediate the increased CVD risk associated with the insulin resistance syndrome (IRS).5 Paradoxically, we and others have shown that higher levels of D-dimer, a product of increased fibrinolysis, predict incident CVD in middle-aged men6 and elderly populations.7 It is therefore important to gain precise knowledge about the process of fibrinolysis with respect to CVD risk.

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Plasmin is the enzyme responsible for fibrinolysis.8 Its production is accelerated by the presence of fibrin and inhibited by PAI-1. Free plasmin is rapidly inhibited by α2-antiplasmin, and the resulting plasmin–α2-antiplasmin complex (PAP) marks plasmin generation, and thus, fibrinolysis. Elevated levels of PAP are associated with the incidence of acute MI in the elderly,9 but to our knowledge, there are no data on the correlates of PAP in the general population. Because ≈80% of fatal MIs occur in older persons,10 studies of the elderly are needed. The Cardiovascular Health Study (CHS) is a cohort study of community-dwelling persons over the age of 65 years.11 Similarly, the Honolulu Heart Project (HHP), in its current form, is a longitudinal population-based study of elderly Japanese-American men.12 We measured PAP levels in subgroups of the CHS (n=400) and the HHP (n=400) who were free of clinical CVD to limit the influence of clinical disease on measurements. We report on the cross-sectional correlates of this fibrinolysis marker inhibited by PAI-1.

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From the Departments of Pathology (P.A.S., M.C., R.P.T.), Biochemistry (P.A.S., R.P.T.), and Medicine (M.C.), University of Vermont, Colchester; the Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle (B.M.P.); the Department of Medicine, University of Hawaii at Manoa (B.R.); the Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md (R.B.); and the Department of Epidemiology, University of Pittsburgh, Pa (L.H.K.).
Correspondence and reprint requests to Russell P. Tracy, PhD, University of Vermont, Aquatec Bldg, T205, 55A South Park Dr, Colchester, VT 05446. E-mail rtracy@salus.uvm.edu
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with respect to traditional and novel CVD risk factors, such as inflammation, and measures of subclinical disease.

**Methods**

**Population**

The definitions of disease and risk factors in the HHP are identical to those in the CHS unless otherwise noted. The CHS cohort included 5201 men and women ≥65 years. Baseline examinations were performed over 1 year beginning in May 1989. These included a medical history, physical examination, and phlebotomy. Subjects were classified at baseline according to the presence or absence of previous clinical CVD. Carotid ultrasound, echocardiogram measurements, blood pressure including the ankle-arm index (AAI), and 12-lead resting ECG were performed to assess subclinical atherosclerosis.

The original HHP cohort was enrolled from 1965 to 1968 and included 8006 Japanese-American men between the ages of 45 and 68 years living on the island of Oahu, Hawaii. A total of 3741 men aged 71 to 93 years old participated in the fourth examination (1991 to 1993), which included a medical history questionnaire, physical examination, blood collection, and classification of clinical CVD status.

A subset of 400 individuals free of baseline clinical CVD was selected from each cohort. The CHS group was evenly divided by sex and among 5 age strata: 65 to 69, 70 to 74, 75 to 79, 80 to 84, and 85+ years. The subset of the HHP cohort included men divided evenly among 4 age strata: 71 to 74, 75 to 79, 80 to 84, and 85+ years.

Blood collection and assay work were completed using the same methods for both studies. Blood specimens from both cohorts were analyzed at the Laboratory for Clinical Biochemistry Research at the University of Vermont, Colchester. All participants gave informed consent, and all work was done under institutionally approved protocols.

**Definitions**

Baseline CVD included MI, angina or use of nitroglycerin, coronary angioplasty, coronary artery bypass surgery, stroke, transient ischemic attack, carotid endarterectomy, intermittent claudication, or a history of peripheral arterial angioplasty or bypass surgery. Hypertension was defined as seated systolic blood pressure ≥160 mm Hg, diastolic pressure ≥95 mm Hg, or self-reported high blood pressure and use of antihypertensive medication. Obesity was defined as weight >130% of ideal body mass by using the body mass index (BMI; weight [kg] / height [m²]). Abnormal glucose tolerance was defined as “impaired” (fasting glucose <140 mg/dL and a 2-hour postchallenge value between 140 and 199 mg/dL) or “diabetes” (fasting glucose >140 mg/dL, glucose >200 mg/dL 2 hours after a glucose load, or use of insulin or oral hypoglycemic agents, based on World Health Organization criteria; use of American Diabetes Association criteria was not in place at the time of data analysis for this project). Dyslipidemia was defined as either a low HDL cholesterol (HDL-C) level (<35 mg/dL for men, <45 mg/dL for women) or a high triglyceride level (>200 mg/dL).

