Relation of Blood Viscosity to Demographic and Physiologic Variables and to Cardiovascular Risk Factors in Apparently Normal Adults

Giovanni de Simone, MD, Richard B. Devereux, MD, Shu Chien, MD, PhD, Michael H. Alderman, MD, Steven A. Atlas, MD, and John H. Laragh, MD

Although increased blood viscosity occurs in several cardiovascular diseases, little is known of factors influencing blood rheology in normal adults. Accordingly, we examined the relations of whole blood viscosity (WBV) to its rheologic determinants (hematocrit level, plasma viscosity, protein concentration, and red cell aggregability and rigidity), to demographic and laboratory variables, and to cardiovascular risk factors in 128 normotensive employed adults. Hematocrit levels accounted for 67–84% of variability of WBV at shear rates from 208 to 0.1 sec\(^{-1}\) with lesser contributions from plasma viscosity, red cell aggregability, and rigidity (multiple \(r=0.95–0.97\)); WBV was predicted accurately from standard measurements of hematocrit and total plasma protein levels (multiple \(r=0.78–0.92\) in “learning” and “test” analysis). Male sex, obesity, dietary Na\(^+\) intake, and increasing age had additive effects on WBV (multiple \(r\geq0.59, p<0.00001\); the last three of these factors and black race independently predicted plasma viscosity (multiple \(r=0.36, p<0.001\)). Among regulators of plasma volume, plasma renin activity and urinary Na\(^+\) excretion bore independent positive relations to WBV. Diastolic and mean blood pressures were independent predictors of WBV and hematocrit levels (all \(p<0.05\)). Conventional risk factors (e.g., triglycerides, obesity, and cholesterol levels) were positively related to WBV or plasma viscosity. Thus, in apparently normal adults, 1) WBV or plasma viscosity are increased by male sex, obesity, high sodium intake, aging, and black race, 2) WBV is positively related to plasma renin activity, 3) WBV or plasma viscosity are related to diastolic and mean blood pressures, triglycerides and cholesterol concentrations, and 4) WBV can be predicted from simple measurements of hematocrit and total plasma protein levels. (Circulation 1990;81:107–117)

Changes in whole blood viscosity (WBV) have been reported in several human cardiovascular diseases,\(^1\)–\(^22\) indicating that blood viscosity may be a major cardiovascular risk factor. A positive relation between blood pressure and blood viscosity or components of blood viscosity has been reported in renovascular and essential hypertension.\(^2\)–\(^8\) Blood viscosity has also been implicated as a determinant of hypertensive cardiac hypertrophy,\(^6\)–\(^8\) and associations have been shown between elevated blood viscosity and peripheral vascular disease.\(^9\)–\(^14\)

Moreover, elevated blood viscosity may be a determinant of coronary artery disease; either indirectly because of its relation with systemic hypertension, a major coronary risk factor, or because of its amplification of the resistance produced by a given degree of coronary artery narrowing, with adverse effects on clinical manifestations of coronary disease\(^15\)–\(^19\) and on maximal myocardial oxygen delivery.\(^20\) Finally, high hematocrit levels adversely affect cerebral blood flow\(^21\) and augment risk of stroke.\(^22\)

Although the above evidence indicates that blood viscosity may be a determinant of cardiovascular morbidity and mortality, relatively little is known of
the relation of blood viscosity to standard cardiovascular risk factors, or of the expected relation of blood viscosity to demographic and laboratory variables in normal subjects, as needed to identify deviations related to defined cardiovascular diseases.

Accordingly, we have studied WBV and its components in an apparently healthy normal population to assess the relation of blood rheology to demographic variables, factors involved in blood volume regulation and sodium homeostasis, and established cardiovascular risk factors. Additional goals of the study were to develop simple equations for predicting WBV from readily available laboratory measurements, to test prospectively the accuracy of these predictions, and to determine the year-to-year biologic variability of WBV and its components in apparently normal adults.

**Methods**

**Subjects**

Subjects were drawn from a cohort representative of normotensive members of a large employed population in New York City as previously described in part. Among 139 potentially eligible subjects, 11 (8%) were excluded because of historic, clinical, or laboratory evidence of cardiovascular, respiratory, endocrine, hepatic, renal, or hematologic disorders; abnormal hemoglobin or hematocrit values; or use of medications. The remaining 128 apparently normal subjects who were studied consisted of 75 men (44 white and 31 black) and 53 women (29 white and 24 black) ranging in age from 27 to 75 years (mean age, 52±12 years). After informed consent was obtained, blood samples were drawn for complete rheologic study on the same morning that echocardiographic testing was performed on one to three occasions between 1985 and 1987. These subjects did not differ in age, sex, race, or blood pressure from the 11 excluded subjects or from other potentially eligible members of this cohort in whom blood viscosity was not determined for logistic reasons.

