Blood Rheology in Patients With Transient Ischemic Attacks

E. Ernst, Dr med, MD, PhD, A. Matrai, Dr med, MD, PhD, and M. Marshall, Dr med, Prof MD, PhD

A complete ischemic stroke is associated with a significant hemorheologic disturbance leading to a rise of the viscous component of the peripheral resistance. This abnormality represents a consequence of the acute event. Nonetheless, it could be causally related to ischemia. In an attempt to clarify this question, 26 patients suffering from transient ischemic attacks were compared with controls in terms of blood and plasma viscosity, hematocrit, blood cell filterability, and erythrocyte aggregation. In patients there was a significant impairment of blood fluidity comprising plasma viscosity, blood cell filterability, and erythrocyte aggregation, suggesting that the flow properties of blood are jeopardized even before an acute stroke. Most likely this is due to the underlying arteriosclerotic process. Our results open the way to speculating that hemorheologic mechanisms might predispose to the development of a stroke by decreasing cerebral blood flow. If this hypothesis were true, it would have important therapeutic implications. (Stroke 1988;19:634–636)

There is ample information on the flow properties of blood after an acute ischemic stroke. These studies unanimously agree that both cellular and plasmatic abnormalities lead to a marked limitation of blood fluidity. Such changes may be looked upon as a consequence of a stroke; however, they could also contribute to the development of ischemia by virtue of their detrimental influence on cerebral blood flow.7,8

A transient ischemic attack (TIA) with hemodynamic relevance is the most relevant stenosis of the internal carotid artery. It represents a precursor of stroke. Little is known about the flow properties of blood in this condition. Our study was aimed at investigating the blood rheology of TIA patients and testing the hypothesis that blood fluidity is impaired not only after, but also before, an ischemic stroke.

Subjects and Methods

Twenty-six consecutive outpatients (12 women, 14 men; aged 50 ± 15 years) with a history of TIAs (a minimum of one attack within the last 4 weeks) and ultrasonic evidence of a stenosis of the internal carotid artery of at least 75% were investigated. A control group (n = 26) was selected to match the age (47 ± 14 years) and sex distributions (12 women, 14 men) of the patients. The frequency and distribution of cardiovascular risk factors (hypertension, smoking, hyperlipidemias, diabetes, obesity) were comparable in both groups (Table 1). The control group did not receive carotid ultrasonography; however, neither history nor auscultation suggested carotid lesions. No participant of this study showed a coagulation disorder or took medications known to affect blood rheology.

In all cases venous blood was drawn after an overnight fast, with minimal venous occlusion and no suction, and was anticoagulated with lithium heparin (final concentration 12.5 units/ml). Within 2 hours of sampling the following tests were performed in duplicate:

1) Blood viscosity at hematocrit 45% at two defined shear stresses at 37°C. After mixing the sample, it was put into a rotational viscometer in which low- and high-shear readings were performed without delay. Standardization was done by a calculation described elsewhere.

2) Plasma viscosity at 37°C. Plasma obtained by centrifugation was prewarmed and measured against water. Knowing the viscosity of water at 37°C, the absolute viscosity of the sample was calculated.


4) Blood cell filterability. The buffy coat was discarded after centrifugation. A 5% erythrocyte suspension in the subject's own plasma was made. One milliliter of this was filtered twice through 5-μm Nuclepore filters (Pleasanton, California) with gravity (100–0 Pa) for 60 seconds. The ratio of erythrocytes that passed the filter to those that could have passed it gave the final index.

5) Erythrocyte aggregation using an automated, transparent cone and plate viscometer. In this instrument a blood sample is maximally disaggregated by shearing. Subsequently, the shearing stops, allowing erythrocytes to aggregate. This process increases light transmission through the sample, which is recorded for a given time, and automatically integrated. Thus, the dimensionless result depicts the speed and final extent of aggregation.

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Table 1. Characteristics of Patients With Transient Ischemic Attacks and Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 26)</th>
<th>Controls (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Women</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Men</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Smoking</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Obesity</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Values are number, except mean age.

Statistical evaluation was done by using the non-parametric test of Wilcoxon and Wilcox for unpaired data. The null hypothesis (no difference between patients and controls) was rejected when \( p \) was < 0.05.

