Association of Plasma Viscosity and Carotid Thickening in a French Working Cohort
Jaime Levenson, Jérôme Gariepy, Muriel Del-Pino, Jean Salomon, Nicolas Denarie, and Alain Simon

Plasma viscosity and intima-media thickness (IMT) are frequently associated with cardiovascular disease and its risk factors. We evaluated the association of rheologic and vascular factors in asymptomatic subjects. Plasma viscosity (coaxial cylinder viscometry) and both preintrusive and intrusive atherosclerosis in the carotid arteries (ultrasonography) were investigated in 246 men and 337 women aged 17 to 65 years from the AXA study, a prospective cohort of healthy workers. Plasma viscosity was positively related to age-adjusted mean bifurcation carotid artery IMT ($P < .01$ for men; $P < .04$ for women) and maximum carotid artery IMT ($P < .01$ for men; $P < .02$ for women), but not to mean common carotid artery IMT. Multivariate adjustment affected these relations to a greater extent in men than in women. The odds ratio (range) of having intrusive atherosclerosis in relation to 1 SD greater plasma viscosity was $2.27$ ($1.52–3.38$) in men and $1.63$ ($1.17–2.26$) in women. Adjustment of age, waist-to-hip ratio, smoking, hypercholesterolemia, hypertension, diabetes, and fibrinogen had very little effect on the magnitude of these odds ratios. Thus, plasma viscosity was associated with carotid thickening, suggesting that rheologic factors are involved in the subclinical phase of atherosclerosis. Am J Hypertens 2000;13:753–758 © 2000 American Journal of Hypertension, Ltd.

KEY WORDS: Plasma viscosity, intima-media thickness, carotid thickening, atherosclerosis.

There are a number of studies in the literature showing that several well-established cardiovascular risk factors (age, gender, blood pressure, total cholesterol, low density lipoproteins (LDL)- and high density lipoproteins (HDL)-cholesterol, triglycerides, cigarette smoking, fibrinogen, diabetes, left ventricular hypertrophy) are associated with two different biomarkers: plasma viscosity$^1$–$^5$ and intima-media thickness of the carotid arteries.$^6$–$^{12}$ Although increased plasma viscosity and carotid intima-media thickness (IMT) were found in separate studies to be related to the incidence of cardiovascular events$^{13}$–$^{19}$ and the severity of atherosclerosis,$^{20}$–$^{22}$ only one study examined the relationship between these factors in population-based samples.$^{23}$ High-resolution ultrasonography is widely used to screen the IMT because it is a simple way of quantifying early changes of the arterial wall, particularly in the carotid artery. However, there are disparities in the studies concerning the arterial segment examined. Some studies focused on IMT measured at the far wall of the common carotid artery where the measurements are less variable than in other segments.$^8,^{12,18}$ Other studies included IMT measurements at the bi-
Single-center, 4-year follow-up of healthy workers, the (Paris, la Défense, France), a cohort of a prospective
were current smokers.
Smoking status was also categorized in subjects who
pack-years) was assessed by questioning the subjects.
$ing blood glucose level

37°C.2 Hypercholesterolemia was defined as a total
(240s
also measured in citrated plasma at high shear rates
method described by Clauss.26 Plasma viscosity was
plasma fibrinogen according to the thrombin time
eaux, France). Citrated plasma was used to measure
use of enzymatic kits (Ektachem DT60 analyzer, John-
tors were carefully evaluated in each subject. Waist
(W) was measured using a cloth tape just above the
level of the lateral iliac crest, below the lower costal
arch at the end of gentle expiration. Hip (H) was
measured at the level of the great trochanters.24 Blood
pressure was measured in the supine position as the
average of three measurements taken from the right
arm after a 10-min rest by using standard sphygmom-
manometric procedures.25 Hypertension was defined
as an SBP $ 160 mm Hg and/or a DBP $ 95 mm Hg,
the presence of antihypertensive drug treatment, or a
combination of these.25 Biologic parameters were mea-
sured on the day of blood collection at the workplace.
Total cholesterol triglycerides, HDL cholesterol after
the precipitation of LDL and very low density lipopro-
proteins (VLDL), and glycemia were measured with the
use of enzymatic kits (Ektachem DT60 analyzer, John-
son & Johnson, Clinical Diagnostics, Issy les Moulin-
eaux, France). Citrated plasma was used to measure
plasma fibrinogen according to the thrombin time
method described by Clauss.26 Plasma viscosity was
also measured in citrated plasma at high shear rates
(240s$^{-1}$) in a couette viscometer with coaxial cylinders
(Low Shear 30, Contraves AG., Zurich, Switzerland) at
37°C.2 Hypercholesterolemia was defined as a total
cholesterol level $ 6.2 mmol/L, the use of lipid-low-
ering drugs, or both.25 Diabetes was defined as a fast-
ing blood glucose level $ 7.8 mmol/L, the use of antidiabetic drugs, or both. Lifelong smoking dose (in
pack-years) was assessed by questioning the subjects.
Smoking status was also categorized in subjects who
were current smokers.