On the same day as blood viscosity measurements were obtained, in most patients, blood samples were obtained for determinations of plasma renin activity (PRA), atrial natriuretic factor (ANF), cholesterol, triglycerides, glucose, plasma protein fractions, fibrinogen and creatinine; 24-hour urine collection was completed to measure excretion of aldosterone, Na+, K+, and creatinine. Arterial blood pressure was measured by arm cuff and mercury manometer with the subject in recumbent position at the end of echocardiographic testing. The first and fifth Korotkoff phases were taken as systolic and diastolic blood pressures, respectively.

**Rheologic Measurements**

Blood samples were obtained, without stasis, from the antecubital vein between 9:00 AM and noon, after an overnight fast, on the same morning as the echocardiographic study. Four determinants of WBV have been considered in this study: hematocrit level, which reflects the relative red blood cell volume, plasma viscosity, red blood cell aggregability, and red blood cell rigidity.

Microhematocrit levels were determined in duplicate by centrifuging the sample at 15,000g for 5 minutes and was corrected for plasma trapping. Plasma and serum protein concentrations were determined using a refractometer (Bausch & Lomb). Plasma fibrinogen was estimated with the method of Ratnoff and Menzie. Protein fractions were measured by means of microzone electrophoresis on cellulose acetate strips.

WBV was determined with a rotational viscosimeter constructed at Columbia University. This instrument has a coaxial cylinder setup with an annular clearance of 0.96 mm in which the sample is placed. The controlled rotation of the inner cylinder results in the transmission of torque to the outer cylinder seated on an airbearing, which is servocontrolled to maintain a constant position by the feedback application of a magnetic counter torque. With the geometry of the cylinders, the shear rate can be calculated from the rotational speed. The viscosity was calculated from the ratio of the torque measurement to the rotational speed with the use of a calibration factor determined with a viscosity standard oil. Viscosity measurements were made at shear rates of 208, 104, 52, 5.2, 0.5, and 0.1 inverse seconds (sec⁻¹); these shear rates approximately encompass the velocity gradients of blood flows in the circulatory system. Plasma viscosity was measured at 52 and 0.5 sec⁻¹, and because this parameter is shear-rate independent, the results were averaged. Duplicate measurements on the same samples agreed better than 5%.

Moreover, because the anomalous dependence of blood viscosity on shear rate can be attributed mainly to the shear-dependent aggregation and deformation of red blood cells, both of these rheologic variables have been estimated with red blood cell suspensions at standardized cell concentration either in autologous heparinized plasma or in 11% albumin-Ringer solution. Both types of cell suspensions were adjusted to a cell volume percentage of 45% and were studied at 208, 104, 52, 5.2, and 0.5 sec⁻¹. This adjustment was necessary to limit the effect of different hematocrit levels on the blood viscosity values; in this way, viscosity of the suspension in heparinized plasma could be attributed mostly to the aggregability of red blood cells, induced by the presence of plasma proteins. Suspension of red cells in albumin-Ringer solution excluded also the possibility of formation of aggregates because of the absence of plasma proteins; thus, the viscosity of this suspension reflects primarily the effect of red blood cell rigidity. For convenience, measurements of viscosity by these two methods will be called red blood cell aggregability and red blood cell rigidity.

All measurements were performed at 37°C.
TABLE 1. Analysis of the Rheologic Determinants of Whole Blood Viscosity in a Normotensive Adult Population Sample

| WBV shear rate (sec⁻¹) | % Contribution | Multiple R² | F     | SE     | p<  
|-----------------------|----------------|-------------|-------|--------|------
| Hct                   | PIv            | RBCA        | RBCR  |        |      |
| 208                   | 76             | 3           | 8     | 3      | 0.95 | 208  | 0.2  | 0.00001 |
| 104                   | 72             | 3           | 12    | 3      | 0.95 | 220  | 0.2  | 0.00001 |
| 52                    | 74             | 3           | 11    | 2      | 0.95 | 212  | 0.2  | 0.00001 |
| 5.2                   | 84             | 9           | 1     | ...    | 0.97 | 451  | 0.5  | 0.00001 |
| 0.5                   | 67             | 1           | 23    | ...    | 0.96 | 362  | 2.7  | 0.00001 |

The percent contribution of each rheologic variable was computed as $R²$ change from previous step in the stepwise model.

