Blood Viscosity and Elevated Carotid Intima-Media Thickness in Men and Women
The Edinburgh Artery Study

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Background—Several hemostatic and rheological factors have been associated with incident cardiovascular events. However, there have been no reports on the relationship of rheological factors with early atherosclerosis and very few on hemostatic factors. We therefore studied the relationship between these factors and carotid intima-media thickness (IMT).

Methods and Results—The Edinburgh Artery Study measured fibrinogen, tissue plasminogen activator (tPA), fibrin D-dimer, von Willebrand factor (vWF), blood and plasma viscosities, and hematocrit as part of its baseline examination during 1988–1989. At the 5-year follow-up, valid measurements of IMT had been recorded in 1106 men and women 60 to 80 years old. In men, blood viscosity ($P \leq .001$) and its major determinants, plasma viscosity, fibrinogen (both $P \leq .01$), and hematocrit ($P \leq .05$), were all linearly related to IMT. Furthermore, blood viscosity, fibrinogen (both $P \leq .01$), and plasma viscosity ($P \leq .05$) remained significantly associated on multivariate analysis. Correcting blood viscosity to a standard hematocrit of 45% had little effect on its association. In men, there was a significantly increased risk of having an IMT above versus below the upper quartile of its distribution (1.05 mm) for SD increases in blood viscosity ($P \leq .01$), fibrinogen, corrected blood viscosity, and plasma viscosity (all $P \leq .05$). With the exception of plasma viscosity, these risks were unaffected by adjustment for other common cardiovascular risk factors. No significant associations were found between any of the hemorheological factors and IMT in women or for tPA, fibrin D-dimer, or vWF in either sex.

Conclusions—These findings suggest that in men, blood viscosity and its major determinants are associated not only with incident cardiovascular events but also with the early stages of atherosclerosis. This may be one explanation for the link between rheological factors and events. (*Circulation*. 1998;97:1467-1473.)

Key Words: carotid arteries ■ blood flow ■ atherosclerosis ■ fibrinogen

Epidemiological studies have shown that certain hemostatic and rheological factors (eg, fibrinogen, viscosity, hematocrit, vWF, tPA, fibrin D-dimer) are associated with incident cardiovascular events. Possible causal mechanisms include effects on thrombogenesis and ischemia. However, these factors could also be important in promoting the endothelial damage and diffuse intimal thickening that constitute the prolonged, asymptomatic phase of the atherosclerotic process. Such early stages of disease can now be assessed accurately by use of high-resolution B-mode ultrasound to measure the IMT of the walls of the carotid arteries. However, only a small number of population-based studies have considered the association of hemostatic factors with IMT. Some of these have involved only fibrinogen, and none have included measurements of blood or plasma viscosity.

In previous reports from the EAS, rheological factors have been strongly associated both with asymptomatic peripheral arterial disease and with the risk of subsequent cardiovascular events (ischemic heart disease or stroke). We have also noted that men are more susceptible to the effects of rheological factors, in particular plasma viscosity, and that this may contribute to the sex differential in cardiovascular disease (Reference 17, and unpublished data, 1997). However, the mechanism behind the greater susceptibility of men is unclear; in particular, it is not known whether it is the thrombotic, ischemic, or atherogenic component of cardiovascular disease that appears to be more sensitive in men to changes in the rheological factors.

The present population-based study investigates the hypothesis that hemostatic and rheological factors are associated with carotid arterial wall thickness and that such effects...
are independent of other “traditional” cardiovascular risk factors. Results are analyzed on a sex-specific basis, allowing us to identify any sex differences in the relationship between a range of rheological and hemostatic factors and IMT.

**Methods**

The EAS is a prospective study of 1592 men and women whose age at baseline ranged from 55 to 74 years. The population was selected at random, in 5-year age bands, from 10 general practices spread socioeconomically across the city. The response rate was 65%, and follow-up of a random sample of 20% of the nonresponders showed no substantial bias. Details of the study population and recruitment have been reported previously. The study was approved by the Lothian Health Board Ethics Committee, and informed consent was obtained from each participant.

**Risk Factor Measurement**

Assessment of all risk factors took place at baseline; participants attended a university clinic, where a self-administered questionnaire was checked and a comprehensive medical examination carried out. The questionnaire included validated questions concerning personal characteristics, smoking, and medical history (including the World Health Organization angina and intermittent claudication questionnaires). The examination was conducted by two pairs of specially trained nurses who took 20 mL of fasting blood. Standing height and weight (without shoes) were measured, and blood pressure was taken from a random-zero sphygmomanometer with the subject in the supine position after a 10-minute rest.