**Ultrasound Arterial Investigation** Echographic in-
vestigations were performed with a real-time, B-mode
ultrasound imager (Ultramark 4, Advanced Technolo-
gie Laboratorie, Les Vlis, France) using a 7.5-MHz
probe. Imaging of the IMT was performed in the far
wall of the right and left common carotid arteries 2 to
3 cm proximal to the bifurcation and in the far wall of
the right and left carotid bifurcation itself, according
to a standardized procedure reported in detail else-
where.8,11,12 Average CCA-IMT was calculated as the
mean value of $147 \pm 44$ point measures performed
along at least 1 cm of the common carotid arteries and
average BCA-IMT as the mean of $18 \pm 11$ point mea-
sures performed along 1 cm of the carotid bifurcation
arteries. For each subject, a total IMT [([left + right]/2)
was taken as a measure of current wall thickness of the
common carotid and bifurcation carotid arteries.
When this measure was missing on one side, the IMT
estimate was based on the measurement of the site for
which a value was available. In bifurcation carotid
arteries, total IMT was not obtained in three patients
because IMT could not be measured on both sides. The
study also included the higher values of IMT (MxCA)
performed in the far wall of the right and left common
and bifurcation carotid arteries. In addition, carotid
artery atherosclerosis was estimated by the occurrence
of plaques, defined as a focal echogenic structure en-
croaching into the vessel lumen having a distance
between the media-adventice interface and the lesion
surface facing the lumen greater than 2 mm. For this,
scanning of the common carotid artery, the carotid
bifurcation, the carotid bulb, and the internal carotid
arteries in multiple longitudinal and transverse planes
was performed.

**Statistical Analysis** Values are expressed as mean $\pm$
SD or, for categorical parameters, as percentage. Com-
parisons of risk factors between groups defined by
tertiles of plasma viscosity were made by ANOVA.
Least-squares linear regression was used to assess the
association of CCA-IMT, BCA-IMT, and MxCA-IMT
across tertiles of plasma viscosity. Multivariate linear
regression was then used to adjust these parameters
for the possible confounding risk factors. Odds ratio
for prevalent carotid artery atherosclerosis per 1 SD
increase in plasma viscosity were computed from
multiple logistic regression model.

**RESULTS**
Table 1 shows mean $\pm$ SD values for cardiovascular
risk factors in tertiles of plasma viscosity stratified by
gender. Significant positive association was found be-
tween plasma viscosity and age, hypertension, and
plasma fibrinogen in men and women. In contrast,
whereas the association with lifelong smoking was
significant only for men, hypercholesterolemia was associated with plasma viscosity only for women.