WBV, whole blood viscosity; Hct, hematocrit; PIv, plasma viscosity; RBCA, red blood cell aggregability; RBCR, red blood cell rigidity.

Plasma Renin Activity, Aldosterone, and Atrial Natriuretic Measurements

PRA was determined by radioimmunoassay of the angiotensin I formed during a 3-hour incubation of plasma at pH 5.7, in the presence of angiotensinase and converting enzyme inhibitors. Urinary aldosterone was measured by radioimmunoassay with a commercially available antibody (Serono).

Plasma ANF was determined with subjects seated shortly before the echocardiographic study. Blood sample were measured by radioimmunoassay with homologous α-human atrial natriuretic peptide antiserum (Peninsula Laboratories, Belmont, California) as previously described in detail.

Blood Biochemical Determinations

Daily salt intake was estimated by determining the 24-hour urinary excretion of sodium. With the same urine collection, the 24-hour excretions of potassium and creatinine were also evaluated with standard analytical techniques. Plasma levels of cholesterol, triglycerides, and glucose were also determined, after at least a 12-hour fast, with standard analytical techniques.

Statistical Analysis

Group mean±SD are reported. Age, sex, race, body size, and salt excretion were used as demographic variables. Obesity was assessed with the body mass index, calculated as the ratio of weight in kilograms to the square of height in meters. Differences in blood viscosity due to sex and race were assessed with the Student's $t$ test, whereas least-squares linear correlation was used to test bivariate relations of viscosity to age, body mass index, and urinary Na⁺ excretion. One- or two-way analysis of variance was used to separate the effects of race, sex, and body mass index, and the Scheffé test was used, when appropriate, for post-hoc comparison. Forward stepwise multiple linear regression analysis was used to identify the demographic variables independently related to blood viscosity.

Cholesterol, triglycerides, glucose, and blood pressure, as well as PRA, ANF, urinary aldosterone, and urinary Na⁺, were treated as independent variables with blood viscosity as the dependent variable, with the effect of demographic variables removed by the technique of partial correlation. Because some measurements were not available in every subject, the occurrence of missing values was taken into account in statistical analyses.

Finally, stepwise multiple regression analysis was used to determine whether WBV at different shear rates could be estimated from readily available measurements of hematocrit and plasma protein concentrations. The accuracy of such equations was tested by using them to predict WBV on a separate occasion, 1 year before or after the index viscosity determination, in 53 subjects. Biologic variability of blood viscosity was assessed by comparing blood viscosity values obtained in different years in the same subjects.

Results

Of the determinants of WBV, hematocrit level was the most important, explaining 69–84% of the variability of WBV (Table 1); among the other determinants, red blood cell aggregability was more important at most shear rates than was plasma viscosity, whereas estimated red blood cell rigidity contributed to the prediction of WBV only at relatively high shear rates.

The protein fractions β1, γ, and fibrinogen were the main determinants of plasma viscosity (53% of the variance). Albumin and α-fractions were also independently and directly correlated to plasma viscosity, but the increase in explained variance was rather low (7%) ($n=117$, multiple $R²=0.63$ for all protein fractions, $F=28$, $p<0.00001$).

Relation Between Demographic Parameters and Blood Viscosity: Sex and Race

Table 2 shows that black men had higher diastolic blood pressures than white men ($p<0.006$) and white women ($p<0.004$) but not black women, and white men had significantly higher PRA and triglycerides levels than black women. However, no difference was found in age and body mass index, or other volume regulatory hormones (ANF and aldosterone) or risk factors between race-sex groups.
WBV was markedly higher in men than in women at every shear rate \((p<0.00001)\), mainly because of higher hematocrit levels \((p=0.00001)\). This sex difference was maintained also in red blood cell aggregability \((p=0.0007-0.0001)\) and rigidity \((p=0.0004-0.00001)\) at all shear rates, two measures of blood viscosity independent of hematocrit level, whereas no sex difference was found in plasma viscosity. Blacks showed higher plasma viscosity \((1.41\pm0.11 \text{ vs. } 1.36\pm0.09 \text{ cP}; p<0.02)\) and a greater red blood cell aggregability at 0.5 sec\(^{-1}\) \((40.66\pm4.46 \text{ vs. } 38.36\pm5.41 \text{ cP}; p<0.01)\), but they did not differ from whites in WBV; \(\beta\)- and \(\gamma\)-globulin levels were also higher in blacks than in whites \((p<0.05)\).