The term “insulin resistance syndrome” (IRS) has been used to describe the clustering of metabolic disorders associated with later onset of non–insulin-dependent diabetes mellitus (NIDDM). In the CHS subgroup, we adopted recently proposed criteria for estimating the metabolic clustering associated with the IRS by summing the number of the following disorders for each subject: dyslipidemia, hypertension, and glucose intolerance. We also included obesity as a metabolic disorder. The stepwise increase in the number of disorders has been proposed to indicate decreasing insulin sensitivity. Diabetics were analyzed separately as the “worst case” of IRS.

Subclinical carotid atherosclerosis in the CHS was described using the maximum percent diameter stenosis in the left or right internal carotid artery or the mean of multiple measurements of minimal intima-media thickness of the common and internal carotid arteries. Data on subclinical atherosclerosis of the carotid arteries were not obtained in the HHP cohort.

**Blood Collection and Analysis**

The CHS blood collection and analysis methods have been reported. Blood was collected in a fasting state, and a special tube designed to prevent in vitro clotting activation was used for most immunoassays. This tube (SCAT-1, Hematologic Technologies, Inc) contained, in whole blood, 4.5 mmol/L EDTA, 0.15 KIU/L aprotinin, and 20 mol/L β-Phe-Pro-Arg-chloromethylketone. Citrated plasma was used for functional assays. Fasting HHP blood samples were collected using identical methods; however, many of the specialized coagulation and inflammation assays described below were available only on CHS samples.

The fibrin fragment D-dimer was measured by ELISA as developed by Collen De Clerck and colleagues, who kindly provided reagents for this and all other fibrinolytic immunoassays. The coefficient of variation (CV) was 7.0%. PAP was measured by ELISA. The CV was 3%. Plasminogen was measured by rate chromogenic assay, with a CV of 3.6%. PAI-1 antigen was measured by ELISA with a CV of 8.4%, and tissue plasminogen activator/PAI complex was measured with ELISAs; with CVs of 7.0% and 14.3%, respectively. C-reactive protein (CRP) was measured by ELISA (antibodies and antigens from Calbiochem) with a CV of 8.9%. Apolipoprotein(a) was measured by ELISA (reagents provided as a gift from Dr Wai-Li Wong, Genentech, Inc, South San Francisco, Calif), with a CV of 7.5%. Factor IXc and factor Xc were measured in plasma by using 1-stage clot-rate assays and the Diagnostica Stago ST4 instrument according to the manufacturer’s recommendations, with CVs of 5.8% and 4.7%, respectively. Fibrinogen and factors VIIc and VIIIc were measured using citrated plasma; lipid and general blood chemistry levels were measured using 4.5 mmol/L EDTA-plasma or serum, respectively, as described. The enzymatic lipid methods for total cholesterol, HDL-C, and triglycerides were performed under certification from the Centers for Disease Control and Prevention, Atlanta, Ga.

**Statistical Analysis**

Identical strategies were used to analyze the 2 data sets. PAP was skewed toward the right, and thus, these values were natural log transformed for most analyses. In the CHS, 4 warfarin users and 1 person with a missing PAP level were excluded (n = 395). Because the HHP data set consisted only of men ≥71 years (n = 400), women (n = 380), and men <70 years (n = 38) were removed from the CHS data set along with a small number of nonwhite men (n = 6) for comparison of PAP correlates between the CHS and the HHP. Bivariate associations for continuous variables were determined by Pearson correlation coefficients, and associations with categorical variables were determined by ANOVA. Because of the large number of analyses performed, the level of significance was defined as P ≤ 0.01. A formal race-interaction term was determined by linear regression for each variable common to both cohorts.

We used linear regression on PAP to explore confounding between PAI-1 and factors associated with the IRS: BMI, HDL-C, triglycerides, glucose levels, and insulin levels. We examined the relationship of AAI, as a measure of subclinical atherosclerosis, with PAP by the number of metabolic disorders (see definitions). Of the nondiabetics, 119 had 0 disorders; 109, 1 disorder; 62, 2 disorders; 29, 3 disorders; and 1 participant had 4 disorders. For analysis we established 3 groups: ≤1 disorder (n = 228), ≥2 disorders (n = 92), and diabetes (n = 73).

