Blood Viscosity in Waldenström’s Macroglobulinemia

By Mart Mannik

Erythrocytes and plasma proteins contribute to viscosity of blood. Therefore, blood viscosity was measured in 16 persons with macroglobulinemia with a cone-plate viscometer at defined shear rates. In each person a significant correlation \( p < 0.001 \) was found between hematocrit and the logarithm of blood viscosity. The regression equation of this relationship in each patient was used to calculate the blood viscosity at several hematocrits. The blood viscosity at a given shear rate and constant hematocrit was significantly correlated \( (p < 0.001) \) with the plasma macroglobulin concentration in g/100 ml. The plasma of patients with macroglobulinemia is a non-Newtonian fluid, but at a given shear rate the plasma viscosity is a function of the macroglobulin concentration. These observations allowed the construction of an equation for calculation of blood viscosity in patients with macroglobulinemia when the hematocrit and plasma macroglobulin concentrations are known.

The hyperviscosity syndrome was noted in the original description of macroglobulinemia by Jan Waldenström.\(^1\) The clinical symptoms and signs of the hyperviscosity syndrome have been correlated with relative serum viscosity, as determined with capillary viscometers.\(^2\) In these studies a high serum macroglobulin concentration tended to be associated with increased serum viscosity and clinical manifestations of the hyperviscosity syndrome. However, considerable variation was noted in the relationship between the serum relative viscosity and the onset of the hyperviscosity syndrome. Since red blood cells contribute significantly to the viscosity of blood,\(^3,4\) the viscosity of whole blood might be expected to correlate better than that of serum with the clinical manifestations of the hyperviscosity syndrome.

Viscosity of fluids [expressed in poise (P) or centipoise (cP)] is their resistance to flow, and it is expressed by the ratio of shear stress (force per unit area, dynes/sq cm) to shear rate. The difference in the velocity (cm/sec) of two fluid planes divided by the distance between them (cm) gives the value for shear rate in 1/sec or sec\(^{-1}\). In Newtonian (ideal) fluids the viscosity is independent of the shear rate; hence their viscosity can be measured by capillary viscometers without controlling the shear rate. In non-Newtonian fluids, including blood, the viscosity increases with decreasing shear rate, and, therefore, viscosity measurements should be obtained under known shear rates. Although all of the instruments used for measurement of viscosity in non-Newtonian fluids have some theoretical shortcomings for the measurement of blood viscosity,\(^3\) rotational viscometers have been most widely used for this purpose.\(^1-7\)
The above considerations suggest that blood viscosity in macroglobulinemia would depend on the hematocrit as well as on the macroglobulin concentration. Somer conducted extensive studies on the blood, plasma, and serum relative viscosity in patients with Waldenström's macroglobulinemia. He used a capillary viscometer with constant high shear rate and found that the mean relative blood viscosity of a group of patients with macroglobulinemia was not significantly higher than in normal persons, even though in some individual patients the blood viscosity was markedly elevated. On the other hand, Rosenblum and Asofsky found that, in macroglobulinemic mice, the relative blood viscosity, measured by capillary viscometer at high shear rate, was a function of both hematocrit and macroglobulin concentration.

In this study the blood viscosity was measured in patients with Waldenström's macroglobulinemia at defined shear rates with a cone-plate viscometer. The relationships between blood viscosity, hematocrit, and macroglobulin concentration were examined, and an equation was constructed for calculation of blood viscosity from known hematocrit and macroglobulin concentration.

