Whole Blood Viscosity and Cerebral Blood Flow

BLOOD has anomalous rheological properties, particularly in certain disease states. It may therefore be necessary to consider these properties when attempting to assess and perhaps to improve the state of a patient’s cerebral circulation. So what evidence is there that cerebral blood flow (CBF) is affected by viscosity?

Before attempting to answer this question, one should be aware of what influences the viscosity of blood. Viscosity is defined as the friction between adjacent layers of a fluid as they move relative to one another. It is impossible to give a single viscosity value for an individual blood sample because viscosity will vary with this relative movement, i.e. with the rate at which it is sheared. The shear rate depends on the diameter of the vessel and the rate of flow, both of which change at different phases of pulsatile flow. Slowly moving blood may have viscosities ten to twenty times higher than the same blood flowing quickly. Another problem is that we have only an approximate idea of what shear rates are relevant in different parts of the circulation. An acceptable compromise is to provide three viscosities for a sample, when measured at low, medium and high shear rates.

Despite the technical problems of measuring blood viscosity and doubts about the relevance of the in vitro values to the in vivo conditions, there are three factors, in addition to shear rate, that are generally accepted to influence it. Firstly, increasing the concentration of either red or white cells raises viscosity substantially. There is a logarithmic relationship between viscosity and hematocrit (Hct) — blood with Hct of 0.50 may have twice the viscosity of that with 0.40. Secondly, raising plasma fibrinogen levels or an abnormal immunoglobulin influence whole blood viscosity both by increasing the plasma viscosity component and by increasing the reversible, red cell — red cell aggregation that occurs at low shear rates. These aggregates are largely responsible for the steep increase in viscosity as flow slows down. Thirdly, the rigidity of the red cells influences how easily they negotiate the microcirculation. Red cells are known to be more rigid in certain haematological disorders, notably in sickle-cell disease, but normal cells can become less flexible under conditions of anoxia and low pH. There are very considerable methodological problems involved in measuring erythrocyte deformability in vitro and perhaps further comment should be reserved until workers in the field can reach agreement on a reliable quantitative method.

Hematocrit and fibrinogen levels can be measured accurately. In the paper on viscosity and CBF by Grotta et al in this issue, actual viscosity measurements were not made but viscosity parameters were calculated from Hct and fibrinogen. For the moment, this is probably a reasonable approach. Currently the Hct, globulin and fibrinogen levels can provide an adequate rheological ‘screen’ in centers without a special interest in viscosity.

What evidence is there then that Hct, globulins and fibrinogen influence CBF? It is well established that CBF is low with the high Hct levels found in polycythemia and is high in anemic patients. The Queen Square group found low flows in the ‘high normal’ Hct range in both polycythemics and patients without any blood disease. Grotta et al now confirm that there is an inverse relationship between CBF and Hct. Furthermore, if the Hct is reduced CBF increases.

There has been some debate as to whether these observations are due to viscosity or to the oxygen carrying capacity of the blood. The implication is that if they are due to oxygen carriage rather than viscosity then it is only a ‘physiological’ rather than a ‘pathological’ phenomenon.

By measuring oxygen content and calculating oxygen delivery before and after venesection, the increase in flow that occurs on hemodilution appears to be largely explicable on the basis of oxygen carrying capacity. However, viscosity probably has some effect because there is a closer relationship between CBF and viscosity than between CBF and Hct in individual patients and symptomatically patients both feel and have been demonstrated to be more alert after venesection. Some patients have an improved oxygen delivery after venesection.

Further evidence as to whether viscosity has any effect on CBF might be acquired by studying patients with plasma viscosity abnormalities. Unfortunately, the situation in the paraproteinemias, where the highest plasma viscosities are found is complex, because such patients are almost invariably anemic. The low Hct will not only tend to counteract the viscosity effect of the paraprotein but also reduce the oxygen carrying capacity. The latter would be expected to raise CBF which might conceal any viscosity effect. An initial study by the Queen Square group indicated that some patients with paraproteinemia had lower flows under the test conditions than controls with a similar degree of anemia. A larger study by the same group contains a number of individuals whose clinical state and CBF seemed unaffected by high paraprotein and plasma viscosity levels with little change after plasmaphoresis. It should be emphasized that these CBF measurements,
using a $^{133}$Xe clearance technique, largely reflect flow through the cerebral cortex. In patients with paraproteinemia the first neurological symptoms suggest impaired perfusion in the posterior circulation.\textsuperscript{19, 20} Measurements of brain stem flow in patients with the so-called "hyperviscosity syndrome" are therefore awaited with interest.