In multivariable linear regression models, AAI and measures of insulin resistance (BMI, dyslipidemia, hyperinsulinemia, and glucose intolerance) were entered initially, followed by variables significantly related to PAP in bivariate correlations. Because we believe that atherosclerosis is strongly related to inflammation (fibrinogen, factor VIIc, and CRP) and procoagulation (F1 + 2 and fibrinopeptide A), markers of these processes were not allowed to replace atherosclerosis in our model. Because PAP and D-dimer are logically closely correlated, we excluded D-dimer from the model for PAP. The predicted difference in PAP for a specified change equivalent to ISD of each independent variable was determined using models without logarithmic transformation of the specified independent variable. The level of significance for multivariable modeling was set at P ≤ 0.05.
TABLE 1. Characteristics of the Entire CHS Cohort, White Men >70 Years in the CHS, and Asian-American Men in the HHP

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHS (All) (n=395)</th>
<th>CHS (Men) (n=154)</th>
<th>HHP (Men) (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>76.97 (7.34)</td>
<td>79.08 (6.32)</td>
<td>76.82 (7.35)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>33 (8.6)</td>
<td>12 (8.1)</td>
<td>113 (30.4)</td>
</tr>
<tr>
<td>Former</td>
<td>145 (37.9)</td>
<td>70 (47.0)</td>
<td>101 (27.2)</td>
</tr>
<tr>
<td>Never</td>
<td>205 (45.0)</td>
<td>67 (45.0)</td>
<td>158 (42.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>133 (33.9)</td>
<td>51 (33.1)</td>
<td>151 (37.9)</td>
</tr>
<tr>
<td>Borderline</td>
<td>85 (21.7)</td>
<td>42 (27.3)</td>
<td>117 (29.4)</td>
</tr>
<tr>
<td>Normal</td>
<td>174 (44.4)</td>
<td>61 (39.6)</td>
<td>130 (32.7)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>74 (18.7)</td>
<td>32 (20.8)</td>
<td>102 (26.2)</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>107 (27.1)</td>
<td>38 (24.7)</td>
<td>85 (21.8)</td>
</tr>
<tr>
<td>Normal</td>
<td>214 (54.2)</td>
<td>84 (54.5)</td>
<td>203 (52.0)</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>25.81 (4.53)</td>
<td>25.87 (3.52)</td>
<td>22.92 (3.27)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL*</td>
<td>1.45 (0.70)</td>
<td>1.47 (0.73)</td>
<td>1.54 (0.84)</td>
</tr>
<tr>
<td>HDL-C, mmol/L*</td>
<td>1.40 (0.40)</td>
<td>1.26 (0.33)</td>
<td>1.35 (0.37)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L*</td>
<td>5.39 (1.00)</td>
<td>4.99 (0.87)</td>
<td>4.90 (0.89)</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L*</td>
<td>17.57 (3.75)</td>
<td>17.78 (3.54)</td>
<td>17.15 (4.38)</td>
</tr>
<tr>
<td>AAI&lt;0.9, n (%)</td>
<td>52 (13.4)</td>
<td>23 (15.0)</td>
<td>41 (11.1)</td>
</tr>
<tr>
<td>Fasting serum insulin, pmol/L*</td>
<td>10.18 (1.45)</td>
<td>10.18 (1.45)</td>
<td>11.02 (1.49)</td>
</tr>
<tr>
<td>Fibrinogen, g/L*</td>
<td>3.06 (1.45)</td>
<td>5.93 (1.45)</td>
<td>6.11 (1.45)</td>
</tr>
</tbody>
</table>

*Values are mean (SD).

Results

Distribution of PAP

The characteristics of the CHS subcohort have been described and are generally similar to those of the CHS subgroup of men only (Table 1). Compared with the HHP cohort, the CHS subgroup of white men 70 was older, had higher levels of fibrinogen and CRP, and included a greater percentage of subjects with an abnormal AAI. The CHS subgroup had a higher frequency of hypertension, diabetes, and current smokers.

PAP levels ranged from 1.3 to 21.8 nmol/L (mean±SD, 6.11±1.45 nmol/L) in the HHP and from 2.6 to 39.3 nmol/L (mean±SD, 6.04±1.45 nmol/L) in the CHS (excluding 2 outliers with values that were >4SDs above the median: 2.6 to 20.3 nmol/L). Final statistical analyses were performed with and without outliers to assess the effect of their removal on the results. Results were similar, and bivariate and multivariate analyses are reported with all values. Similar to our findings in the CHS, PAP levels increased with age (r=0.001) in the HHP. There was no significant difference in PAP level by sex.