MATERIALS AND METHODS

Patients Subjected to Study

Ten or twenty milliliters of blood was obtained for study from patients who had either macroglobulinemia or benign monoclonal hypergammaglobulinemia with an IgM protein. The presence of macroglobulinemia was established by serum protein electrophoresis on cellulose acetate membranes and by immunoelectrophoretic identification of the IgM monoclonal protein. The patients with macroglobulinemia had a progressive clinical course and required appropriate therapy. The presence of benign monoclonal hypergammaglobulinemia was suspected in patients who were asymptomatic, had no Bence Jones proteins, and showed no increase of the monoclonal protein during followup of 1–2 yr. The patients are listed in Table 1 with their diagnosis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Macroglobulin Concentration (g/100 ml)</th>
<th>Hematocrit (%)</th>
<th>Plasma Viscosity 115 sec (cP)</th>
<th>Blood Viscosity 115 sec (cP)</th>
<th>Blood Viscosity 11.5 sec (cP)</th>
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<td>AP</td>
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*M, Waldenström's macroglobulinemia.
†BMH, benign monoclonal hypergammaglobulinemia with macroglobulin.
macroglobulin concentration, original hematocrit, plasma viscosity at 115 sec$^{-1}$, and blood viscosity at 115 and 11.5 sec$^{-1}$.

**Viscosity Measurements**

The blood viscosity was measured with a LVT1/2 Wells-Brookfield cone-plate viscometer, equipped with eight shear rates, ranging from 230 to 1.15 sec$^{-1}$ (Brookfield Engineering Laboratories, Inc., Stoughton, Mass.). The temperature of the sample cup was maintained during all measurements at 37.0°C ± 0.5°C with a constant-temperature water circulator. Standard oils (Cannon Instrument Co., State College, Pa.) with known viscosity were used as standards for viscosity at 37°C. The reproducibility of viscosity measurements was less than ±4% (2 SD) of the stated viscosity when the scale readings were over 5.0 on the viscometer.

Blood specimens were obtained from normal persons and 16 patients. Clotting was prevented by the addition of 100 U of heparin in 0.10 ml for every 10 ml of blood. All measurements were conducted on the day the blood was drawn. However, storage at 4°C overnight did not alter the viscosity. Prior to viscosity measurements, the fluids were warmed to 37.0°C, a 1.50-ml aliquot of the fluid (blood, plasma, or standard oil) was pipetted into the cup of the viscometer, the chamber was closed, and the fluid was “sheared” at 60 rpm for 5 min prior to the first reading to permit temperature equilibration. Subsequent readings were taken at lower shear rates after the torque indicator had stabilized. Prior to charging the instrument with another specimen, the cone was removed; the plate and the cone were thoroughly cleaned with soap and distilled water. The gap between the cone and the plate was adjusted prior to the next experiment.

Hematocrit of the macroglobulinemic or normal blood was varied by either removal or addition of autologous plasma. The hematocrit was determined with an International Micro-Capillary Centrifuge (International Equipment Co., Needham Heights, Mass.). All blood samples were fully mixed by 15-20 gentle inversions of the tube to achieve complete mixing of cells and plasma prior to sampling for hematocrit and viscosity measurements.

**Protein Studies**

The total protein of each plasma sample was determined by refractometry with a TS meter (American Optical Corp., Buffalo, N.Y.). An aliquot of the same sample was submitted to electrophoresis on cellulose acetate membrane in a Beckman Microzone cell (Beckman Instruments, Fullerton, Calif.) under standard conditions. The membranes were stained with Ponceau S stain and scanned by densitometer. The protein peak was carefully delineated and the concentration of Waldenström's macroglobulin was then calculated from the total serum protein and the percentage of protein under the peak. No attempt was made to allow for normal plasma proteins that were present under the macroglobulin peak. Hereafter, the Waldenström's macroglobulin will be referred to as macroglobulin for ease of expression.

**Analysis of Data**

Once the viscosity of normal blood was measured at several hematocrits, the hematocrit was plotted against linear and logarithmic values of the measured viscosity in centipoise. Since this plot did not suggest a simple relationship between the two parameters, and since a fifth-power polynomial relationship had been described between hematocrit and the logarithm of blood viscosity, the data were analyzed for polynomial regression with the BMD 05R program using a CDC 6400 computer. The best mathematical description of the relationship between the measured values was judged by the highest F value.

