Whole Blood Viscosity Parameters and Cerebral Blood Flow

J. Grotta, M.D., R. Ackerman, M.D., J. Correia, Ph.D., G. Fallick, and J. Chang

SUMMARY This report describes the statistical relationship of several whole blood viscosity parameters and cerebral blood flow (CBF) in 53 consecutive patients and normal controls. Significant correlations were present between CBF and serum fibrinogen (P = .05), hematocrit (P < .05), and a relationship involving both fibrinogen and hematocrit (P < .01).

We conclude that heightened whole blood viscosity does correlate with decreased cerebral blood flow in the ranges measured in our patients, that both fibrinogen and hematocrit must be taken into consideration in viscosity determinations, and that changes in viscosity may have an important effect on CBF in regions of low flow.

Stoke, Vol 13, No 3, 1982

A NUMBER OF FACTORS have been identified following acute cerebral infarction which may result in decreased cerebral blood flow (CBF). These include arterial obstruction, increased intracranial pressure due to cerebral edema, systemic hypotension, and local factors affecting vascular tone such as the release of tissue metabolites and biproducts of cellular injury. However, in some cases these processes may not be sufficient to explain why CBF falls to levels low enough to cause tissue infarction. Experimental findings implicate increased whole blood viscosity as an alternative possible explanation for decreased CBF in some clinical situations. This happens particularly when flow is already reduced to marginal levels because whole blood viscosity will increase as flow falls and increased viscosity causes increased resistance to flow.

Following cerebral infarction, recent studies of CBF using positron emission tomography (PET) and earlier studies using xenon-133 CBF measurements have shown that, while some brain regions demonstrate depression of CBF in the early phases of infarction, CBF may remain low, may increase back towards normal, or in some regions even increase above normal levels in the days following infarction. These observations are consistent with a theory implicating a role for increased blood viscosity in acute infarction. Although an increase in whole blood viscosity associated with reduced cerebral perfusion early in infarction may cause an initial further reduction in CBF, the flow might still be restored to the ischemic or infarcted region because viscosity change is a dynamic and potentially reversible phenomenon.

Even in patients with cerebrovascular disease but without cerebral infarction, diffuse depression of CBF cannot always be explained by obstructive vascular disease and may in part be the result of increased whole blood viscosity. We have shown in another report that patients with transient ischemic attacks (TIAs) and extracranial vascular disease but without cerebral infarction have diffusely reduced CBF. This reduction is greatest in patients with multiple large vessel stenosis or occlusion. However, improvement in blood flow did not always occur following removal of the hemodynamically significant carotid stenosis by endarterectomy.

The most important determinants of whole blood viscosity are the hematocrit and serum fibrinogen concentration (although other plasma proteins may also play a role). Increases in either of these variables within physiologic ranges will result in increased viscosity but the effects on CBF are less well defined. Thomas and co-workers have recently stimulated interest in the effect on CBF of high viscosity due to elevated hematocrit. They found significantly lower CBF in patients with hematocrit in the range 47–53 (mean 49) than in a group with hematocrit in the range 36–46 (mean 42). Phlebotomy in the former group resulted in an increase in blood flow. Haggard also examined the relationship between hematocrit and CBF, but found that a rise in hematocrit from 30 to 60 caused no effect on CBF in dogs.

Increased fibrinogen and viscosity occur in peripheral vascular insufficiency, myocardial infarction, and cerebral infarction. Ott’s data on patients with recent cerebral infarction indirectly suggests a relationship between fibrinogen and CBF. Ott’s data demonstrates a correlation between viscosity and fibrinogen on the one hand, and an inverse relationship between viscosity and CBF on the other. Recently, Thomas et al. demonstrated a rise in CBF in 8 hyperfibrinogenemic patients treated chronically with Clofibrate.

This paper examines the statistical relationship between whole blood viscosity, the important determinants of viscosity (namely hematocrit and fibrinogen), and CBF in 53 consecutive patients studied in the CBF laboratory at the Massachusetts General Hospital Stroke Center.

Methods

Patients

Hematocrit and fibrinogen were measured in 46 consecutive patients and 7 controls at the time of cere-
bral blood flow studies which were performed using the 133-xenon inhalation technique. The subjects are categorized by clinical diagnosis in Table 1. CT and/or angiographic correlation was obtained in all patients except the two in the miscellaneous group and the controls. Control subjects were drawn from healthy hospital employees and ranged in age from 28 to 66 years. Patients were included in the TIA group if they had a transient neurological disturbance referable to the carotid or vertebrobasilar circulation lasting less than 24 hours, a normal neurological exam at the time of the CBF study, and no evidence of cerebral infarction on CT. Patients included in the cerebral infarct group had a fixed deficit at the time of the CBF study, though the interval between the stroke and xenon CBF study ranged from one day to four years. The miscellaneous group included one patient with migraine and one with possible polycythemia vera.