Results

There were no significant differences in blood viscosity between TIA patients and controls. Hematocrit was slightly but nonsignificantly higher in patients, and blood cell filterability was significantly reduced. Plasma viscosity and erythrocyte aggregation were significantly increased in patients compared with controls (Table 2). An attempt was made to correlate rheologic abnormalities with either the severity (frequency of symptoms) or the duration of TIA history. No significant correlations were found.

Discussion

Our results show a significant limitation of blood fluidity in patients with a history of TIsAs and stenoses of the internal carotid artery of >75%. The abnormality is confined to changes in blood cell filterability, erythrocyte aggregation, and plasma viscosity. One might expect that the increase in viscosity is reflected in low-shear viscosity readings, which, however, are only marginally elevated in patients. Thus, our results confirm that low-shear viscosity is burdened by methodologic variations rendering this technique relatively insensitive. Recently it was shown that leukocyte rheology is disturbed in ischemic stroke, which may well be the reason for the observed decrease in blood cell filterability. If this were true, the fact that the abnormality is not reflected in high-shear viscosity readings would be explainable from a theoretical point of view.

Two other studies, so far published only as abstracts, have reported hemorheologic abnormalities in TIA patients. In one, an elevation of yield stress (reflecting the strength of erythrocyte aggregation) was reported. In the other, all the variables we tested in our present study were demonstrated to be pathological. Our own group has recently shown blood fluidity to be impaired in hemiplegic migraine, which is also thought to be a precursor for ischemic events.

Blood rheology influences cerebral blood flow physiologically and pathologically. High viscosity due to elevated hematocrit or to increased plasma viscosity is associated with low cerebral blood flow. It was postulated that plasma viscosity, erythrocyte deformability, and erythrocyte aggregation (precisely those variables that were significantly altered in our present study) are more important than ex vivo blood viscosity. The influence of blood fluidity on cerebral blood flow can be expected to be more pronounced when autoregulation is impaired, as in severe cerebrovascular disease. Hence, a decrease in blood fluidity could be considered a treatable risk factor for ischemic strokes. This hypothesis is supported by an increasing amount of evidence: high normal hemoglobin or hematocrit and high fibrinogen levels, which are indicators for hyperviscosity, are independent primary risk factors for stroke. Furthermore, the incidence of stroke is increased in the presence of diseases associated with pathologic flow properties of blood. Eliminating accepted cardiovascular risk factors such as smoking reduces the incidence of strokes and simultaneously normalizes blood rheology. Finally, rheologic abnormalities can be shown in epidemiologic and clinical studies to persist long after an acute stroke, indicating that the limitation of blood fluidity is not solely a consequence of the acute event.

In summary, we have demonstrated a hemorheologic deficit in TIA patients, leading to an increase of viscous resistance. It is suggested that the hemorheologic changes potentiate the ill effects of a vascular lesion in terms of blood perfusion and thus predispose to hypoperfusion and stroke.

References


Table 2. Hemorheologic Variables in Patients With Transient Ischemic Attacks and Controls

<table>
<thead>
<tr>
<th></th>
<th>Blood viscosity (mPa-sec)</th>
<th>Plasma viscosity (mPa-sec)</th>
<th>Hematocrit (%)</th>
<th>Blood cell filterability (units)</th>
<th>Erythrocyte aggregation (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>11.2 ± 4.2</td>
<td>4.5 ± 0.6</td>
<td>1.29 ± 0.12*</td>
<td>46.6 ± 3.7</td>
<td>0.58 ± 0.14*</td>
</tr>
<tr>
<td>Controls</td>
<td>10.3 ± 3.8</td>
<td>4.6 ± 0.7</td>
<td>1.19 ± 0.006</td>
<td>44.8 ± 5.6</td>
<td>0.66 ± 0.11</td>
</tr>
</tbody>
</table>

Values are mean ± SD. \( \tau \), shear stress (dyn/cm²).

*\( p < 0.05 \) different from control.
41. Ernst E, Matrai A: Abstention from chronic cigarette smoking normalizes blood rheology. Thrombos Res 1987;4:75-77

Key Words • cerebral ischemia, transient • rheology
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