The measured blood viscosity at several hematocrits in each patient was analyzed as the dependent variable of the hematocrit. A linear regression between hematocrit and logarithm of blood viscosity was calculated for each patient, thus permitting the calculation of blood viscosity of each patient at hematocrits of 0%, 20%, 30%, and 40%. These calculated blood viscosity values at constant hematocrit were then related to the macroglobulin concentration.

In order to construct an empirical equation between the measured blood viscosity and the hematocrit and macroglobulin concentration, the measured blood viscosities at all hematocrits and macroglobulin concentrations were analyzed with the BMD 03R program for multiple regression. The viscosity values, or logarithms thereof, were analyzed against linear and logarithmic
values of hematocrit and macroglobulin concentration as the two independent variables. The best fit for the relationships was judged by the highest F value.

RESULTS

Studied on Normal Blood

Blood was obtained from four normal persons, and the hematocrit was varied from 5% to 64% by addition or removal of plasma. Viscosity measurements were performed at 115 sec\(^{-1}\) on plasma and blood specimens. Nine to 15 different hematocrit values were examined on each blood specimen. The hematocrit and viscosity values were analyzed by computer to determine the best equation to describe the relationship between these measurements. The best fit was obtained when the hematocrit was related to the logarithm of viscosity by a fourth power polynomial (see Fig. 1). Of note is that above the hematocrit of 60%, the viscosity rose precipitously due to the last term in the equation.

The viscosity of red blood cells, obtained from two normal persons and washed free of plasma proteins, suspended in phosphate-buffered saline, was measured at several hematocrits. These data are also plotted in Fig. 1. The relationship between hematocrit (up to hematocrit 55%) and viscosity was described by a linear equation between the hematocrit and logarithm of viscosity.

Studies on Macroglobulinemic Bloods

Each time blood was obtained from a patient, the blood viscosity was measured at the original hematocrit, as well as at other hematocrits achieved by removal or addition of plasma. The blood and plasma of all patients with macroglobulinemia behaved as non-Newtonian fluids, i.e., the viscosity increased with the decrease of shear rate (see Fig. 2). In patients with high levels of macroglobulin, the blood viscosity could not be measured at 230 sec\(^{-1}\) because the readings on the viscometer exceeded the scale. However, in most pa-
patients, readings could be obtained at 115 sec⁻¹, but even at this shear rate the viscosity could not be measured with all specimens when the blood was adjusted to high hematocrits. Since the shear rate in arterioles has been calculated to be around 100 sec⁻¹, the data obtained at 115 sec⁻¹ were selected for detailed analysis. Also, data obtained at 11.5 sec⁻¹ were examined in detail.

The blood viscosities of each patient at 115 and 11.5 sec⁻¹ were plotted against hematocrit. A linear relationship existed between the hematocrit and logarithm of blood viscosity in all patients. The correlation coefficients ranged from 0.9820 to 0.9999 (for all coefficients $p < 0.001$) for this relationship. In Fig. 3 the viscosities at 115 sec⁻¹ are plotted against hematocrits for four macroglobulinemic bloods. Similar relationships existed at shear rates of 11.5 sec⁻¹.

\[ \log(\eta) = a \times \text{Hct} + b, \]