Viscosity Studies

Hematocrit using a Coulter counter was obtained at the time of each study along with hemoglobin and erythrocyte sedimentation rate. Serum fibrinogen determinations were performed using a modified San Slyke method. The normal range of fibrinogen in our laboratory is 0.15–0.35 gm%.

The interaction of fibrinogen and hematocrit on viscosity can be represented by an estimate of yield shear stress (YSS) described by Merrill.

\[ YSS = 13.5 \times 10^{-6} C_f^2 (Hct - 6)^3 \]

where \( C_f \) is the fibrinogen concentration in gm% and Hct is the hematocrit.

CBF Determinations

CBF measurements were performed in all subjects at rest using the 133-xenon inhalation method. Most patients also had studies during sustained voluntary hyperventilation. The CBF instrument was built in our cerebral blood flow laboratory and uses 12–14 NaI detectors over each hemisphere with 5 cm collimation. Xenon-133 was administered for one minute at a concentration of approximately 7 mCi/liter, and the washout curves were obtained over 14 minutes 45 seconds. The curves were fitted using a modified Marquardt algorithm, and only flow gray values were utilized in this study. CBF values for studies done at rest were corrected to a PaCO₂ of 40 mm Hg using a correction factor developed on normal control subjects in our laboratory (1.7 cc/100/min per 1 mm Hg change in PaCO₂). Partition coefficient was corrected for hemoglobin concentration as described by Hoedt-Rasmussen. Although regional CBF data was obtained, only 19 of 53 patients had focal CNS pathology so that the average of the two mean hemispheric flow values for each subject was used in our statistical analyses. Mean arterial blood pressure (MABP) was determined for each study from the average of three blood pressure readings using a sphygmomanometer. Percent CO₂ reactivity was defined as the percent decrease in CBF with hyperventilation divided by the change in pCO₂ in mm Hg:

\[ \frac{\text{CBF Resting} - \text{CBF Hyperventilation}}{\text{CBF Resting}} \times 100. \]

pCO₂ Resting – pCO₂ Hyperventilation

The normal mean cerebral blood flow gray measurement in our laboratory based on 42 control subjects (mean age 36) is 66 ± 8 cc/100 gm/min. The mean age of patients studied for this report was 55, and mean CBF for 6 control subjects of this age in our laboratory is 67 ± 7. Normal percent CO₂ reactivity for 7 normal subjects in 1.9.

Statistical Analysis

Statistical correlations were performed by linear regression analysis of resting cerebral blood flow on various independent variables thought to be related to viscosity including YSS, natural logarithm of YSS.

### Table 1 CBF Studies by Clinical Category

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of patients</th>
<th>Mean CBF (cc/100 gm/min)</th>
<th>Mean age (yrs)</th>
<th>Mean MABP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls</td>
<td>7</td>
<td>56 ± 17</td>
<td>44 ± 16</td>
<td>86 ± 9</td>
</tr>
<tr>
<td>Asymptomatic bruit</td>
<td>7</td>
<td>44 ± 7</td>
<td>62 ± 10</td>
<td>100 ± 15</td>
</tr>
<tr>
<td>TIA</td>
<td>11</td>
<td>41 ± 12</td>
<td>62 ± 6</td>
<td>95 ± 9</td>
</tr>
<tr>
<td>Cerebral infarct</td>
<td>16</td>
<td>44 ± 11</td>
<td>55 ± 17</td>
<td>94 ± 11</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>3</td>
<td>44 ± 10</td>
<td>53 ± 14</td>
<td>85 ± 9</td>
</tr>
<tr>
<td>Post-operative endarterectomy</td>
<td>4</td>
<td>39 ± 8</td>
<td>54 ± 5</td>
<td>97 ± 9</td>
</tr>
<tr>
<td>or STA-MCA anastomosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVM</td>
<td>3</td>
<td>51 ± 11</td>
<td>40 ± 9</td>
<td>83 ± 10</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2</td>
<td>48 ± 11</td>
<td>50 ± 22</td>
<td>98 ± 21</td>
</tr>
<tr>
<td>Overall mean:</td>
<td></td>
<td>45 ± 12*</td>
<td>55 ± 14*</td>
<td>93 ± 12†</td>
</tr>
</tbody>
</table>