Correlates of PAP

PAP was positively correlated with fibrinogen and CRP (Table 2) but had a negative relationship with BMI and insulin. There was a positive relationship between PAP and HDL-C and an inverse correlation with triglycerides. PAP was not correlated with LDL-C or total cholesterol. There were also no significant correlations with pack-years of smoking (former or current smokers), smoking status, hypertensive status, diabetes, or estrogen use in women (CHS only; data not shown). Major correlates of PAP did not differ by smoking status (never-smokers versus former or current smokers; data not shown).

Both cohorts showed an inverse association between AAI (as a measure of subclinical atherosclerosis) and PAP (significant only in the total CHS group). There were no associations with other markers of subclinical disease, including carotid artery stenosis, the internal or common carotid artery thickness, left ventricular mass, major ECG abnormalities, or a composite subclinical disease variable (CHS only; data not shown).

Although there was a suggestion of a stronger relationship between PAP levels and BHI in the Japanese-American men and a weaker association with AAI, we were unable to detect an interaction by race. However, the power of the current study to observe a formal interaction was low. As expected, an interaction by race. However, the power of the current study to observe a formal interaction was low. As expected, the role of PAI-1 as a fibrinolysis inhibitor (Table 3). In a model to predict PAP, when PAI-1 was included as a covariate, the relationships of the other individual IRS variables to PAP were attenuated (Table 4).

We explored the relationship between PAP and AAI (as a measure of atherosclerosis) after stratification based on an increasing number of IRS-related metabolic disorders (Figure 1). A formal test for interaction did not reach significance (P=0.26). However, although all confidence intervals overlapped, PAP appeared more strongly associated with AAI in...
TABLE 3. Pearson Correlation Coefficients Between Study Variables and PAP in the CHS Men and Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHS (All) (n=395)</th>
<th>Fibrinolytic Factors</th>
<th>Procoagulant Factors</th>
<th>Plasminogen, % normal</th>
<th>In PAI-1, ng/mL</th>
<th>tPA-PAI complex, nmol/L</th>
<th>In LP(a), mg/dL</th>
<th>In fibrin fragment D-dimer, ng/mL</th>
<th>ln fragment 1-2, nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.26†</td>
<td>−0.29‡</td>
<td>−0.13†</td>
<td>0.21†</td>
<td>0.47‡</td>
<td>0.15†</td>
</tr>
</tbody>
</table>

Lp(a) indicates lipoprotein(a).
†P<0.01; ‡ P<0.001.

The relationship of PAP levels to ankle-arm blood pressure index (AAI) and insulin resistance. We adopted recently proposed criteria that estimated insulin resistance19 by summing the number of the following disorders for each subject: dyslipidemia, hypertension, and glucose intolerance. We also included obesity as a metabolic disorder. Of the nondiabetics, 119 had 0 disorders; 109, 1 disorder; 62, 2 disorders; 29, 3 disorders; and 1, 4 disorders. For analysis we made 3 groups: 35 = 1 disorder, 36 = 2 disorders, and diabetes. The P value indicates the significance of the linear trend for PAP level (dependent variable) and tertiles of AAI.

were associated with AAI in bivariate analyses and could replace AAI in the final model when we allowed them to compete for entry.

**Discussion**

Regarding the correlates of PAP, the major findings in this study are the following: (1) PAP levels were associated with inflammation and procoagulant activity as assessed by factors such as fibrinogen and CRP and F1 and fibrinopeptide A, respectively. (2) PAP was negatively associated with factors associated with the IRS (BMI, insulin, and triglycerides), at least partly mediated by PAI-1 levels. (3) PAP was associated with AAI, a measure of subclinical atherosclerosis. (4) In subgroups with 2 or more characteristics of the IRS or in those with NIDDM, the relationship between PAP and AAI appeared weaker than in subgroups with fewer IRS features.

TABLE 4. Standardized Regression Estimate (SRE)* for CHS (n=395) Variables Associated With the IRS, Before and After Adjustment for PAI-1, Calculated From Individual Linear Regression Models With PAP as the Dependent Variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>SRE*</th>
<th>SRE* Adjusted for PAI-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>−0.78‡</td>
<td>−0.63‡</td>
</tr>
<tr>
<td>Glucose Fasting, mmol/L</td>
<td>−0.20</td>
<td>−0.14</td>
</tr>
<tr>
<td>Glucose 2-Hour, mmol/L</td>
<td>−0.26</td>
<td>−0.14</td>
</tr>
<tr>
<td>Insulin Fasting, pmol/L</td>
<td>−0.27‡</td>
<td>−0.17‡</td>
</tr>
<tr>
<td>Insulin 2-Hour, pmol/L</td>
<td>−0.25‡</td>
<td>−0.07</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>−0.21</td>
<td>−0.09</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.43‡</td>
<td>0.29</td>
</tr>
</tbody>
</table>

*SRE is an estimate of the change in PAP based on a 1-SD change in the predictor variable listed.
†P<0.01; ‡ P<0.001.