The blood samples were taken between 9:30 AM and 12:30 PM to minimize diurnal variation in the levels of biochemical, hemostatic, and rheological factors. Fibrinogen was measured in citrated plasma by a thrombin-clotting turbidimetric method in a centrifugal analyzer. tPA antigen levels were estimated by an ELISA (Biopool). tPA antigen levels were estimated by an ELISA (Biopool). vWF was also assayed with an ELISA (DAKO). Blood and plasma viscosities were measured in KEDTA blood (1.5 mg/mL) at high shear rates (>300 s⁻¹) in a Coulter-Harkness viscometer at 37°C. Hematocrit was measured with a Hawksley microcentrifuge and reader. Serum total cholesterol was measured on a Cobas Bio-analyzer (Roche Products) with standard kits. The coefficients of variation for each of the hemostatic and rheological factors were as follows: fibrinogen, 2.1%; tPA, 9.8%; fibrin dimer, 15%; vWF, 7.7%; blood viscosity, 1.2%; plasma viscosity, 0.9%; and hematocrit, 0.6%.

**Measurement of Carotid Atherosclerosis**

B-mode ultrasound scanning was performed by four specially trained staff members on the 1156 participants who attended their 5-year follow-up examinations between November 1992 and March 1994. Complete details of the self-administered follow-up questionnaire and the examination procedure have been previously published.

The B-mode ultrasound scan was performed with the subject in the supine position by use of an ATL UM9, HDI Duplex Scanner (Advanced Technology Laboratories), with a 10-MHz transducer providing imaging at 10 MHz and spectral Doppler at 7 MHz. The scanning protocol involved examination of the carotid arteries in both transverse and longitudinal planes. Measurement of IMT was made at the point on the far wall of the common carotid artery, 2 cm proximal to the bifurcation, from the longitudinal scan plane that showed the intima-media boundaries most clearly with maximum image magnification. The distance between the two cursors positioned on the boundaries of the intima and media was recorded to the nearest 0.1 mm as the IMT. The procedure was repeated for each side of the neck.

The higher of the values of IMT recorded for the right and left sides of the neck was used as the measure of disease throughout all subsequent analyses. IMT was recorded for only one side of the neck in 27 participants (2.4%), and this value was used in the analysis. The current analysis was repeated using the mean of the left and right sides, and the results were almost identical to those using the maximum.

**Data Analysis**

Information from the questionnaires and recording forms was checked by the clinic staff and entered onto a DBASE IV database. Data files were then transferred to the university mainframe computer for analysis by the SPSS and SAS statistical packages.

The distribution of IMT was positively skewed, and a logarithmic transformation was used in all tests that assume approximate normality of the dependent variable. Blood viscosity was corrected to a standard hematocrit of 45% by the formula of Matrai et al. Relative blood viscosity (corrected blood viscosity/plasma viscosity) was calculated as a measure of red cell deformability. The distributions of tPA and vWF were positively skewed and required a square root transformation. Fibrin dimer was more heavily skewed, and a logarithmic transformation was necessary. Pack-years was calculated as a measure of lifetime smoking history (years of smoking multiplied by the average number of packs smoked per day). As expected, the distribution was highly skewed, with a small number of very heavy smokers; a square root transformation was used throughout the analysis.

Pearson correlation coefficients were calculated to examine the relationship between each of the hemostatic and rheological factors and three common risk factors (total cholesterol, systolic blood pressure, and pack-years of smoking). These three risk factors were chosen because they had previously been shown to have an independent relationship with IMT in this population, whereas other risk factors such as alcohol consumption and obesity showed no independent effect. Least-squares linear regression was used to assess the association between hemostatic and rheological factors and IMT measured after adjustment for age. Multivariate linear regression was then used to adjust these effects for the three potential confounders: total cholesterol, systolic blood pressure, and pack-years of smoking.

The population was divided into quartiles based on the sex-specific distributions of IMT because there are large differences in the distribution of IMT between men and women. Mean values for each of the risk factors were calculated across these quartiles. Finally, logistic regression was used to calculate age-adjusted odds ratios of having a raised IMT (above the upper quartile of its distribution) for every 1 SD increase in each of the risk factors. The odds ratios were then adjusted further for the potential confounding effects of pack-years, total cholesterol, and systolic blood pressure.