*Range 18–80.
†Range 17–84.
†Range 73–128.
TABLE 2 Mean, Standard Deviation and Range of Hematocrit, Fibrinogen, YSS, and CBF for Fifty-Three Studies

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>39.3</td>
<td>4.3</td>
<td>28–52</td>
</tr>
<tr>
<td>Fibrinogen (gm%)</td>
<td>33</td>
<td>.11</td>
<td>16–62</td>
</tr>
<tr>
<td>YSS (dynes/cm²)</td>
<td>.0585</td>
<td>.0435</td>
<td>.0068–.2639</td>
</tr>
<tr>
<td>CBF (cc/100 gm/min)</td>
<td>45.3</td>
<td>11.9</td>
<td>17.7–80.0</td>
</tr>
</tbody>
</table>

(1nYSS), fibrinogen, hematocrit, and erythrocyte sedimentation rate. Since theoretically both fibrinogen and hematocrit contribute to whole blood viscosity, multiple variable regression was performed combining these two measurements together in a single relationship to resting CBF. Since cerebral vascular resistance is partly a function of the viscosity of the perfusing blood, correlations were also performed between cerebrovascular resistance and fibrinogen, hematocrit, and YSS.

Data analysis was performed in this fashion for the overall group of 53 subjects, and also for several subgroups which we felt might display an especially large or small effect of viscosity on CBF. These subgroups included 25 patients with no structural brain disease drawn from the TIA, asymptomatic bruit, control, and miscellaneous groups. Patients were also subdivided by: resting CBF range (≥ 50, 36–49, and ≤ 35), response to hyperventilation (CO₂ reactivity ≥ 1.9 or < 1.9), MABP (≥ 100 or < 100), and diagnostic category. Cerebral vascular resistance was calculated as cerebral perfusion pressure divided by CBF. Cerebral perfusion pressure is equal to the difference between MABP and cerebral venous pressure; but, since venous pressure is only a few mm Hg, cerebral resistance = MABP/CBF.

Results

Tables 1 and 2 summarize the mean, standard deviation, and range of hematocrit, fibrinogen, YSS, and CBF in the patients studied. In the overall patient population and all subgroups, mean CBF was below the normal range for our laboratory. By no means, then, should these patients be considered to have “normal” cerebral circulation.

Because the mean and standard deviation of YSS was so close in our patients, the 1nYSS was employed in order to make the distribution of data points more normal (fig. 1).

Table 3 summarizes the statistically significant correlations in our 53 studies and subgroups. Analysis of the data for the entire group of 53 subjects and for the group of 25 patients with no structural brain disease demonstrated a strong relationship between 1nYSS and both CBF and cerebral resistance (figs. 1, 2). These relationships were highly significant.

The relationship of 1nYSS and CBF was stronger at lower levels of flow. Dividing the 53 patients into three subgroups according to resting CBF, only the group with CBF ≤ 35 showed a correlation between viscosity and blood flow with p ≤ 0.5 (fig. 3). However, when the heterogenous sample size of the subgroups is taken into consideration (Fisher's Z statistic), there was no statistically significant trend toward a stronger relationship between viscosity and CBF at lower flow rates.

A strong correlation between 1nYSS and CBF was present in a number of other subgroups. Included among these were patients with cerebral infarction, representing the single largest diagnostic category of patients with structural brain lesions. Patients with normal blood pressure (MABP < 100) and normal CO₂ reactivity (≥ 1.9) had a much stronger association of 1nYSS and CBF than did patients with MABP ≥ 100 or with impaired response to hyperventilation.

Fibrinogen and hematocrit each correlated with CBF at the p ≤ 0.5 level when examined independently (fig. 4), but when fibrinogen and hematocrit were considered together in the form of YSS the correlation with CBF was stronger than when these variables were considered individually. A significant negative correlation was found between hematocrit and fibrinogen themselves (table 3), implying that these two variables do not exist independently and probably do interact.

Although a combination of fibrinogen and hemato-
crit in the form of YSS was more closely related to CBF than was either of these two variables considered independently. YSS is a viscosity parameter applicable to a stationary column of blood. In our studies and in most clinical situations where blood flow can be measured in vivo, CBF is well above the range where YSS should accurately reflect viscosity. Therefore, we attempted to arrive at a relationship of fibrinogen and hematocrit more applicable to levels of CBF measured in our patients. We performed multiple variable regression analysis of fibrinogen and hematocrit against CBF, there is a statistically significant association between CBF and both serum fibrinogen and hematocrit. We performed multiple variable regression analysis of fibrinogen and hematocrit against CBF, there is a statistically significant association between CBF and both serum fibrinogen and hematocrit. There is also a correlation between CBF and an expression of the interaction of fibrinogen and hematocrit on viscosity. This interaction can be represented both by YSS and by an experimentally derived formula applicable to the blood flow range seen in our patients. This correlation is present over a wide range of CBF, and adds support to previous clinical and laboratory evidence that viscosity factors may affect CBF measurements.