Sex influenced hematocrit levels and WBV independently of race (Figure 1). Men also had increased red blood cell aggregability at 104 sec\(^{-1}\) \((p<0.05)\) and rigidity at 208, 104, and 52 sec\(^{-1}\) \((0.02<p<0.0006)\), but these sex differences were significant only for the white population.

**Age**

Weak positive correlations were also found between age and WBV at 0.5 sec\(^{-1}\) \((p<0.02)\), red blood cell aggregability at 52 sec\(^{-1}\) \((p<0.03)\), and plasma viscosity \((p<0.05)\), possibly because positive correlations between age and \(\alpha_1\)-, \(\alpha_2\)-, and \(\beta_1\)-globulins \((n=127, r=0.23, 0.25, \text{ and } 0.29, \text{ respectively}; 0.008<p<0.0008)\).

**Obesity**

Significant direct correlations were found between body mass index and WBV at every shear rate \((r=0.27-0.33; 0.004<p<0.0002)\), attributable to rela-
tions of body mass index to hematocrit level \((p<0.04)\) and plasma viscosity \((p<0.02)\). No relation was detected between obesity and red blood cell aggregability or rigidity.

Because univariate analysis indicated that body size may be as important as sex in determining blood viscosity values, the population sample was divided into normal and overweight subjects, with body mass index partition values \(\leq 25\) kg/m\(^2\) for women and \(\leq 27\) kg/m\(^2\) for men.\(^{35}\) Analysis of blood viscosity was performed after stratification for sex, race, and body mass index with two-way analysis of variance. Body mass index exerted a significant independent influence on hematocrit level, plasma viscosity, and WBV at all shear rates. Figure 2 shows the effect of body mass index on sex- and race-adjusted average values of WBV at shear rates of 208, 104, and 52 sec\(^{-1}\) as well as hematocrit level and plasma viscosity; the effect on WBV at lower shear rates was of the same magnitude \((p<0.0001)\). Moreover, among the protein fractions, body mass index was directly and independently related to the levels of fibrinogen \((p<0.01)\).

**Blood Pressure**

Systolic, diastolic, and mean blood pressure were directly correlated to WBV at all shear rates \((r=0.24–0.26\) for systolic blood pressure, \(r=0.24–0.28\) for diastolic blood pressure, and \(r=0.26–0.29\) for mean blood pressure, \(0.007<p<0.0001)\). Significant relations were also found between blood pressure and hematocrit level \((r=0.19, 0.20, \) and 0.21, respectively, all \(p<0.05)\) and plasma viscosity \((r=0.21, 0.24,\) and 0.25, respectively, all \(p<0.01)\). Systolic blood pressure was correlated to age in the entire population sample \((r=0.40, p<0.00001)\). Table 3 shows that black race, age, WBV at 208 sec\(^{-1}\), and body mass index were independent predictors of mean blood pressure \((\text{multiple } r=0.51, \text{SEE}=10 \text{ mm Hg}, p<0.000001)\). Blood viscosity at 208 sec\(^{-1}\) was also an independent predictor of diastolic blood pressure \((\text{multiple } r=0.44, \text{SEE}=9, p<0.000001)\) but not of systolic blood pressure. After removing the effect of age, race, and body mass index, by partial correlation, a significant independent relation existed between diastolic and mean blood pressure and WBV at all shear rates as well as hematocrit levels \((p=0.17–0.23, \text{all } p<0.05)\).

**Salt Intake**

Urinary \(Na^+\) excretion was positively related to WBV at every shear rate \((n=115, \text{partial } r=0.28–0.38, p<0.004)\), independently of sex and PRA, which had been shown to be related to \(Na^+\) excretion in preliminary analyses because of positive relations between \(Na^+\) excretion and hematocrit levels \((\text{partial } r=0.29, p<0.002)\) and plasma viscosity \((\text{partial } r=0.25, p<0.005)\). Positive independent relations were also found for \(Na^+\) excretion with total plasma proteins \((\text{partial } r=0.26, p<0.004)\) and y-globulin \((\text{partial } r=0.21, p<0.05)\). No correlation was detected between urinary \(Na^+\) excretion and red blood cell aggregability or rigidity.

**Multivariate Relations of Demographic Factors to Blood Viscosity**

In multivariate analyses, sex and race were treated as categorical variables, assigning the value 1 to women and blacks and 2 to men and whites. Table 4 shows results of the analysis. Male sex and higher body mass index, urinary \(Na^+\) excretion, and age were independently related to WBV at all shear rates.