where $\eta$ is the viscosity, Hct is the hematocrit, and $a$ and $b$ are constants. The correlation coefficients for each patient are indicated. The dashed line shows the relationship between logarithm of viscosity and hematocrit for normal blood as shown in Fig. 1.
For each patient the equation for the regression line between hematocrit and logarithm of viscosity was calculated. From these equations the blood viscosity was calculated for hematocrits 20%, 30%, and 40% in order to compare the relationship between the blood viscosity and plasma macroglobulin concentrations. The best correlation was observed when the plasma macroglobulin concentration was correlated with the logarithm of blood or plasma viscosity. These relationships are plotted in Fig. 4, at shear rate of 115 sec⁻¹ and in Fig. 5 at shear rate of 11.5 sec⁻¹; the formulas for the relationships are given. The correlated coefficients were highly significant (p < 0.001). In Fig. 4, when the macroglobulin concentrations become zero, then the regression line indicates a viscosity less than expected for normal plasma. Similar trends were apparent for hematocrits of 20%, 30%, and 40%, as compared to the values for normal blood in Fig. 1. This might be expected, since normal IgM and other plasma proteins contribute to blood viscosity. Therefore, the plasma macroglobulin concentration was correlated with the measured plasma viscosity and calculated blood viscosity at hematocrits 20%, 30%, and 40% for the six specimens that contained less than 2.0 g/100 ml of macroglobulin. These correlations were not significant (correlation coefficients were 0.3795, 0.2955, and 0.2334, respectively, for hematocrit 20%, 30%, and 40%). On the other hand, when the correlation coefficients were calculated for specimens with macroglobulin concentrations in excess of 2.0 g/100 ml, then the correlation coefficients and slopes and intercepts of the regression lines changed relatively little in comparison to values indicated in Fig. 4. Similar results were obtained on the calculated viscosities for the shear rate at 11.5 sec⁻¹.

For each blood the equation for the regression line between hematocrit and...
The logarithm of blood viscosity was used to calculate the plasma viscosity. The correlation coefficient between all measured plasma viscosities and calculated plasma viscosities was 0.9989 ($p < 0.001$) with a slope of 0.9978 and intercept of 0.035.

The linear equation for the logarithm of viscosity of blood for each patient has the formulation

$$\log \eta = a + bH$$  \hspace{1cm} (1)

where $\eta$ is the viscosity in centipoise, $a$ is the log of plasma viscosity, $b$ is the slope of the regression line, and $H$ is the hematocrit in per cent. The $a$ term (intercept) increased as the plasma macroglobulin concentration increased. This is demonstrated in Fig. 4 and Fig. 5 by the correlation between macroglobulin concentration and plasma viscosity ($r = 0.9806$, $p < 0.001$ and $r = 0.9021$, $p < 0.001$, respectively). The term $b$, i.e., slope of the regression line, tended to decrease as the macroglobulin concentration increased (see examples in Fig. 3).

Since for each patient a good correlation existed between the logarithm of blood viscosity and hematocrit, and since a good correlation existed between the calculated logarithm of blood viscosity at a given hematocrit and the plasma macroglobulin concentration, attempts were made to establish a formula that would predict blood viscosity when the hematocrit and plasma macroglobulin concentration are known. The BMD 03R program for multiple regression was used; linear and logarithmic values of viscosity at 115 sec$^{-1}$, hematocrit and macroglobulin concentration were examined on 44 measurements on specimens with more than 2.0 g/100 ml of macroglobulin. The measured values on specimens with less than 2.0 g/100 ml of macroglobulin were
omitted because in these bloods a significant relationship did not exist between
the blood viscosity and macroglobulin concentration, and such patients have
not developed the hyperviscosity syndrome. The best fit was obtained when
the logarithm of viscosity was related to hematocrit and macroglobulin con-
centration. The following formula expressed the relationship:

\[
\log \eta = 0.1710 + 0.1005M + 0.0090H
\]

where \( \eta \) is viscosity in centipoise at 115 sec\(^{-1}\), \( M \) is macroglobulin concentra-
tion in g/100 ml, and \( H \) is hematocrit in per cent. The variations in the in-
dependent variables (hematocrit and macroglobulin concentration) accounted for
95% of the variations in the dependent variable (measured viscosity). The value
of this equation was further tested by calculating the blood viscosity for each
patient with more than 2.0 g/100 ml of macroglobulin at the original hemato-
crit. The correlation coefficient between the measured blood viscosity and
calculated blood viscosity was 0.9347 (\( p < 0.001 \)). The same equation ade-
quately predicated the plasma viscosity. The correlation coefficient between
measured and calculated plasma viscosity was 0.9202 (\( p < 0.001 \)). Furth-
more, the plasma viscosity (1.49 cP) was close to that of normal plasma when
the hematocrit term and macroglobulin term in the equation (2) were set at
zero.