**Results**

Of the 1592 subjects who were recruited at baseline, 1156 (72.6%) attended the 5-year follow-up examination and completed the questionnaire, 131 (8.2%) did not attend the examination but returned their questionnaire, and there were 203 deaths (12.8%). Ultrasound scans were of an acceptable quality for measurement of IMT in 1106 (95.7%) of the 1156 who attended the examination. There was no significant difference (P > .05) in the distributions of sex or social class between the baseline population and the subgroup who attended the follow-up examination. In this population, men were found to have significantly higher age-adjusted mean IMT values than women (0.85 mm, with a 95% CI of 0.82 to 0.87, versus 0.79 mm, with a 95% CI of 0.77 to 0.82). The correlations between the hemorheological factors and total
cholesterol, systolic blood pressure, and pack-years are shown in Table 1. Plasma viscosity showed the strongest correlation with total cholesterol in both sexes. In men, systolic blood pressure was most strongly correlated with tPA, whereas blood pressure showed the strongest correlation with fibrinogen, blood and plasma viscosities, and corrected blood viscosity (all $P \leq .05$) each maintained a statistically significant relationship to IMT. In contrast, Table 2 shows that none of these rheological factors were significantly related to carotid IMT in women ($P > .05$). No significant association was observed between tPA, fibrinogen, tPA, or vWF and IMT in either sex.

Table 3 gives the age-adjusted mean levels of the hemostatic and rheological factors by quartile of IMT in men and women. As expected from the analyses in Table 2, in men, significant linear trends across quartiles of IMT were noted for fibrinogen, blood and plasma viscosities, and corrected blood viscosity (all $P \leq .01$), with hematocrit just failing to reach statistical significance ($P = .067$). No significant linear trends were seen for any of the hemorheological factors across quartiles of IMT in women or for tPA, fibrinogen, tPA, or vWF in either sex.

Odds ratios of having a carotid IMT value above versus below the upper quartile of its distribution for a unit (SD) increase in each of the hemostatic and rheological factors are presented in Table 4. In men, after adjustment for age, standard unit increases in fibrinogen ($P = .05$), blood viscosity ($P \leq .01$), corrected blood viscosity ($P \leq .05$), and plasma viscosity ($P \leq .01$) were significantly associated with increased risk of having a carotid IMT above the upper quartile.
viscosity \((P<.05)\) significantly raised the likelihood of having an elevated IMT. Adjustment for pack-years, total cholesterol, and systolic blood pressure had very little effect on the magnitude of these odds ratios, with the exception of plasma viscosity, which was reduced to marginal nonsignificance \((P \approx .07)\). The odds ratios for each of the viscosity measurements were then further adjusted for plasma fibrinogen level, and there was little change in their significance levels (data not shown). Table 4 shows that none of the hemorheological factors were associated with an increased IMT in women. Again, tPA, fibrin \( \alpha \)-dimer, and vWF showed no relationship to IMT in either sex.

### Discussion

The relationships between a range of hemostatic and rheological factors and carotid IMT, a measure of early atherosclerosis, have been studied in a large representative sample of the general population. To the best of our knowledge, this is the first epidemiological study of the association between rheological factors and IMT. Blood viscosity and its major determinants (hematocrit and plasma viscosity) and fibrinogen, which is an important determinant of plasma viscosity, were strongly associated with IMT in men. Importantly, these relationships were independent of three major traditional cardiovascular risk factors: total cholesterol, blood pressure, and lifetime smoking history. Furthermore, for men, unit increases in the levels of fibrinogen, blood and plasma viscosities, and corrected blood viscosity significantly increased the risk of having an elevated IMT (above the upper quartile of its distribution). In contrast, none of these rheological variables showed any significant association with carotid IMT in women. Our results support the hypothesis that rheological factors may have a significant and independent effect on early carotid atherogenesis in men. This relationship may be one mechanism for the association of these factors with incident stroke and IHD events in men in this cohort.\(^8\)
One important feature of the present study was that the hemostatic and rheological factors were measured at baseline, 5 years before the IMT measurement. Although this reduced the potential bias of studies in which risk factors are measured retrospectively, it introduced two other sources of bias. First, the risk factor levels may have changed over the 5-year follow-up period; they may even have changed differentially by level of IMT. Second, since a sizable proportion of the cohort either died or did not attend the follow-up examination for a variety of reasons, biased estimates of the risk factor–IMT relationship may result. Both sources of bias are likely to reduce the power of the statistical tests; they would not cause variables to appear significant when they were unrelated to IMT, nor would they reverse a true relationship.

