Association of Blood Pressure With Fibrinolytic Potential in the Framingham Offspring Population

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Background—Hypertension is an established risk factor for acute coronary events. Because fibrinolytic and hemostatic factors are also associated with cardiovascular disease, we examined the relations of systolic and diastolic blood pressures (SBP and DBP) to levels of plasminogen activator inhibitor antigen, tissue plasminogen activator antigen, fibrinogen, factor VII, von Willebrand factor, fibrinogen, and plasma viscosity in subjects of the Framingham Offspring Study.

Methods and Results—We studied 1193 men and 1459 women after the exclusion of subjects with known cardiovascular disease and those receiving anticoagulant or antihypertensive therapy. Linear regression models were used to evaluate SBP and DBP as predictors of fibrinolytic and hemostatic factor levels in separate sex models, with adjustment for age, body mass index, smoking, diabetes, total cholesterol, HDL, triglycerides, alcohol intake, and estrogen use (in women). In both sexes, levels of plasminogen activator inhibitor and tissue plasminogen activator antigen were positively related to SBP and DBP (P<0.001). Plasma viscosity was positively related to SBP (P=0.008) and DBP (P=0.001) in women only. There was no association between SBP or DBP and fibrinogen, factor VII, or von Willebrand factor in either sex.

Conclusions—These data suggest that impaired fibrinolysis may play an important role in the pathogenesis of cardiovascular disease in hypertensive patients. (Circulation. 2000;101:264-269.)

Key Words: hypertension ■ fibrinolysis ■ cardiovascular diseases

Hypertension is an important risk factor for myocardial infarction and stroke,1-5 which may be due to the accelerated development of atherosclerosis and increased shear stress, leading to plaque rupture. Hypertension also clusters with other risk factors, such as hypertriglyceridemia, obesity, and insulin resistance.6,7 Because myocardial infarction and stroke, which are both complications of hypertension, predominantly occur due to thrombosis rather than to hemorrhage,8-10 hypertension may exert its effect in part through promotion of a prothrombic state. Hemostatic factors such as fibrinogen,10-14 factor VII (FVII),10,11 von Willebrand factor (vWF),10,14,15 viscosity,16-20 and impaired fibrinolytic potential as indicated by elevated levels of plasminogen activator inhibitor (PAI-1)21,22 and tissue plasminogen activator (tPA) antigen23-25 have been associated with increased risk for cardiovascular disease (CVD). Accumulating data support the association of blood pressure with a prothrombic state.20,26-36 but epidemiological evidence is incomplete. The aim of the present study was to examine the relations of fibrinolytic and hemostatic factors to systolic and diastolic blood pressure (SBP and DBP). We measured levels of plasma viscosity, fibrinogen, FVII, vWF, tPA antigen, and PAI-1 antigen in men and women enrolled in the Framingham Offspring Study.

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Methods

Study Population

The study subjects were members of the Framingham Offspring Study, a population-based cohort study started in 1971 to evaluate CVD incidence and risk factors. The design and methodology of the Framingham Offspring Study have been reported in detail.37,38 The participants are children of subjects or spouses of participating children in the original Framingham Heart Study. The great majority of the subjects are white. For this cross-sectional analysis, we collected data from 3799 subjects (1792 men, 2007 women) studied between January 1991 and June 1995, during the fifth Framingham Offspring Study examination cycle.

Data were collected from each subject during a visit to the Framingham Heart Study clinic. Subjects were studied throughout the year, with no predetermined preference for season of the year. Blood pressures were measured to the nearest 2 mm Hg with a mercury column sphygmomanometer on the left arm after the subject had been seated quietly for 5 minutes. Two readings obtained by the physician were averaged to calculate the SBP and DBP. The use of any medications, including antihypertensives, anticoagulants, and...
TABLE 1. Clinical Characteristics of Framingham Offspring Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Men (n=1193)</th>
<th>Women (n=1459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.2±9.7</td>
<td>53.0±9.6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>127±16</td>
<td>121±18</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>77±10</td>
<td>72±10</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.9±4.2</td>
<td>26.3±5.3</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>201±35</td>
<td>205±38</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>43.8±11.6</td>
<td>57.0±15.1</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>156±115</td>
<td>128±101</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>5.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Alcohol, oz/wk</td>
<td>3.6±4.5</td>
<td>1.8±2.6</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>HRT, %</td>
<td>...</td>
<td>16</td>
</tr>
</tbody>
</table>

*Values are mean±SD or percentage.