**Relationship of Blood Viscosity to Clinical Symptoms and Signs**

Twelve of the 16 patients examined in this study had Waldenström’s macro-
globulinemia in view of their progressive clinical course and the need for
treatment with chlorambucil. In several patients the blood viscosity was ex-
amed at a time when they were already partially treated. As a result, in-
sufficient data were available on patients with the clinical symptoms and signs
of the hyperviscosity syndrome to permit correlation of the blood viscosity
measurements and clinical findings.

In two patients (D.J. 4/1972 and V.J. in Table 1), mild to moderate retinal
changes were present at the time of blood viscosity measurements. In both
patients the blood viscosity at the shear rate of 115 sec\(^{-1}\) was close to or above
10 cP. At 11.5 sec\(^{-1}\) the blood viscosity was 14.0 and 16.4 cP in these patients.
With plasmapheresis the physical findings improved, and blood viscosity de-
creased to about 7 cP at 115 sec\(^{-1}\). Clearly, more observations are needed to
correlate the clinical abnormalities to blood viscosity measurements.

**DISCUSSION**

In vitro studies of normal blood have clarified the reasons for non-Newton-
ian behavior of this fluid. At very low shear rates the viscosity of normal blood
reaches hundreds of centipoise. With increasing shear rate the viscosity de-
creases. At shear rates in excess of 100 sec\(^{-1}\) the viscosity of normal blood be-
comes Newtonian, i.e., with further increase of the shear rate the viscosity does
not decrease. Direct examination of blood under varying flow conditions in a
modified cone-plate viscometer showed that, in normal blood red cell, aggrega-
tion occurs at shear rates of below about 50 sec\(^{-1}\). This aggregation and
correspondingly high viscosity were due to the presence of fibrinogen and serum
In addition, the decrease of blood viscosity at higher shear rates is due to deformation of erythrocytes. Aldehyde-treated, hardened erythrocytes show a Newtonian behavior at even low shear rates. The deformation of red cells becomes particularly important at high hematocrits (60% and higher), where flow would practically cease if the red cells were rigid. Above shear rates of 50 sec⁻¹ normal red cells develop maximal deformation, and their membrane is thought to achieve tank tread-like motion around the cell content.

In this study the blood of patients with macroglobulinemia was shown to have elevated viscosity, dependent both on the hematocrit and macroglobulin concentration. Since patients with macroglobulinemia have no known abnormalities of red cells that would contribute to increased blood viscosity, the macroglobulin seems to cause increased red cell aggregation and rouleaux formation, leading to increased blood viscosity in this disorder. In normal blood the relationship between hematocrit and logarithm of viscosity was empirically described by a fifth-power polynomial equation, when hematocrits up to 90% were examined. In this study a fourth-power polynomial equation described this relationship, most likely because hematocrits up to 65% were examined (Fig. 1). At higher hematocrits a fifth-power polynomial equation might have described the relationship. In contrast, in each patient with macroglobulinemia, the relationship between the logarithm of blood viscosity and hematocrit was described by a linear equation within the range of examined hematocrits. The reason for this difference is not clear, but the failure to disrupt all aggregates and rouleaux formation by the shear rate of 115 sec⁻¹ might be an explanation.

Earlier studies at a defined high shear rate failed to find a correlation between blood viscosity and macroglobulin concentration in patients with Waldenström’s macroglobulinemia. This may have been due in part to the variations in hematocrit, particularly since a correlation was found between macroglobulin concentration and serum viscosity. In this study, when calculated blood viscosity of different patients at defined hematocrits was related to macroglobulin concentration, a significant (p < 0.001) correlation was found between the logarithm of blood viscosity and macroglobulin concentration (see Figs. 4 and 5).