Table 2 presents the average CCA-IMT, BCA-IMT, and MxCA-IMT distributed by tertiles of plasma viscosity in men and women, both unadjusted and when adjusted for age and either for age, waist-to-hip ratio, current smoking, hypertension, hypercholesterolemia, and diabetes (Model A), or for plasma fibrinogen (Model B). Unadjusted CCA-IMT increased significantly \( (P < .01) \) across tertiles of plasma viscosity only in women; however, the significance was eliminated by adjusting for age and for the previously mentioned factors. Mean bifurcation-IMT and MxCA-IMT were significantly higher \( (P < .001 \text{ for men and women}) \) as plasma viscosity levels increased from the first to the third tertile. Similar results were observed for carotid artery atherosclerosis (Fig. 1; \( P < .001 \text{ for men and women}) \). In both genders, after adjustment for age the association between BCA-IMT, MxCA-IMT, carotid artery atherosclerosis, and tertile of plasma viscosity persisted for men \( (P < .01) \) and for women \( (P < .04) \). Further adjustment for age, waist-to-hip ratio, current smoking, hypertension, hypercholesterolemia, and diabetes reduced the significance of the association of MxCA-IMT and carotid artery atherosclerosis with plasma viscosity in men and women \( (P < .05) \), but the BCA-IMT associated with plasma viscosity was reduced to marginal nonsignificance \( (P < .065) \) in men. Except for carotid artery atherosclerosis, none of the carotid wall thickening parameters was associated with plasma viscosity tertiles in men, when additionally adjusted for plasma fibrinogen. In contrast, this adjustment increased the statistical significance between BCA-IMT \( (P < .01) \), MxCA-IMT \( (P < .01) \), carotid artery atherosclerosis \( (P < .001) \), and plasma viscosity tertiles in women.

### TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION DISTRIBUTED BY TERTILES OF PLASMA VISCOSITY

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
<th>ANOVA or ( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>M 42 ± 9</td>
<td>42 ± 9</td>
<td>45 ± 9</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>W 41 ± 9</td>
<td>41 ± 8</td>
<td>44 ± 8</td>
<td>.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>M 0.93 ± 0.06</td>
<td>0.94 ± 0.05</td>
<td>0.95 ± 0.05</td>
<td>.08</td>
</tr>
<tr>
<td></td>
<td>W 0.79 ± 0.08</td>
<td>0.79 ± 0.06</td>
<td>0.80 ± 0.06</td>
<td>.26</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>M 138 ± 11</td>
<td>137 ± 11</td>
<td>142 ± 17</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>W 130 ± 10</td>
<td>133 ± 11</td>
<td>135 ± 13</td>
<td>.02</td>
</tr>
<tr>
<td>Diastolic</td>
<td>M 85 ± 9</td>
<td>84 ± 10</td>
<td>87 ± 14</td>
<td>.40</td>
</tr>
<tr>
<td></td>
<td>W 79 ± 9</td>
<td>81 ± 9</td>
<td>83 ± 9</td>
<td>.01</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>M 11</td>
<td>13</td>
<td>30</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>W 2</td>
<td>6</td>
<td>14</td>
<td>.01</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>M 23</td>
<td>34</td>
<td>39</td>
<td>.10</td>
</tr>
<tr>
<td></td>
<td>W 37</td>
<td>30</td>
<td>34</td>
<td>.52</td>
</tr>
<tr>
<td>Never</td>
<td>M 46</td>
<td>32</td>
<td>32</td>
<td>.12</td>
</tr>
<tr>
<td></td>
<td>W 46</td>
<td>57</td>
<td>51</td>
<td>.25</td>
</tr>
<tr>
<td>Lifelong smoking dose, pack/year</td>
<td>M 9 ± 12</td>
<td>10 ± 10</td>
<td>13 ± 15</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>W 6 ± 8</td>
<td>6 ± 9</td>
<td>8 ± 12</td>
<td>.19</td>
</tr>
<tr>
<td>Lipid levels, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>M 5.45 ± 0.92</td>
<td>5.59 ± 0.92</td>
<td>5.64 ± 1.12</td>
<td>.43</td>
</tr>
<tr>
<td></td>
<td>W 5.13 ± 0.91</td>
<td>5.23 ± 0.96</td>
<td>5.60 ± 1.08</td>
<td>.001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>M 1.43 ± 0.37</td>
<td>1.45 ± 0.33</td>
<td>1.36 ± 0.15</td>
<td>.18</td>
</tr>
<tr>
<td></td>
<td>W 1.76 ± 0.40</td>
<td>1.80 ± 0.41</td>
<td>1.65 ± 0.40</td>
<td>.02</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>M 1.26 ± 0.73</td>
<td>1.30 ± 1.30</td>
<td>1.44 ± 1.14</td>
<td>.55</td>
</tr>
<tr>
<td></td>
<td>W 0.83 ± 0.41</td>
<td>0.88 ± 0.55</td>
<td>1.12 ± 0.63</td>
<td>.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>M 20</td>
<td>27</td>
<td>34</td>
<td>.11</td>
</tr>
<tr>
<td></td>
<td>W 15</td>
<td>14</td>
<td>28</td>
<td>.01</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>M 5.46 ± 0.62</td>
<td>5.62 ± 0.61</td>
<td>5.55 ± 0.09</td>
<td>.40</td>
</tr>
<tr>
<td></td>
<td>W 5.21 ± 0.48</td>
<td>5.24 ± 0.68</td>
<td>5.37 ± 0.70</td>
<td>.12</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>M 0</td>
<td>1</td>
<td>2</td>
<td>.40</td>
</tr>
<tr>
<td></td>
<td>W 0</td>
<td>1</td>
<td>3</td>
<td>.19</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>M 2.73 ± 0.46</td>
<td>3.24 ± 0.57</td>
<td>3.99 ± 0.85</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>W 2.71 ± 0.52</td>
<td>3.43 ± 0.64</td>
<td>4.03 ± 0.78</td>
<td>.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Tertiles cut-points for plasma viscosity are 1.197 and 1.234 mPa.s. M = men; W = women.
The odds ratio of having carotid artery atherosclerosis in relation to a 1-SD greater plasma viscosity concentration was 2.27 (1.52–3.38) in men and 1.63 (1.17–2.26) in women (Table 3). The aforementioned adjustment had very little effect on the magnitude of these odds ratios.