**Table 3. Multivariate Analysis of Predictors of Blood Pressure in Normotensive Adults**

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>% Contribution</th>
<th>Sex</th>
<th>BMI</th>
<th>UNa</th>
<th>Age</th>
<th>Race</th>
<th>WBV</th>
<th>Multiple R</th>
<th>SD</th>
<th>F</th>
<th>p&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>...</td>
<td>4</td>
<td>...</td>
<td>15</td>
<td>6</td>
<td>...</td>
<td>...</td>
<td>0.50</td>
<td>10</td>
<td>13</td>
<td>0.00001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>...</td>
<td>2</td>
<td>...</td>
<td>11</td>
<td>6</td>
<td></td>
<td></td>
<td>0.44</td>
<td>7</td>
<td>9</td>
<td>0.00001</td>
</tr>
<tr>
<td>Mean</td>
<td>...</td>
<td>3</td>
<td>...</td>
<td>8</td>
<td>10</td>
<td>6</td>
<td></td>
<td>0.51</td>
<td>7</td>
<td>10</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

The percent contribution of the demographic variables and whole blood viscosity was computed as \(R^2\) change from previous step in the stepwise model.

BMI, body mass index; UNa, 24-hour \(Na^+\) urinary excretion; WBV, whole blood viscosity at the shear rate of 208 sec\(^{-1}\).
Plasma relation of biochemical urinary aldosterone subjects

Body mass aldosterone was involved in a significant difference, especially among black subjects (p<0.01, Table 2).

The relation of the hormones (PRA, ANF, and aldosterone) involved in blood volume regulation to WBV was assessed, independently of age, sex, race, body mass index, and urinary Na⁺ excretion, with the partial correlation coefficient procedure. Table 5 shows that PRA was directly related to WBV at 208, 104, 52, 5.2, and 0.5 sec⁻¹, independently of sex and race, which were its demographic determinants (n=120, partial r=0.20–0.27, 0.03<p<0.008). PRA was also independently related to hematocrit levels (n=115, partial r=0.22, p<0.02). No correlation was found between 24-hour urinary aldosterone and rheologic parameters.

ANF was inversely related to WBV at 208, 104, and 52 sec⁻¹ (r=−0.26–0.29, 0.02<p<0.008); after removing the significant independent effects of age and urinary Na⁺ excretion, the partial correlation coefficient approached but did not reach statistical significance (0.08<p<0.06) at higher shear rates.

Relation Between Blood Viscosity and Conventional Risk Factors

Conventional risk factors were equally prevalent in the different race-sex subgroups with the exception of

<table>
<thead>
<tr>
<th>Table 4. Multivariate Analysis of Demographic Determinants of Whole Blood Viscosity in Normotensive Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBV shear rate (sec⁻¹)</strong></td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>208</td>
</tr>
<tr>
<td>104</td>
</tr>
<tr>
<td>52</td>
</tr>
<tr>
<td>5.2</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>0.1</td>
</tr>
<tr>
<td>Hematocrit</td>
</tr>
<tr>
<td>Plasma viscosity</td>
</tr>
</tbody>
</table>

The percent contribution of the demographic variables was computed as R² change from previous step in the stepwise model.

WBV, whole blood viscosity; BMI, body mass index; UNa, 24-hour Na⁺ urinary excretion.

Table 5. Plasma Renin Activity and Whole Blood Viscosity in Normotensive Adults

<table>
<thead>
<tr>
<th>Factors</th>
<th>% Contribution</th>
<th>F</th>
<th>p&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>12</td>
<td>18</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>6</td>
<td>9</td>
<td>0.003</td>
</tr>
<tr>
<td>Sex</td>
<td>...</td>
<td>0.5</td>
<td>NS</td>
</tr>
<tr>
<td>UNa</td>
<td>...</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>...</td>
<td>0.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age- and race-adjusted relation between plasma renin activity and whole blood viscosity in normotensive adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBV shear rate (sec⁻¹)</strong></td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>208</td>
</tr>
<tr>
<td>104</td>
</tr>
<tr>
<td>52</td>
</tr>
<tr>
<td>5.2</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>0.1</td>
</tr>
</tbody>
</table>