The distribution of IMT in any population study is highly dependent on how precisely it is measured and on the settings of the scanning equipment. In the present study, a single measurement of IMT was taken on each side of the neck. IMT was measured to the nearest 0.1 mm, which was a constraint imposed by the ultrasound scanner. Given the somewhat narrow distribution of IMT in this population, the authors accept that this may have led to a relatively large measurement error and a subsequent loss of statistical power to detect significant associations. Previous large population studies have used a variety of techniques to measure IMT, and in contrast to the present study, all have used multiple measurements of the carotid artery in their calculation of IMT. The ARIC study used an average of 11 measures spaced evenly over the far wall of the left common carotid artery. In contrast, the Kuopio Ischemic Heart Disease study used a mean of six values of IMT (three measures on each side of the neck) and the Cardiovascular Health Studies an average of two values. However, given these differences in techniques of measurement, there is still some consistency in the mean levels of IMT and its variation across the four population studies. Needless to say, future epidemiological research involving carotid IMT as a measure of early atherosclerosis would benefit from standardization of both the scanning equipment and the protocol for measurement.

Previous studies have shown that IMT, measured by B-mode ultrasound, is a valid and accurate marker for the early, subclinical stages of atherosclerosis. A strong relationship between carotid IMT and the ankle-brachial pressure index, a measure of peripheral occlusive arterial disease, has already been demonstrated within this population, suggesting that IMT is also a marker for generalized atherosclerosis. Although a number of epidemiological studies have considered the relationship between hemostatic factors and the occurrence of symptomatic cardiovascular disease, few have studied the influence of these variables on the early stages of atherosclerotic development in large population samples. Others have used small samples or selected patient groups and the results cannot be extrapolated reliably to the general population. Analyses in the

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**TABLE 4. Odds Ratios of IMT >1.05 mm (Men) and >0.95 mm (Women) for a 1 SD Increase in Each of the Hemostatic and Rheological Factors**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (+0.62 g/L)</td>
<td>1.27 (1.04, 1.55)*</td>
<td>0.98 (0.80, 1.21)</td>
</tr>
<tr>
<td>tPA (+0.55 [ng/mL] 0.5)</td>
<td>0.90 (0.73, 1.12)</td>
<td>0.91 (0.73, 1.13)</td>
</tr>
<tr>
<td>Fibrin d-dimer (+1 ln ng/mL)</td>
<td>1.37 (0.95, 1.98)</td>
<td>0.76 (0.50, 1.14)</td>
</tr>
<tr>
<td>vWF (+1.99 [IU/dL] 0.5)</td>
<td>1.04 (0.84, 1.24)</td>
<td>0.98 (0.80, 1.21)</td>
</tr>
<tr>
<td>Hematocrit (+3.42%)</td>
<td>1.13 (0.93, 1.39)</td>
<td>1.13 (0.93, 1.39)</td>
</tr>
<tr>
<td>Blood viscosity (+0.57 mPa · s)</td>
<td>1.36 (1.10, 1.67)†</td>
<td>1.32 (1.04, 1.59)*</td>
</tr>
<tr>
<td>Corrected viscosity (+0.39 mPa · s)</td>
<td>1.29 (1.04, 1.59)†</td>
<td>1.24 (1.01, 1.53)*</td>
</tr>
<tr>
<td>Relative viscosity (+0.25 mPa · s)</td>
<td>1.16 (0.94, 1.43)</td>
<td>0.93 (0.76, 1.15)</td>
</tr>
<tr>
<td>Plasma viscosity (+0.09 mPa · s)</td>
<td>1.24 (1.01, 1.53)*</td>
<td>0.93 (0.76, 1.15)</td>
</tr>
</tbody>
</table>