The situation is simpler in people with high plasma fibrinogen levels because they tend to have a normal Hct. Grotta et al\textsuperscript{21} confirm that CBF is adversely influenced by high fibrinogen\textsuperscript{22} but to a lesser extent than by Hct. Furthermore, lowering fibrinogen using clofibrate has been shown to normalize flow.\textsuperscript{21}

It now seems likely that under normal physiological conditions, the delivery of oxygen has a more important influence on blood flow than does viscosity. However, the rheological properties of blood may become critical under pathological circumstances. A low flow whatever its cause may be potentially harmful in a patient at risk from stroke. High\textsuperscript{22, 23} or high normal Hb\textsuperscript{24} and Hct\textsuperscript{25} and presumably low CBF predispose TIA and stroke. Although Hct does not seem to be correlated with the degree of atheroma, Harrison et al\textsuperscript{26} have reported that carotid occlusion is more likely with increasing Hct and that the size of the resulting infarct is related to the Hct level. Although the former observation may be partly due to the influence of red cell ADP on platelet activity,\textsuperscript{27} the latter is probably flow dependent. The slower flow with higher Hct may limit the efficiency of alternative blood supply through collateral vessels. This hypothesis is difficult to test because of the practical and theoretical problems of accurate CBF measurements in the penumbra of a recent infarct. Interestingly, patients whose Hb has abnormally high oxygen affinity maintain a high CBF despite high Hct and viscosity\textsuperscript{28} and do not seem to be prone to occlusive vascular disease.\textsuperscript{29}

Grotta et al\textsuperscript{21} rightly emphasize the importance of viscosity factors in low flow states. Under these circumstances, whether there is a low blood volume, poor cardiac output, or a more peripheral problem, distal to a tight stenosis or even more dangerously, a combination, shear rates will fall and viscosity may increase many times. This will tend to slow flow even further. A viscous, viscious circle might be entered, with progressive slower flows favoring thrombus formation. Conversely, any improvement in flow results in an increase in shear rates and a reduction in viscosity.

Fortunately, high whole blood viscosity is often amenable to treatment. A high Hct from dehydration should be treated promptly with fluid replacement. Otherwise Hct can be lowered quickly by isovolemic venesection. The possible risks of venesection need to be considered\textsuperscript{31, 32} and further work is indicated especially to clarify the effect on platelet function.\textsuperscript{33} The optimal Hct for oxygen delivery in healthy individuals is probably around 0.30.\textsuperscript{34} In the arteriosclerotic, who may have impaired cardiac reserve, aiming at a value of 0.40 is probably more realistic. Abnormally high levels of paraprotein may be removed by plasmaphere-

\textsuperscript{20} Fibrinogen can be lowered acutely using eg. arvin (Ancrod)\textsuperscript{35} and chronically using eg. clofibrate.\textsuperscript{21}

Indeed, one of the most pressing arguments in favor of considering these viscosity factors seriously in patients with or at risk from cerebral infarction is that they may be modified relatively easily, whereas correction of other facets of a complex vascular problem may be both more difficult and more hazardous.

D. J. Thomas, M.D.
St. Mary's Hospital, W2 and
Institute of Neurology, Queen Square
London, England

References
Intra-Operative Monitoring and Internal Shunts: Are They Necessary in Carotid Endarterectomy?

The purpose of carotid endarterectomy is to reduce the risk of future stroke. Unless the incidence of stroke related to the surgery is extremely low, there is little likelihood of benefit for patients. It is widely held that clinically significant ischemia is a relatively common sequel to temporary carotid clamping. As a result, there has been great emphasis since the inception of carotid endarterectomy on the development of methods to protect the brain from ischemic insult, and to identify those patients at particular risk. The use of local or regional anaesthesia, which undoubtedly exaggerates the risk of ischemia, has given way to the use of general anaesthesia which increases the tolerance of the brain to temporary carotid occlusion by enhancing cerebral blood flow, reducing cerebral metabolic requirements, and improving the control of arterial gas concentrations.

However, anxiety persists regarding the possibility of intra-operative stroke directly attributable to critical reductions in flow during cross-clamping. The result is a voluminous and generally uncritical clinical literature in which prominent advocates offer contradictory advice as to the necessity and best means of affording cerebral protection by the use of intra-operative monitoring and internal shunts. These are more than minor technical matters for the surgeon, and a rational resolution of the controversies raised is highly desirable. The expectation of perfect results from carotid endarterectomy is increasingly great, and the prospect of litigation, however unjustified, is constantly present. If the likelihood of hemodynamic ischemia is not as great as generally supposed, then undue emphasis has been given to this aspect of the surgical problem and perhaps insufficient emphasis to patient selection, anaesthetic technique, and the importance of meticulous surgery. As well, certain assumptions regarding the ischemic tolerance of the brain may be brought into question. Internal shunts are not without their own risks, and may provide the surgeon with a false sense of security. Their unwarranted use will expose the patient needlessly to the risk of embolization of atheromatous debris, or intimal dissection and acute occlusion, and may limit the exposure of the plaque and the adequacy of the endarterectomy. What are surgeons and other practitioners with an interest in this procedure to think in the face of this conflicting advice regarding monitoring and shunts? Why has a consensus not been possible to date?

The report of Hunter et al in this issue of STROKE purporting to establish that carotid "back" pressure measurements are useful in determining the need for an internal shunt during carotid endarterectomy does not help in resolving the issue. They suggest that a significant proportion of patients undergoing carotid endarterectomy require a shunt to prevent post-operative neurological complications, but provide no compelling evidence for such a claim, and make no reference to an important body of literature that does not support such a contention. They argue that a "back" pressure of less than 25 mmHg (whether this is mean, systolic, or diastolic pressure is not specified) represents a critical threshold value for ischemia that demands a shunt to avoid stroke. They offer no convincing objective evaluation of this threshold value. A back pressure less...
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D J Thomas

doi: 10.1161/01.STR.13.3.285

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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