Blood Sampling and Analysis

Blood samples were collected between 8 and 9 AM from an antecubital vein with subjects in the supine position after an overnight fast to minimize circadian variations. For the determination of plasma levels of PAI-1 and tPA antigen, blood was anticoagulated with 3.8% trisodium citrate (9:1, vol/vol) and kept on crushed ice until centrifugation. Plasma was separated by centrifugation at 2500g for 30 minutes at 4°C. Plasma aliquots were quickly frozen and stored at −70°C for subsequent analysis. PAI-1 antigen levels were determined with a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) according to the description of Declerck et al.39 (TintElize PAI-1; Biopool AB). Levels of tPA antigen also were obtained with the use of an ELISA according to a procedure described by Ranby et al.40 Fibrinogen levels were determined according to the method of Clauss.41 Factor VII antigen levels were measured with a commercially available ELISA kit (Diagnostica Stago). vWF antigen levels were measured according to an ELISA technique.42 Plasma viscosity was measured in specimens previously frozen at −80°C with the use of a Brookfield viscometer. The intra-assay coefficient of variation in our laboratory was 9.6% for PAI-1, 5.5% for TPA, 2.6% for fibrinogen, 8.8% for vWF, and 3.0% for FVII.

Statistical Analysis

Data on clinical characteristics are presented as mean±SD. Logarithmic transformation was performed for variables that were severely skewed (PAI-1, tPA antigen). Linear regression models were used to evaluate hemostatic factors in relation to blood pressure as a continuous variable.43,44 Unadjusted results are presented first, followed by the primary analyses, with adjustment for age, BMI, lipids (total cholesterol, HDL cholesterol, triglycerides), smoking, diabetes, alcohol intake, and HRT (in women). Data on clinical characteristics are presented as mean±SD. The results of regression models are presented as the increment per 10 mm Hg of blood pressure, with 95% CI values. Statistical significance was established at a 2-sided α level of 0.05.

Results

Subject Characteristics

The clinical characteristics of subjects are shown in Table 1. A total of 1193 men and 1459 women met the entry criteria, of whom 259 (22%) men and 237 (16%) women were hypertensive as defined by a blood pressure of ≥140 mm Hg.

TABLE 2. Association of Hemostatic Factors With SBP

<table>
<thead>
<tr>
<th></th>
<th>10 mm Hg SBP Increase (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD*</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log PAI-1, ng/mL</td>
<td>2.97±0.62</td>
<td>0.05 (0.03, 0.07)</td>
</tr>
<tr>
<td>Log t-PA, ng/mL</td>
<td>2.19±0.43</td>
<td>0.03 (0.01, 0.04)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>296.62±55.42</td>
<td>−0.83 (−2.78, 1.13)</td>
</tr>
<tr>
<td>FVII, %</td>
<td>97.44±15.17</td>
<td>0.14 (−0.44, 0.72)</td>
</tr>
<tr>
<td>vWF, %</td>
<td>125.86±46.66</td>
<td>−1.27 (−3.04, 0.50)</td>
</tr>
<tr>
<td>Plasma viscosity, cps</td>
<td>1.236±0.096</td>
<td>0.0002 (−0.004, 0.004)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log PAI-1, ng/mL</td>
<td>2.72±0.69</td>
<td>0.03 (0.01, 0.05)</td>
</tr>
<tr>
<td>Log t-PA, ng/mL</td>
<td>1.95±0.48</td>
<td>0.03 (0.01, 0.04)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>304.96±56.55</td>
<td>0.97 (−0.70, 2.63)</td>
</tr>
<tr>
<td>FVII, %</td>
<td>101.51±16.23</td>
<td>0.24 (−0.26, 0.75)</td>
</tr>
<tr>
<td>vWF, %</td>
<td>124.89±44.39</td>
<td>0.04 (−1.39, 1.47)</td>
</tr>
<tr>
<td>Plasma viscosity, cps</td>
<td>1.246±0.093</td>
<td>0.0004 (0.001, 0.007)</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, diabetes, smoking status, alcohol intake, total cholesterol, HDL cholesterol, triglycerides, and (for women) HRT.
systolic or 90 mm Hg diastolic, in accordance with the sixth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Of the 496 subjects defined as hypertensive, 354 (71%) were hypertensive at 1 or more prior examinations, with an average duration of 11 years from the examination at which hypertension was first documented.