DISCUSSION

The main finding of this study is that plasma viscosity was found to be associated with increased mean IMT of the carotid bifurcation and maximum thickness of the carotid arteries in both genders, but not with mean IMT of the far wall common carotid arteries. The lack of significant relation between CCA-IMT and plasma viscosity in our study, which contrasts with the results observed in the carotid bifurcation, may be related to the complex pattern of blood velocity distribution inside the arterial lumen. In the straight distal CCA, blood flow is laminar and a symmetrical velocity profile is generally observed. This contrasts with the blood flow characteristics of the carotid bifurcation, in which fluid blood can disturb and an asymmetrical velocity profile occurs, resulting in lower shear stress.27 The almost 55% greater IMT in the carotid bifurcation than in the common carotid artery is in line with the hypothesis that rheologic factors might have a greater role for arterial thickening in vessel bifurcations.27,28 The relation between plasma viscosity and BCA-IMT or MxCA-IMT persisted after adjustment of other cardiovascular risk factors, many of which demonstrated a strong association with atherogenesis.

To our knowledge, the Edinburg Arteries Study (EAS) cohort of men and women aged 60 to 80 years is the only study before this one that reported an association among blood viscosity, its major determinants, and intima-media thickness. There are, however, some differences with regard to IMT measurements. In contrast with EAS, which used a single measurement of the maximum far wall IMT of the common carotid artery, in our study a large number of IMT measures at the same site were performed by an automated computerized system every 10 μm along at

**TABLE 2. GENDER-SPECIFIC MEAN COMMON, MEAN BIFURCATION, AND MAXIMUM CAROTID ARTERY INTIMA-MEDIA THICKNESS (IMT) BY TERTILES OF PLASMA VISCOSITY**

<table>
<thead>
<tr>
<th></th>
<th>Plasma Viscosity Tertiles, mPa.s</th>
<th>Main Effects, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Middle</td>
</tr>
<tr>
<td>Men (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean common carotid IMT (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.542 ± 0.102</td>
<td>0.550 ± 0.128</td>
<td>0.567 ± 0.116</td>
</tr>
<tr>
<td>Mean bifurcation carotid IMT (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.816 ± 0.248</td>
<td>0.895 ± 0.302</td>
<td>1.097 ± 0.615</td>
</tr>
<tr>
<td>Maximum carotid IMT (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.05 ± 0.292</td>
<td>1.106 ± 0.404</td>
<td>1.358 ± 0.713</td>
</tr>
<tr>
<td>Women (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean common carotid IMT (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.492 ± 0.070</td>
<td>0.508 ± 0.080</td>
<td>0.530 ± 0.096</td>
</tr>
<tr>
<td>Mean bifurcation carotid IMT (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.746 ± 0.197</td>
<td>0.777 ± 0.254</td>
<td>0.892 ± 0.388</td>
</tr>
<tr>
<td>Maximum carotid IMT (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.927 ± 0.244</td>
<td>0.969 ± 0.305</td>
<td>1.118 ± 0.496</td>
</tr>
</tbody>
</table>

Values are ± SD. Tertiles cut-points for plasma viscosity are 1.197 and 1.234 mPa.s. n = number.