Since good correlations were found between blood viscosity at a given shear rate and hematocrit in each patient, and between blood viscosity and macroglobulin concentration at defined hematocrits, then an empirical relationship was established between these two variables to allow calculation of blood viscosity (at shear rate of 115 sec⁻¹) from known hematocrit and macroglobulin concentration. The derived equation (see Results) adequately predicted the blood viscosity from measured hematocrit and macroglobulin concentration when the latter exceeded 2.0 g/100 ml. The same equation also allowed calculation of plasma viscosity when the hematocrit term became zero. At this time no physiologic explanation can be offered for the numeric values of constants in this equation. Furthermore, the usefulness of this equation should be further tested by measurement of blood viscosity and calculation of blood viscosity in additional patients with macroglobulinemia, particularly in patients with high concentration of macroglobulin.

In this study not enough patients with the clinical hyperviscosity syndrome...
were encountered to permit correlation of the blood viscosity at a given shear rate with the clinical symptoms and signs attributable to excessive viscosity. Only two patients had clinical findings of this syndrome, in both, the blood viscosity at 115 sec\(^{-1}\) was around 10 centipoise. Interestingly, clinical symptoms and signs of the hyperviscosity syndrome were found in a patient with multiple myeloma whenever the blood viscosity at the same shear rate (115 sec\(^{-1}\)) exceeded 10 cP.\(^{20}\)

The question of what shear rate should be used to measure blood viscosity in patients with macroglobulinemia remains uncertain. In normal individuals the shear rate of blood varies markedly throughout the vascular system. Chien\(^{13}\) calculated that in arteries the shear rate is close to 100 sec\(^{-1}\), increases to almost 1000 sec\(^{-1}\) in capillaries where the red cells have to undergo maximal deformation to pass through the small lumen, and drops to about 10 sec\(^{-1}\) in venules and small veins. Since in patients with macroglobulinemia the plasma volume is increased proportional to relative serum viscosity,\(^{21}\) the shear rates may be altered in parts of the circulation. The marked dilatation of retinal veins in some patients with macroglobulinemia could be explained by the increased blood volume. Furthermore, sluggish blood flow and even stoppage of flow has been noted in conjunctival vessels of patients with macroglobulinemia.\(^22\) In macroglobulinemic mice, Rosenblum observed that the transit time of red cells was not significantly altered in cerebral microcirculation, but plasma flow was diminished,\(^{23}\) presumably due to the increased viscosity.

In this study the macroglobulin concentration was determined by plasma protein electrophoretic patterns. This technique is readily available. However, the total protein in the macroglobulin peak also includes some normal plasma proteins, including fibrinogen. Furthermore, this technique does not permit the identification and quantification of 7S IgM molecules that have been described in some patients with macroglobulinemia.\(^{24,25}\) If the plasma or blood viscosity of a patient with macroglobulinemia is lower than expected from the electrophoretic studies, then the presence of significant 7S IgM protein might be suspected, since the 7S IgM contributes less to serum viscosity than a corresponding absolute amount of 19S IgM.\(^{26}\) Such patients were not encountered in this study, but small amounts of 7S IgM may have been present in several patients. On analytic ultracentrifugation, the serum of patients with macroglobulinemia has polymers of 19S IgM with correspondingly higher sedimentation coefficients.\(^{27}\) Contribution of these polymers to blood viscosity has not been explored. The immunochemical quantification of IgM was not selected in this study, since this method measures total, rather than monoclonal, IgM and gives falsely high values in the presence of 7S IgM, when 19S IgM standards are used.\(^{28}\)

In order to further clarify the pathophysiology of the hyperviscosity syndrome in patients with macroglobulinemia, additional parameters, such as oxygen delivery to tissues and cardiac work, need to be related to blood viscosity. The data presented here indicate that the macroglobulin concentration and hematocrit influence blood viscosity and therefore dehydration of these patients, and excessive transfusions should be avoided to prevent undue increase of blood viscosity.
ACKNOWLEDGMENT

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