**Associations With SBP**

In unadjusted analyses, SBP was associated with levels of all 6 hemostatic factors in both sexes (in men, \(P<0.0001\) for log PAI-1, log tPA, and fibrinogen, and \(0.01<P<0.025\) for FVII, vWF, and plasma viscosity; in women, \(P<0.0001\) for all 6 factors). Results from regression models that adjusted for covariates (age, BMI, smoking, diabetes, alcohol intake, triglycerides, total and HDL cholesterol, and HRT in women) are shown in Table 2. Increased levels of PAI-1 antigen and tPA antigen remained highly associated with increased SBP (\(P<0.001\) in both sexes). In addition, plasma viscosity was directly associated with SBP in women (\(P=0.008\)) but not in men (\(P=0.91\)), whereas neither fibrinogen, FVII, nor vWF remained associated with SBP in men (\(P>0.15\)) or in women (\(P>0.25\)).

Figure 1 shows PAI-1 antigen levels (mean and 95% CI) for men and women as a function of SBP adjusted for covariates. Men had higher PAI-1 antigen levels than women; moreover, PAI-1 levels increased markedly with increased SBP in both men and women. Similar results are shown for tPA antigen in Figure 2. In men, the full regression model accounted for 33% of the variance for log PAI-1 and 31% of the variance for log tPA (DBP accounted for 1.9% and 1.6%, respectively). Corresponding data for women were 39% of the variance for log PAI-1 and 38% of the variance for log tPA (with DBP accounting for 0.5% and 0.6%).

**Associations With DBP**

In unadjusted analyses, DBP was associated with levels of log PAI-1 and log tPA antigen in both sexes (\(P<0.0001\), with FVII (in men \(P=0.003\); in women \(P<0.0001\)), and with fibrinogen and plasma viscosity in women (\(P<0.0001\)). Results from regression models with covariates are shown in Table 3. Increased levels of PAI-1 and tPA antigen remained highly associated with increased DBP (\(P<0.001\) in both sexes). Plasma viscosity remained associated with DBP in women (\(P=0.001\)), and vWF was negatively related to DBP in men (\(P=0.03\)). Neither fibrinogen, FVII, nor plasma viscosity was associated with DBP in men (\(P>0.13\)), nor were fibrinogen, FVII, or vWF in women (\(P>0.75\)). In men, the regression model accounted for 33% of the variance for log PAI-1 and 31% of the variance for log tPA (DBP accounted for 1.9% and 1.6%, respectively). Corresponding data for women were 39% of the variance for log PAI-1 and 38% of the variance for log tPA (with DBP accounting for 0.5% and 0.6%).

Partial correlation analyses showed that in men, the unadjusted associations of SBP with fibrinogen and vWF were accounted for by their joint relations with age, whereas the associations of SBP and DBP with FVII were accounted for by age and BMI. The relation of plasma viscosity with SBP was accounted for by age. Partial correlation analyses in women demonstrated that age accounted for the association of SBP with vWF, whereas the relations of SBP and DBP with fibrinogen and FVII were accounted for by age and BMI.

**Discussion**

**Fibrinolysis and Hypertension**

We studied 2652 participants in the Framingham Offspring Study and found that increasing SBP and DBP were associated with impaired fibrinolytic potential. PAI-1 antigen levels increased as a function of rising SBP and DBP in men and women. This association persisted even after adjustment for age, BMI, smoking, diabetes, alcohol intake, triglycerides, HDL, total cholesterol, and HRT (in women). Similar findings were observed for tPA antigen. Although impaired fibrinolysis has been mainly evaluated with the use of PAI-1, high concentrations of tPA antigen also reflect impairment of the fibrinolytic system, because most of the tPA antigen
measured is complexed with PAI-1 and is inactive.45,47 Furthermore, elevated levels of both tPA antigen and PAI-1 antigen are predictors of CVD risk.21–25 Therefore, these findings of increasing PAI-1 and tPA antigen levels in relation to increasing blood pressure are compatible with a decreased fibrinolytic state in hypertensive men and women.

Prior studies that evaluated the association of hemostatic factors and hypertension are limited by smaller sample size6,34–36 or lack of adjustment for 1 or more of the following variables: metabolic factors (diabetes, triglycerides),28,29 alcohol intake,28,29,32 HRT,13,17,48 or use of antihypertensive therapy.32–34 All of these are potential confounders and may alter hemostatic levels.

A study by Jansson et al31 compared 84 untreated hypertensive subjects who had elevated cholesterol levels with 55 control subjects matched for age, sex, and BMI. They found a positive association of plasma PAI-1 levels with triglycerides, total cholesterol, and DBP. Although these results support the presence of a decreased fibrinolytic state in hypertension, several differences among the 2 groups were not adjusted for in the analysis. The hypertensive group had higher triglyceride levels, a higher proportion of smokers, and a tendency toward a higher BMI, all of which may decrease fibrinolysis. More recently, Wall et al35 studied 39 young men with borderline hypertension. The mechanism whereby increasing blood pressure may lead to decreased fibrinolysis is complex and involves multiple factors.49 In our study, PAI-1 antigen levels remained associated with increased blood pressure even after adjustment for known confounders, including hypertriglyceridemia and diabetes.