Model A: Adjusted for age, waist-to-hip ratio, current smoking, hypertension, hypercholesterolemia, and diabetes. Model B: same covariates as Model A plus fibrinogen.

FIG. 1. Percent of subjects with carotid artery atherosclerosis in men and women according to plasma viscosity tertiles.
TABLE 3. GENDER-SPECIFIC ODDS RATIOS FOR CAROTID ARtery ATHEROSCLEROSIS IN RELATION TO EACH 1-SD INCREASE IN PLASMA VISCOSITY

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.27 (1.52–3.38)</td>
<td>1.63 (1.17–2.26)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>2.24 (1.43–3.50)</td>
<td>1.48 (1.07–2.05)</td>
</tr>
<tr>
<td>Multivariate-adjusted*</td>
<td>2.06 (1.27–3.36)</td>
<td>1.64 (1.07–2.52)</td>
</tr>
<tr>
<td>Plus fibrinogen</td>
<td>1.90 (1.02–3.54)</td>
<td>1.72 (1.20–2.48)</td>
</tr>
</tbody>
</table>

SD = standard deviation; CI = confidence interval.
* Adjusted for age, waist-to-hip ratio, cigarette smoking, hypercholesterolemia, hypertension, and diabetes.

least 1 cm of the artery, and the real values of thickness were calculated as the average of at least 100 measures. The lack of association between plasma viscosity and CCA-IMT is not discrepant with the results observed in the EAS cohort, because the approach that quantifies the maximum IMT may identify an advanced status of arterial thickening. Our study also included maximum IMT, with results similar to those of the EAS cohort for men. We also observed a positive relationship between maximum IMT and plasma viscosity in women.

A striking result of our study concerns the loss of the association of plasma viscosity with BCA-IMT and MxCA-IMT only in men when fibrinogen was introduced into the multiple regression. Fibrinogen is associated with most of the cardiovascular risk factors and with carotid IMT, is a strong predictor of cardiovascular events, and related to subclinical extracoronary and coronary atherosclerosis. However, the respective roles of plasma viscosity and fibrinogen to estimate cardiovascular events were difficult to differentiate in the Caerphilly and Speedwell studies. The fact that the relationship between plasma viscosity and BCA-IMT and MxCA-IMT was difficult to differentiate in the Caerphilly and Speedwell studies. The fact that the relationship between plasma viscosity and BCA-IMT and MxCA-IMT was successful only independent of fibrinogen for women may be attributable to the difference in gender interindividual variance in plasma viscosity and fibrinogen. The correlations of plasma viscosity and fibrinogen were 0.71 for men and 0.62 for women, suggesting that the higher interindividual variance in plasma viscosity in men (51%) than in women (39%), attributable to the variance in fibrinogen, can explain the gender difference observed in the study.

Another aspect contributing to the fibrinogen-independent relation of arterial thickening and plasma viscosity concerns the severity and extension of atherosclerosis. Our study includes the identification of focal areas of disease or arterial plaques on the overall carotid tree, defined as an echogenic structure encroaching into the vessel lumen and having a distance between the media-adventice interface and the lesion surface > 2 mm. We found that the presence of confirmed subclinical carotid artery atherosclerosis was strongly related to the higher values of plasma viscosity. Indeed, of the 30 men and 29 women having a focal disease area, 67% and 72%, respectively, were included in the higher tertile of plasma viscosity. After controlling for age and other risks factors, the strength of having carotid artery atherosclerosis in relation to plasma viscosity remained significantly elevated. Further adjustment for plasma fibrinogen level had very little effect and the statistical significance still remained high. These results strongly suggest that rheologic modification of blood may play a role in atherogenesis, namely, in the severity of arterial disease.

In conclusion, the results of the present study indicate that plasma viscosity was independently associated with carotid artery atherosclerosis and strengthen the hypothesis that increased plasma viscosity may be one mechanism linking rheologic factors to atherogenesis, namely in the carotid segments in which fluid blood can disturb.

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