UNa, 24-hour urinary Na⁺ excretion; BMI, body mass index; WBV, whole blood viscosity.
triglyceride levels over 200 mg/100 ml, which were disproportionately frequent in white men (nine of 44 or 20% vs. five of 84 or 6% in the remaining subjects); hematocrit levels showed the most striking sex difference (p<0.00001) (Table 2). Fifteen or 11% of subjects smoked moderately. Comparison of the smoking group with a nonsmoking group matched for sex (eight men and seven women) age (mean, 49±10 years), race (nine blacks and six whites), and body mass index (25±4) revealed trends toward slightly higher viscosity in smokers that did not attain statistical significance at any shear rate (e.g., 4.8±0.6 vs. 4.5±0.6 cP at 104 sec⁻¹ and 82.5±17.8 vs. 79.5±19.2 cP at 0.1 sec⁻¹). Smoking did not enter as a significant categorical variable in any of the multiple regression analysis models evaluating factors independently related to WBV and its components. Furthermore, the results of the all the analyses of the rheologic data performed in this study were not affected by exclusion of the smokers.

No significant correlation was found between blood pressure and cholesterol, triglyceride, and glucose levels. However, in multivariate models, age, sex, and body mass index were independently related to plasma glucose levels (n=120, multiple r=0.44, p<0.00001); after removing the effect of these variables, no independent relation was found between glucose levels and WBV, hematocrit level, plasma viscosity, or red blood cell aggregability and rigidity.

Age and sex were independent determinants of plasma cholesterol (n=120, multiple r=0.46, p<0.00001), which was not independently related to WBV. Nevertheless, cholesterol levels showed a significant independent correlation with plasma viscosity (n=116, partial r=0.26, p<0.005), probably because of relations between cholesterol and α, and β, protein fractions (n=120, partial r=0.38 and 0.34, p<0.00001 and 0.0001, respectively), reflecting the protein binding of cholesterol; a significant correlation was also found between plasma cholesterol and α (partial r=0.24, p<0.009), β (partial r=0.21, p<0.02), and γ (partial r=0.18, p<0.05) protein fractions, independently of age and sex.

Race, sex, body mass index, and age were independently related to plasma triglycerides (n=120, multiple r=0.42, p<0.0001). After removing the effect of these demographic variables, a significant correlation was observed between plasma triglycerides and WBV at 104 (n=117, partial r=0.20, p<0.04), 52 (partial r=0.19, p<0.05), and 0.1 sec⁻¹ (partial r=0.21, p<0.04). Triglycerides showed also an independent correlation with red blood cell rigidity at 104, 52, 5.2, and 0.5 sec⁻¹ (n=88, partial r=0.22–0.23, p<0.04), but no correlation with hematocrit level, plasma viscosity, or red blood cell rigidity.

The independent relations of the six major risk factors considered (smoking, cholesterol, triglycerides, glucose, systolic blood pressure, and obesity) to WBV were also studied. At every shear rate, plasma triglycerides level was the closest correlate of blood viscosity among risk factors (Table 6). Body mass index was the second variable always present in the model, and systolic blood pressure entered the model only at 0.5 sec⁻¹. At every shear rate, 11–18% of the variance of blood viscosity could be explained by these models, which did not involve demographic determinants, except for body mass index, which is a measure of obesity, and systolic blood pressure.

**Prediction of Blood Viscosity From Hematocrit Level and Plasma Protein Determination**

In univariate analysis, WBV was closely related to hematocrit and plasma protein levels at all shear rates [r=0.81–0.89, p<0.00001 for hematocrit (SEE=0.36, 0.32, and 0.28 cP at 52, 104, and 208 sec⁻¹); r=0.39–0.45, p<0.00005 for plasma proteins]. Table 7 shows that hematocrit and total plasma protein levels yielded an excellent predictive model for WBV at every shear rate (multiple r=0.85–0.91). The accuracy of the equations was tested in 53 study subjects who had blood viscosity measured again at an interval of at least 1 year from their index evaluation. The biologic variability of blood viscosity was assessed by relating blood viscosity values of different years. Close correlations between measured WBV and that calculated from hematocrit and plasma protein levels on the second study were found at all shear rates (r=0.78–0.92, p<0.00001), whereas direct measurements of WBV in different years in the same individual were less closely correlated to each other.

### Table 6. Conventional Cardiovascular Risk Factors to Whole Blood Viscosity in Normotensive Adults

<table>
<thead>
<tr>
<th>WBV shear rate (sec⁻¹)</th>
<th>Standardized β coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smoking</td>
</tr>
<tr>
<td>208</td>
<td>...</td>
</tr>
<tr>
<td>104</td>
<td>...</td>
</tr>
<tr>
<td>52</td>
<td>...</td>
</tr>
<tr>
<td>5.2</td>
<td>...</td>
</tr>
<tr>
<td>0.5</td>
<td>...</td>
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<tr>
<td>0.1</td>
<td>...</td>
</tr>
</tbody>
</table>

In this model, only the coefficients are represented with single F step-values significant at p<0.05 (the F-to-enter of the analysis was 3.9). The standardized β coefficients indicate the importance of each independent variable on the variance of the dependent variable (whole blood viscosity).