Cumulative $R^2$ = 0.45.

*Estimate of specified change for the variables is based on a 1-SD increase in the predictor variable with ln PAP as the dependent variable.
Subclinical Disease
Our study is the first to indicate a relationship between PAP and a marker of subclinical atherosclerosis, the AAI. This finding is significant, given the recent report that PAP predicts incident MI in the elderly, independently of subclinical disease.9 The lack of relationships with other markers of subclinical disease, such as carotid artery stenosis or wall thickness, may be due to the relatively small number of subjects in this study and the robust nature of AAI as a marker of atherosclerotic burden.16

Either age or F1+2 could replace AAI in the statistical model. This is not surprising, since we have recently reported in this same cohort that the known age-related increase in AAI was associated with increased thrombin generation.32 Because PAP is correlated with prothrombin fragment F1+2 and age, our results may extend these observations to fibrinolysis status, confirming the relationships observed between subclinical CVD and D-dimer,34 another marker of fibrinolysis.

Inflammation
CVD has features of a chronic inflammatory disease, including mild elevations of acute-phase proteins (ie, fibrinogen, CRP, and factor VIIc), a number of which have been reported to be risk markers for CVD.1,2,3,5,6 The independent associations of PAP with related fibrinolysis factors such as plasminogen and D-dimer and with inflammation-sensitive proteins are consistent with a linking role for fibrinolysis between inflammation and atherosclerosis. Fibrin degradation products have been shown to induce the synthesis and release of the proinflammatory cytokine interleukin-6 from monocytes,37 suggesting a physiological mechanism that conjoins fibrinolysis and inflammation.

PAI-1 and Components of the IRS
Even though higher levels of PAP and PAI-1, observed in some but not all studies,3,4,5,8,10 are both positive predictors of CVD events, increases in PAI-1 are usually associated with decreases in PAP.39 Therefore, PAI-1 has been proposed to mediate some of the adverse hemostatic complications of the IRS.40 Our findings suggest that the degree of IRS present may modify the relationship observed between PAP and the risk of CVD events. For example, a relationship between PAP and CVD may be less obvious in an obese population or in a population with a high frequency of diabetics. The apparently stronger association of PAP with AAI when the population has fewer metabolic disorders supports this position (Figure 1). A lowered fibrinolytic response to subclinical disease in subjects with hyperinsulinemia or glucose intolerance (and higher PAI-1 levels) is consistent with the premise that depressed plasmin generation may enhance progression of atherosclerosis in subjects with features of the IRS. Our recent case-control study of PAP in the CHS9 contained too few subjects to explore these results, and more work is needed to explore these relationships.

Race
The relationships between PAP and hematologic and metabolic variables were similar in the HHP and the CHS, confirming the associations we have observed in a second population. There was a suggestion of a stronger relationship between BMI and PAP levels in Japanese-American men and a weaker association of PAP with AAI, CRP, and smoking. Although these differences were nonsignificant, our power to detect small differences was limited.

The strengths of the current study include the exclusion of clinical CVD as a potential confounder; carefully designed parent studies with appropriate blood collection and storage procedures; assessment of independence through multivariate analyses; and the use of 2 separate racial groups to confirm associations. The major weaknesses are the cross-sectional design and lack of generalizability owing to the selection criteria of the parent studies.

The relationship between inflammation and fibrinolysis is complex, and the biology is incompletely understood. Our results suggest that plasmin generation, as measured by PAP level, is closely associated with ongoing fibrinolysis, subclinical atherosclerosis, and inflammation. Furthermore, PAP levels reflect levels of the major fibrinolysis inhibitor, PAI-1, and increasing levels of PAI-1, as found with the degree of the IRS, may diminish the relationship observed between plasmin generation and atherosclerosis. Thus, insufficient plasmin generation in the setting of a high PAI-1 may be a molecular mechanism for increased thrombosis in subjects with features of the IRS. Taken together with the finding of higher PAI-1 levels as predictors of MI,9 PAP concentration may have different relationships with incident disease, depending on the baseline characteristics of the population studied, ie, presence of the IRS. Larger studies with stratification by IRS characteristics are required to answer these questions.

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Pamela A. Sakkinen, Mary Cushman, Bruce M. Psaty, Beatriz Rodriguez, Robin Boineau, Lewis H. Kuller and Russell P. Tracy

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