In contrast to these small case-control studies, as part of a large cohort study, the Northern Sweden Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study, Eliasson et al32 performed a cross-sectional analysis of 1558 participants, of whom each had blood samples drawn to determine plasma fibrinogen, tPA, and PAI-1 activity. In men, but not in women, DBP predicted low tPA activity and high PAI-1 activity. PAI-1 activity increased with triglycerides and BMI in both sexes. A high PAI-1 activity was correlated with SBP in men and women. Of note, subjects with a history of myocardial infarction or stroke, with diabetes, hypertensive subjects receiving treatment, and women receiving HRT were included in the analysis. A substudy addressed this issue by excluding all of these subjects, leaving a total of 1260 participants; in the multiple linear regression model, the association of tPA activity with DBP was no longer significant. BMI and hypertriglyceridemia were the strongest predictors of PAI-1 and tPA activity in that study.32

Hypertension has been closely related to obesity, hyperlipidemia, and glucose intolerance, all elements of the "insulin resistance syndrome."6,7 Furthermore, plasma insulin is thought to be an important regulator of PAI-1 activity, either directly or indirectly through plasma triglyceride concentrations.69 In our study, PAI-1 antigen levels remained associated with increasing blood pressure after adjustment for known confounders, including hypertriglyceridemia and diabetes. Therefore, although PAI-1 activity is strongly correlated with hyperinsulinemia and triglycerides, it appears that PAI-1 antigen levels are independently associated with hypertension. The mechanism whereby increasing blood pressure may
result in impaired fibrinolysis is unclear, but it may be related to the increase in shear stress or endothelial dysfunction.

Other Hemostatic Factors and Hypertension

Because fibrinogen, plasma viscosity, vWF, and FVII levels are all associated with the risk of CVD, we also determined their associations with hypertension. After adjustment for potential confounders, plasma viscosity was associated with DBP but not SBP. There was no significant association of fibrinogen or FVII with blood pressure and a modest inverse association of vWF antigen with DBP in men.

The association of plasma viscosity with hypertension has been shown by several investigators to be independent of hematocrit. As a result, plasma proteins, and in particular fibrinogen, an important determinant of plasma viscosity, are thought to contribute to increased plasma viscosity. In contrast to our findings, the Edinburgh Artery Study found a relation of plasma viscosity to SBP and DBP in men, which persisted independent of hematocrit and fibrinogen. Elevated fibrinogen levels have not been consistently associated with hypertension. In the MONICA study, fibrinogen was correlated with blood pressure in both men and women; however, in a regression analysis, fibrinogen remained independently associated with SBP in women only. Other abnormalities of hemostatic factors, such as elevated levels of vWF and FVII, have also been associated with hypertension, but possible confounding variables were not adjusted for in the analysis, including smoking, serum glucose, BMI, and hypertension treatment. The adjustment for these variables in our study may explain the lack of an independent association of blood pressure with fibrinogen, FVII, and vWF antigen. This is supported by our partial correlation analyses, which showed that differences in age and BMI accounted for the association of these variables with blood pressure in our study sample.

Study Strengths and Limitations

In comparison with previous studies that examined the relations of hemostatic and fibrinolytic factors to blood pressure, our study has the benefit of a large sample and a statistical model that better addresses known confounders, including triglycerides and diabetes, in the analysis of PAI-1. In addition, the Framingham Heart Study has the benefit of a broad population, which in this case was selected with respect to treatment with antihypertensive medication. A cross-sectional study such as ours, however, is always limited by unrecognized confounding variables. In addition, the use of mild criteria for hypertension as defined by the Sixth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure and shorter duration of hypertension may account for the negative associations found with fibrinogen and vWF.

Conclusions

Hypertension is known to be a major risk factor for CVD. Although antihypertensive treatment does reduce the risk of CVD, the results are usually not commensurate to what would be predicted on the basis of observational studies. This discrepancy may be in part attributable to contributing factors such as a prothrombic state, which is related to blood pressure level but is not corrected with antihypertensive treatment. Our finding that increased blood pressure is associated with decreased fibrinolytic potential and increased plasma viscosity supports the presence of a prothrombic state in hypertension. These data suggest that impaired fibrinolysis may play an important role in the pathogenesis of CVD in hypertensive subjects. Modification of this hypercoagulable state may have a beneficial effect on the increased CVD risk in subjects with hypertension.

Acknowledgments

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References


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