Whole blood viscosity is a difficult parameter to measure accurately. Viscometer measurements can take up to one minute to perform and in that time red cell aggregation and sedimentation occurs causing in-
accurate readings. In addition, extrapolation of viscosity readings from a viscometer in vitro to the cerebral microcirculation may be inaccurate because viscosity will vary from one locus to another within the circulation depending upon the regional flow rate. These difficulties with viscometer measurements make it useful to develop a mathematical approximation of viscosity based on easily measured viscosity determinants such as serum fibrinogen and hematocrit.

We found that while fibrinogen and hematocrit each correlate with CBF, an even stronger relationship was present when these variables were combined in a single viscosity parameter. The negative relationship between fibrinogen and hematocrit themselves suggest some interaction between these variables. Although it is known that fibrinogen is absorbed to red cells, there is no explanation in the blood rheology literature why fibrinogen should decrease with an increase in hematocrit.

The best relationship of hematocrit and fibrinogen to the CBF levels seen in our 53 patients seems to be represented by the linear formula:

\[
\text{CBF} = 103 - 40(C_f) - \text{Hct}
\]

Though this expression of the relationship of viscosity to CBF is more statistically significant than is the relationship of YSS to CBF, a more accurate model would probably be non-linear because of the non-Newtonian characteristics of whole blood. Experimental studies examining the effect of CBF of manipulating fibrinogen and hematocrit will be necessary in order to derive a more accurate relationship of these variables.

Viscosity factors may contribute to unexplained diffuse depression of CBF seen in some patients. Furthermore, in patients with acute cerebral ischemia and infarction, it is possible that increased whole blood viscosity (largely the result of fibrinogen induced red cell aggregation) causes further reduction of CBF in areas where flow is already low. Studies of the effect of artificial reduction of serum fibrinogen on CBF and the extent of neuropathological damage in an animal stroke model may help determine if this might be a useful form of therapy in acute cerebral infarction.