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*P<.05; †P<.01.
‡Adjusted for age, total cholesterol, systolic blood pressure, and pack-years of smoking.
present study have been performed on a sex-specific basis, primarily because of large sex differences in the distribution of IMT and also because there are substantial sex differences in the relationships between IMT and traditional cardiovascular risk factors. Previous studies addressing the relationship of IMT to hematological variables have focused primarily on plasma fibrinogen. Fibrinogen may promote atherosclerosis through various mechanisms, including increases in platelet aggregation, fibrin formation, and blood viscosity and decreased fibrinolysis. Pathological studies have suggested that fibrinogen may be particularly important in early atherosclerotic development. Both the ARIC Study and the Cardiovascular Health Study reported significant associations between fibrinogen and IMT on univariate analyses, but these relationships were weakened after adjustment for other cardiovascular risk factors, including smoking. However, as in the present study, ARIC noted that the relationship remained significant after adjustment for smoking in men. Results from other studies have not provided conclusive evidence for the role of fibrinogen. Positive correlations with IMT have been reported in population samples of elderly subjects and in a smaller sample of young people 10 to 19 years old. In contrast, others, including the Kuopio Ischemic Heart Disease study, have reported either very weak associations or no association between fibrinogen and IMT, particularly on multivariate analyses.

Although epidemiological studies have demonstrated a relationship between tPA antigen and cardiovascular disease or events, only ARIC has reported its association with IMT in a large population study, which was significant on univariate analysis but became nonsignificant after multivariate adjustment. However, the present study found no significant univariate relationship between tPA and IMT in either sex. Similarly, fibrin D-dimer, a marker of increased fibrin turnover, was not significantly associated with IMT in the present study, confirming the findings from ARIC. VWF, which like tPA antigen may be a marker of endothelial disturbance, activates aggregation of platelets and promotes their adhesion to damaged subendothelium. Results from the present analysis again confirm those from the ARIC Study: there appears to be no consistent relationship between VWF and IMT in either sex. Hence, the associations of tPA, fibrin D-dimer, and VWF and incident cardiovascular disease in the EAS may not be mediated through association with atherosclerosis but rather through prothrombotic effects.

The most striking result from the present study was the strong, independent relationship between blood viscosity and its major determinants (hematocrit, plasma viscosity, and fibrinogen) and IMT in men. Indeed, IMT was found to be more strongly associated with these rheological factors than with a range of traditional cardiovascular risk factors, which have already been studied in this population. After adjustment for three common cardiovascular risk factors, unit increases in fibrinogen and blood viscosity were each associated with significant increases in the risk of men of having an elevated IMT. The association between blood viscosity and IMT remained significant after correction to a standard hematocrit of 45% and also after adjustment for fibrinogen. This suggests that the viscosity-IMT relationship is not simply due to the contributions of these two major determinants of blood viscosity. In contrast, the data suggested that no significant relationship existed in women. This could have been partly a result of the relatively smaller range of variation in the distribution of IMT in women, although the finding is in agreement with that of a French population study. With such a large sample size, it could be argued that although the associations observed in men were statistically significant, they may not be of biological significance. However, an odds ratio of almost 1.4 for blood viscosity would suggest that viscosity does have a real effect on early atherosclerosis. Recently, Cortellaro and coworkers reported that hematocrit was related to 16-month progression of IMT in 64 patients with peripheral arterial disease.

Elevated blood viscosity may promote atherosclerotic development by increasing platelet adhesion to the subendothelium, by increasing protein infiltration into the arterial wall, and by altering local shear forces at sites of atherogenesis. Through such effects, blood viscosity may be one mechanism by which many other risk factors promote atherosclerosis. We have reported elsewhere that the higher incidence of cardiovascular events in men in the EAS may be partly explained by a sex difference in susceptibility to rheological factors (Reference 17, and unpublished data, 1997). The present analysis provides strong evidence to suggest that in men, the atherogenic component of cardiovascular disease may be more susceptible to elevated blood viscosity and supports our previous findings of a sex difference in susceptibility to peripheral atherosclerosis with increases in viscosity. Possible explanations for the greater susceptibility of men to viscosity could relate to sex differences in vascular geometry and wall shear forces.

Results from this population-based study provide strong evidence to suggest that blood viscosity and its major determinants may be important risk factors for the development of early atherosclerosis in men. This relationship appears to be independent of other common cardiovascular risk factors. These findings need to be confirmed from other large prospective studies, especially those that have estimated both progression and regression of atherosclerosis.

Acknowledgment

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References


27. SPSS Advanced Statistics Guide. Chicago, Ill.: SPSS Inc; 1990.


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