Whole Blood Viscosity Parameters and Cerebral Blood Flow

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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.

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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 another 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 blood 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 were 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 verteobasilar 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 hematoglobin and erythrocyte sedimentation rate. Serum fibrinogen determinations were performed using a modified San Slyke method. The normal range of fibrinogen in our laboratory is .15-.35gm%.

The interaction of fibrinogen and hematocrit on viscosity can be represented by an estimate of yield shear stress (YSS) described by Merrill. This viscosity parameter is the force required to start movement in a stationary column of blood and is represented by the formula:

\[ YSS = 13.5 \times 10^{-4} C_f^2 (Hct - 6)^3 \]

where \( C_f \) is the fibrinogen concentration in gm% and \( Hct \) is the hematocrit.\textsuperscript{30, 31}

**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 PaCO\(_2\) 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 PaCO\(_2\)). Partition coefficient was corrected for hemoglobin concentration as described by Hoedt-Rasmussen.\textsuperscript{32} 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 CO\(_2\) reactivity was defined as the percent decrease in CBF with hyperventilation divided by the change in pCO\(_2\) in mm Hg.

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

\[ \text{pCO}_2 \text{Resting} - \text{pCO}_2 \text{ Hyperventilation} \]

The normal mean cerebral blood flow gray measurement in our laboratory based on 42 control subjects (mean age 36) is 66 ± 8cc/100gm/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 CO\(_2\) 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>
<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>3</td>
<td>51 ± 11</td>
<td>40 ± 9</td>
<td>83 ± 10</td>
</tr>
<tr>
<td>AVM</td>
<td>2</td>
<td>48 ± 11</td>
<td>50 ± 22</td>
<td>98 ± 21</td>
</tr>
<tr>
<td>Miscellaneous</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.
(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 = \( \frac{\text{MABP}}{\text{CBF}} \).

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. No correlation was found between sedimentation rate and CBF.

Although a combination of fibrinogen and hematocrit...
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 resting CBF in our patients and arrived at the relationship CBF = 103-40(C)-Hct. Both variables were highly significant (p < .005) and the r² for this relationship was .218.

Discussion

Our data indicates that, in a heterogenous sample of patients with cerebrovascular disease and overall low 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

![Figure 2](http://stroke.ahajournals.org/)

Figure 2. Regression for lnYSS vs cerebral resistance (MABP/CBF) in 53 patients.
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
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