References

1979
Hemodynamics in Extracranial Vascular Disease: Effect of Endar-
3. Jones FH, Dyken ML, King R: Cerebral Blood Flow, Metabolism and
Mean Arterial Pressure Changes Following Unilateral Internal Carotid
and Endarterectomy: Cerebral Ischemia and Elevated Sys-
4. Obrist WD, Silver D, Wilkinson WE, et al: The \(^{133}\)Xe Inhalation
Method: Assessment of eCBF in Carotid Endarterectomy (In T.W.
Langfitt, L.C. McHenry, M. Reivich, and H. Wollman (Eds),
Cerebral Circulation and Metabolism, New York, Springer Ver-
lag, pp. 398-401, 1975
5. O'Brien MD: Ischemic Cerebral Edeama: A Review. Stroke 10:
623-628, 1979
6. Sokoloff L, Aspects of Cerebral Circulatory Physiology of Rel-
7. Purves MJ: Control of Cerebral Blood Vessels: Present State of the
8. Eisenberg S: Blood Viscosity and Fibrinogen Concentration Fol-
dowing Cerebral Infarction. Circ Suppl II, 33 & 34: 10-14, 1966
10. Ott EO, Laderner G, Lechner H: Relationship between Disturbed
Rheological Properties and Cerebral Hemodynamics in Recent Ce-
Cerebral Metabolism and Perfusion: Mapping by Emitted Compu-
ted Tomography of \(^{18}\)FDG and \(^{13}\)NH\(_{3}\). Ann Neuro1 8: 47-60, 1980
ed with Hemispheric Blood Flow in Cerebral Infarction. Stroke 2:
383-394, 1971
14. Naritomi H, Meyer JS, Deshmukh VD, and Pollock P: Non-inva-
sive Measurement of Regional Cerebral Blood Flow in TIAs and
Stroke Due to Carotid and Vertebrobasilar Disease (In D.H. Ing-
var and N.A. Lassen (Eds.). Cerebral Function, Metabolism, and
15. Tohgi H, Uchiyama S, Ogawa M, et al: The role of Blood Con-
stituents in the Pathogenesis of Cerebral Infarction. Acta Neurtl Scand
Suppl 72, 60: 616-617, 1979
16. Matsuda T, Murakami M: Relationship Between Fibrinogen and
18. Haggendal E, Nilsson NJ, Norback B: Effect of Blood Corpuscle
364: 3-12, 1964
19. Haggendal E, Norback B: Effect of Viscosity on Cerebral Blood
contribution of haematocrit, plasma fibrinogen and other proteins.
Clin Sci 31: 87-93, 1966
22. Haggendal E, Nilsson NJ, Norback B: Effect of Blood Corpuscle
364: 3-12, 1964
23. Haggendal E, Norback B: Effect of Viscosity on Cerebral Blood
24. Dormandy JA, Goyle KB, Reid HL: Treatment of Severe Intermittent
Claudication by Controlled Defibrination. Lancet 1: 625-626,
1977
Subjects and in Patients Suffering from Coronary Occlusion and
Changes After Acute Myocardial Infarction. Circ 51: 1079-1084,
1975
27. Schmid Schonbein H: Rheological Properties of the Blood Under
Normal and Pathological Conditions. (In Zulch J., et al., Brain
28. Kobatake K, Shinohara Y, Yamamoto M: Red Blood Cell Aggre-
gation in Occlusive Cerebrovascular Disease. Acta Neurtl Scand
Suppl 72, 60: 612-613, 1979
The Viscosity Factor. Cerebral Vascular Disease 2, 9th Salz-
burg Conference. Amsterdam-Oxford, Excerpta Medica, pp. 211-
215, 1979
31. Merrill EW, Cheng CS, Pelletier GA: Yield Stress of Normal
Human Blood as a Function of Endogenous Fibrinogen. J Appl
Physiol 26: 1-3, 1969
32. Hoet-Rasmussen K, Sveinsdottir E, Lassen N: Regional Cerebral
Blood Flow in Man Determined by Intra-Arterial Injection of Ra-
33. Lassen NA: Cerebral Blood Flow and Oxygen Consumption in
34. Phillips MJ, Harkness J. Annotation: Plasma and Whole Blood
35. Fischer EG: Impaired Perfusion Following Cerebrovascular Stasis.
Ann Neurol 8: 36-39, 1977
Aggregation in Occlusive Cerebrovascular Disease. Acta Neurtl Scand
Suppl 72, 60: 612-613, 1979
The Viscosity Factor. Cerebral Vascular Disease 2, 9th Salz-
burg Conference. Amsterdam-Oxford, Excerpta Medica, pp. 211-
215, 1979
38. Schmid Schonbein H: Rheological Properties of the Blood Under
Normal and Pathological Conditions. (In Zulch J., et al., Brain
39. Kobatake K, Shinohara Y, Yamamoto M: Red Blood Cell Aggre-
gation in Occlusive Cerebrovascular Disease. Acta Neurtl Scand
Suppl 72, 60: 612-613, 1979
The Viscosity Factor. Cerebral Vascular Disease 2, 9th Salz-
burg Conference. Amsterdam-Oxford, Excerpta Medica, pp. 211-
215, 1979
41. Merrill EW: personal communication.
42. Merrill EW, Cheng CS, Pelletier GA: Yield Stress of Normal
Human Blood as a Function of Endogenous Fibrinogen. J Appl
Physiol 26: 1-3, 1969
43. Hoet-Rasmussen K, Sveinsdottir E, Lassen N: Regional Cerebral
Blood Flow in Man Determined by Intra-Arterial Injection of Ra-
44. Lassen NA: Cerebral Blood Flow and Oxygen Consumption in
46. Fischer EG: Impaired Perfusion Following Cerebrovascular Stasis.
Arch Neurol 29: 361-366, 1973
47. Fischer EG, Ames A, Hedley-White ET, O'Gorman S: The Ass-
essment of Cerebral Capillary Changes in Acute Global Ischemia
and Their Relationship to the “No-Reflow Phenomenon.” Stroke
8: 36-39, 1977
Aggregate in Blood Flow II Effect on Apparent Viscosity of Blood.
Klin Wschr 54: 159-167, 1976
49. Merrill EW, Gilliland ER, Lee TS, Salzman EW: Blood Rheology:
Effect of Fibrinogen Deduced by Addition. Circ Res 18: 437-446,
1966
Whole blood viscosity parameters and cerebral blood flow.
J Grotta, R Ackerman, J Correia, G Fallick and J Chang

*Stroke*. 1982;13:296-301
doi: 10.1161/01.STR.13.3.296

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/13/3/296

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/