Progress Review

Hemorheology of the Cerebral Circulation in Stroke

JAMES H. WOOD, M.D., AND DAVID B. KEE, JR., M.D.

ARTERIAL STENOSIS, thrombosis, embolization and vasospasm often produce a reduction in regional brain perfusion to levels which result in focal cerebral ischemia. The metabolic consequences of this ischemic insult produce neurologic deficits which may be reversible or irreversible, depending upon both the depth and duration of the ischemia.1 Therefore, the study of factors influencing cerebral blood flow in the normal and pathological state has assumed a prominent position in the field of cerebrovascular disease.

Both surgical and medical modalities have been proposed as therapeutic options for the prevention, reversal and amelioration of ischemic neurologic deficits. Carotid endarterectomy and extracranial-to-intracranial arterial bypass have become routine surgical procedures for patients with selected forms of cerebrovascular disease. Unfortunately, in instances of acute focal cerebral ischemia, the efficacy of these procedures performed as emergencies is limited by the time requirements for radiological assessment, patient preparation, and execution of these operations. Nevertheless, if the treatment of ischemic stroke is to be successful, early reperfusion of the ischemic brain regions is imperative.

As opposed to surgical revascularization, medical manipulation of blood viscosity offers an effective and rapid means of increasing perfusion to acutely ischemic cerebral regions.3 In addition, such therapy may serve as an adjunct to the surgical treatment of cerebrovascular disease,4 as well as the chronic management of patients with reduced cerebral perfusion. Awareness of hemorheologic parameters influencing cerebral perfusion allows a rational approach to the clinical treatment of focal cerebral ischemia.

Basic Principles

Hemorheologic studies are primarily concerned with blood viscosity. Viscosity represents a measure of internal friction, which, in laminar flow systems, correlates shear stress to shear rate.3 The term shear rate is almost synonymous with velocity gradient. Blood flow in any given cerebral vessel has a range of velocities with that of axial flow being greater than that of peripheral flow. If the geometry of that vessel is constant, shear rate is directly proportional to velocity of blood. The lowest shear rates occur in the venules of the microcirculation.

Factors determining blood viscosity include hematocrit, erythrocyte aggregation, erythrocyte flexibility,5 platelet aggregation and plasma viscosity.7 Finally, blood viscosity varies inversely with the shear rate such that at lower flow rates, viscosity increases, and as the flow increases, blood viscosity is reduced. This property of blood is dependent upon blood viscosity factors, particularly erythrocyte flexibility and aggregation.8 The influence of other factors on blood viscosity, such as the Fahreus effect, screening effect and the inversion phenomenon depend upon blood vessel diameter.

Blood Flow in the Macrocirculation

Blood flow through conductance vessels (i.e., diameters larger than 100 μ) has been classically, although imprecisely, described by the Hagen-Poiseuille equation,

\[ Q = \frac{\Delta P \pi r^4}{8 L \eta} \]

where Q is blood flow, P is the pressure gradient, r is vessel radius, L is vessel length, and \( \eta \) is viscosity. This equation not only demonstrates the inverse relationship between blood flow and viscosity, but also suggests that the only variables which may be manipulated in the clinical setting to improve blood flow are the pressure gradient, vessel radius and viscosity. Unfortunately, the Hagen-Poiseuille equation describes the flow of Newtonian fluids and blood behaves in a non-Newtonian fashion with blood viscosity increasing as the shear rate decreases. Thus, the Hagen-Poiseuille equation does not precisely describe the relationship between blood flow and blood viscosity especially at low shear rates.5,8 Under normal conditions in healthy individuals, the pressure gradient and radius of conductance vessels are the major determinants of cerebral blood flow. However, in areas of focal cerebral ischemia which have lost their capacity to pressure autoregulate7 and, in which vessels radius is maximal,10 the blood viscosity assumes great importance in the determination of cerebral perfusion.

Hematocrit is a major factor influencing blood viscosity11,12 and its importance increases as the shear rate decreases (fig. 1). Clinically important is the observation that the steepest portion of the blood viscosity-hematocrit curve occurs within physiologic ranges of hematocrit. This curve shifts to the left as the shear rate decreases. Thus, a reduction in hematocrit within the physiologic range (30-50%) reduces blood viscosity more profoundly at the lower shear rates representative of low flow states.1

In conductance vessels, erythrocyte aggregation

From the Division of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia 30322.

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Figure 1. Influence of hematocrit on viscosity at varying rates of shear (within parentheses by each curve). The steep portion of the curve representing a low shear rate is within the physiological range of hematocrit. (Modified with permission from Stone HO, Thompson HK, Schmid-Nielson K: Influence of erythrocytes on blood viscosity. Am J Physiol 214: 913–918, 1968)

also influences blood viscosity. The normally reversible aggregation of erythrocytes is dependent upon the shear rate and the surface characteristics of these cells, such as membrane structure, electrostatic forces, presence of macromolecules (particularly fibrinogen), as well as metabolic factors, such as osmolarity and blood pH. Erythrocytes clump or aggregate as the shear rate decreases and disaggregate as the shear rate increases. With laminar blood flow, the largest erythrocyte aggregates occur axially in the central low shear areas, while disaggregation tends to occur in high shear regions along the vessel walls. Blood viscosity is increased in proportion to the degree of erythrocyte aggregation.