WBV, whole blood viscosity; BMI, body mass index; SBP, systolic blood pressure.
Table 7. Predictive Analysis of Whole Blood Viscosity at Six Different Shear Rates in Normotensive Adults, by Using Hematocrit and Plasma Proteins

<table>
<thead>
<tr>
<th>WBV shear rate (sec(^{-1}))</th>
<th>Multiple R</th>
<th>SEE (cP)</th>
<th>F</th>
<th>p&lt;</th>
<th>Regression equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>208</td>
<td>0.88</td>
<td>0.3</td>
<td>232</td>
<td>0.00001</td>
<td>WBV=0.12 hematocrit+0.17 total plasma−2.07</td>
</tr>
<tr>
<td>104</td>
<td>0.87</td>
<td>0.3</td>
<td>191</td>
<td>0.00001</td>
<td>WBV=0.12 hematocrit+0.19 total plasma−2.13</td>
</tr>
<tr>
<td>52</td>
<td>0.87</td>
<td>0.3</td>
<td>199</td>
<td>0.00001</td>
<td>WBV=0.14 hematocrit+0.22 total plasma−2.60</td>
</tr>
<tr>
<td>5.2</td>
<td>0.91</td>
<td>0.8</td>
<td>311</td>
<td>0.00001</td>
<td>WBV=0.46 hematocrit+0.62 total plasma−14.25</td>
</tr>
<tr>
<td>0.5</td>
<td>0.87</td>
<td>4.8</td>
<td>124</td>
<td>0.00001</td>
<td>WBV=1.89 hematocrit+3.76 total plasma−78.42</td>
</tr>
<tr>
<td>0.1</td>
<td>0.86</td>
<td>9.1</td>
<td>169</td>
<td>0.00001</td>
<td>WBV=3.53 hematocrit+6.36 total plasma−119.47</td>
</tr>
</tbody>
</table>

WBV, whole blood viscosity.

\(r=0.47–0.82, \quad 0.0004<p<0.00001\) because of the variability of hematocrit levels \((r=0.78, \quad \text{SEE}=2\%\), \(p<0.00001\)), plasma viscosity \((r=0.57, \quad \text{SEE}=0.1 \text{ cP}, \quad p<0.00005\)) and plasma protein concentrations \((r=0.46, \quad \text{SEE}=0.56 \text{ g/100 ml}, \quad p<0.00007\)). As an example, Figure 3 shows the relations between predicted and observed viscosity and viscosity measured on different occasions at a shear rate of 208 sec\(^{-1}\).

Discussion

Blood is a non-Newtonian fluid because of the presence of blood cells, which causes blood viscosity to be shear rate dependent.\(^{30}\) As a consequence, hematocrit level was more important than plasma viscosity as a determinant of WBV (Table 1). Red blood cell aggregability depends on hematocrit and plasma protein concentrations,\(^{29}\) which is the main determinant of plasma viscosity and, hence, also a determinant of WBV. As expected, red blood cell rigidity contributed independently to WBV at the highest shear rates, which encompass the physiologic flow conditions in the microcirculation, especially the microvessels representing the sites of major resistance.\(^{28,30}\) The exceptionally close correlation between hematocrit levels and WBV at 5.2 sec\(^{-1}\) in this population sample appears to account for the unexpectedly low estimated contribution of red blood cell aggregability in the multivariate analysis.

Relation of Demographic Variables to Blood Rheology

Sex was the demographic variable most related to WBV. This difference was mostly due to the higher hematocrit levels in men, but is also persisted in measurements of blood viscosity performed at a standardized hematocrit level of 45% (red blood cell aggregability and rigidity). A sex influence on hematocrit level has been previously reported in large populations.\(^{34,36}\) Kaber et al\(^{36}\) reported significant sex difference in native blood viscosity, though they did not find any sex difference after rheologic data were normalized to a standard hematocrit level of 45% by means of regression equations. Differences in technical approach, as well as possible differences in subject selection, or in variable effects of other covariates such as body size, salt intake, blood pressure, age, and race may account for this apparent difference from our study with regard to red blood cell rigidity and aggregability.

The dependence of WBV on hematocrit level was most evident at the highest shear rates considered. Although these relations may reflect influences of sex on regulation of red cell mass, hematocrit level has also been shown to be inversely related to plasma volume,\(^{37,38}\) and more recently, a close inverse relation between hematocrit and ANF values has been reported in experimental\(^{39,40}\) and clinical studies.\(^{32}\) Thus, the sex-related difference in blood viscosity could also be influenced by sex-related differences in plasma volume regulation. Possible interdependence of plasma volume regulation and WBV is suggested in this study by the significant independent positive relation of blood viscosity to PRA and by the trend toward an independent negative relation with ANF levels. In the present study, ANF showed an inverse relation with WBV at several shear rates in bivariate analysis, which failed to reach statistical significance when age and urinary Na\(^+\) excretion were considered in multivariate analyses. Because under normal circumstances, urinary Na\(^+\) excretion reflects salt intake, the strong influence of Na\(^+\) excretion on WBV also suggests that high salt diets increase blood viscosity, probably by enhancing water excretion\(^{41}\); these findings raise the possibility that blood viscosity may play a role in sodium-induced systemic hypertension\(^{42}\) as well as the increased risk of vascular damage and cardiac hypertrophy associated with high salt diets.\(^{24,43–45}\)

Although no direct measurement of plasma volume has been performed in this study, our findings suggest that plasma volume is most likely involved in the significant direct relation between blood pressure and blood viscosity, which parallels previous findings demonstrating inverse relations between plasma volume and diastolic blood pressure and total peripheral resistance in hypertensive and normotensive subjects.\(^{46–48}\)
and insulin levels, reported in obese subjects, may explain the association between obesity and high plasma viscosity we found in this study.

Relation of Conventional Risk Factors to Blood Rheology

This study shows that an increase in several conventional risk factors is associated with and may contribute directly to increases in blood viscosity.

Body habitus has been considered a demographic variable and a risk factor, in accord with evidence relating obesity to cardiovascular risk. Univariate and multivariate analyses revealed possible relations between body mass index and WBV at all shear rates. Smoking is the most explored risk factor in relation to blood viscosity and a correlation between smoking and increased blood viscosity and hematocrit level is well known, especially among heavy smokers. In our population sample, the number of smokers was low (only 15 of 129 subjects), and none smoked heavily. Accordingly, the lack of a significant relation between smoking and blood rheology in our data may indicate that the smoking "stimulus" was too small to produce a detectable effect. We studied the relation between blood viscosity and risk factors after removing the effect of demographic variables known to influence risk factors. Our findings indicated that plasma triglyceride levels were positively related to blood viscosity, apparently through an association with red blood cell rigidity. Ankelkort and Kiesewetter reported that cholesterol and triglycerides cause rigidification of erythrocytes because of metabolic relations between lipoprotein fractions and cell membrane. In the present study, the total cholesterol level was found to be related to plasma viscosity, possibly because of the strong relation between cholesterol and plasma lipoproteins. No relation was found between plasma glucose levels and blood viscosity or its determinants, probably because the minimal hyperglycemia present in some subjects was not sufficient to cause alteration in red blood cells.

Prediction of Blood Viscosity From Hematocrit Levels and Plasma Protein Determinations

In this study, we also developed and performed a preliminary prospective test of the accuracy of simple regression equations to predict WBV from hematocrit and total plasma protein levels, which are generally available laboratory tests. The prediction of WBV from these equations showed a degree of error that was smaller than the relatively modest biologic variability between blood viscosity measurements on separate occasions in the same subjects. The advantage of our equations compared with previously reported equations derived solely from hematocrit values is that addition of plasma protein concentration reduced the standard deviation of predicted WBV about the regression line by 10–15% compared with prediction obtained with hematocrit values alone. One factor preventing such equations from predicting blood viscosity exactly is that plasma viscosity is
determined not only by the concentration but also by the charge and the shape of plasma proteins.\textsuperscript{58} Another limitation of the equations is that they are valid only throughout the range of hematocrit (32–53\%) and plasma protein concentrations (5.4–9.5 g/100 ml) observed in our subjects; therefore, these equations should not be applied to cases with values outside these ranges. Thus, prediction of WBV from hematocrit and total plasma protein concentrations, while not absolutely accurate, is precise enough to be potentially useful for cross-sectional and longitudinal studies of large population samples in which direct blood viscosity measurements cannot be performed for logistic reasons.

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KEY WORDS • blood pressure • sex • obesity • plasma proteins • hematocrit • triglycerides • cholesterol
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