Although erythrocyte flexibility is an important determinant of blood viscosity at any hematocrit in vessels of any radius, this factor relates more to the microcirculation. The low internal viscosity of the erythrocyte promotes great flexibility of its membrane which maintains blood in the fluid state, even at exceptionally high hematocrits. Platelet aggregation affects blood viscosity and blood flow by two mechanisms: (a) platelet aggregates may precipitate intravascular coagulation and generate thrombus; and (b) platelet aggregates may obstruct arteriolar and capillary vessels. Platelet aggregation, unlike erythrocyte aggregation, is generally irreversible. As erythrocyte aggregation increases, smaller platelet particles within the axial stream move to the outer laminae of flow where shear rates are highest. Platelets within these high shear laminae are exposed to injury and thereby increase their adhesiveness and aggregation. Thus, erythrocyte aggregation may secondarily exacerbate platelet aggregation, further increasing blood viscosity and decreasing blood flow.

Plasma viscosity is largely influenced by the presence of macromolecules such as fibrinogen and \( \alpha-2 \)-macroglobulin. Elevated plasma fibrinogen concentrations in turn augment erythrocyte aggregation. Although elevation plasma viscosity may influence blood flow through vessels at any radius, the hemorheologic contributions of plasma viscosity requires further study.

Blood Flow in the Microcirculation

By definition, cerebral microcirculation begins at the level of penetration of 30–70 \( \mu \) diameter arterioles into the brain substance. Vessel size is gradually reduced to a precapillary arteriolar diameter of 14–25 \( \mu \) with the smallest capillary diameter being approximately 4–6 \( \mu \). The venules of the microcirculation tend to mirror the arterioles with respect to their diameter at a given cortical depth, gradually increasing in size until they exit the brain substance to become the conductance venous system within the subarachnoid space.

Studies of blood flow and viscosity within the microvasculature are more complex and have required capillary models. The Fahreus and Cindqvist first described an apparent decrease in viscosity of blood flowing through tubes of progressively smaller diameter. The Fahreus effect, partially accounted for the inaccuracy of the Hagen-Poiseuille equation to predict blood viscosity in capillary tubes of a diameter below 0.3 mm. This blood viscosity reduction in small capillary tubes is postulated to be secondary to the observed reduction in hematocrit that occurred as the tube diameter decreased. This observation is termed the inversion phenomenon and the vessel radius at which this inversion occurs is defined as the critical radius. Thus, this reversal of the Fahreus effect occurs at a vessel diameter approaching the diameter of the erythrocyte. The Fahreus effect has been found to vary as a function of the feed hematocrit (the hematocrit of...
blood entering the capillary tube) and the flow velocity within the capillary. With constant flow, the Fahreus effect varies linearly with the feed hematocrit, however, at unsteady flow rates, the Fahreus effect is variable. The Fahreus effect has also been found to be inversely proportional to the hematocrit in larger diameter tubes and independent of hematocrit in smaller tubes.

In addition, a screening effect which mechanically reduces the hematocrit as the erythrocytes enter into the ostia of capillary tubes whose diameter is less than 60 μ increases as the flow rate decreases. This screening effect appears to be less influenced by tube hematocrit than the Fahreus effect.

Similar to that in conductance vessels, blood flow and viscosity in the microcirculation also vary with hematocrit, erythrocyte flexibility, platelet aggregation and plasma viscosity. The exact hematocrit in the microcirculation is disputed. The hypothesis that the contribution of the erythrocyte to blood viscosity in the microcirculation is less significant than that observed in the systemic circulation is based upon studies observing that the hematocrit within the initial segment of capillary-sized tubes approaches a value approximately two-thirds that of the systemic hematocrit and that the hematocrit ratio for brain and subarachnoid vessels is about 0.69. However, Dintenfass found that the critical capillary radius at which the inversion phenomenon occurs is directly related to the capillary hematocrit. Therefore, the relationship of blood flow and viscosity within the microcirculation with respect to hematocrit appears to be more complex than that observed in the conductance vessels and requires further investigation.

Erythrocyte aggregation may profoundly modify cerebral blood flow in the microcirculation. As opposed to the larger size of conductance vessels, the smaller diameter of the capillaries may undergo actual plugging or obstruction by sufficiently-sized erythrocyte aggregates. Since erythrocyte aggregation is shear-rate dependent, this aggregation may be enhanced within the microcirculation in ischemic regions where the blood flow and, consequently, the shear rates are depressed. This augmentation of erythrocyte aggregation would further increase blood viscosity and reduce blood flow, thus producing a vicious cycle.

Both the marked flexibility and low internal viscosity of the human erythrocyte are major determinants of blood flow in the microcirculation. Experimental demonstrations of a critical radius as low as 2 μ imply a remarkable deformability of normal erythrocytes under appropriate flow conditions. This flexibility decreases with aging of the erythrocyte and the spleen functions to sequester these cells as they become more rigid, thus assuring that circulating erythrocytes are optimally suited to flow within the microcirculation. The aging processes, as well as various hemoglobinopathies, decrease erythrocyte flexibility with potentially adverse effects on perfusion through the microcirculation.

Blood flow in the microcirculation is also affected by platelet aggregation. As platelet aggregates increase, the vessel radius at which the inversion phenomenon occurs also increases. Platelets, having almost no flexibility, behave as rigid particles, thus producing an increase in blood viscosity in direct proportion to their concentration.

As in conductance vessels, normal and pathologic levels of plasma proteins, particularly fibrinogen, theoretically affect viscosity and blood flow in the microcirculation.

Hemorheology in Experimental Cerebral Ischemia

Pathologic alterations in the rheologic factors of blood may underlie or result from acute reductions in brain perfusion. Experimental attempts have been made to favorably manipulate these factors to improve cerebral blood flow.

Ischemia secondary to either acute or progressive decreases in regional cerebral perfusion compromises neuronal activity and, subsequently, produce neurologic deficit. As the depth of ischemia increases, membrane pumps fail and neuronal death occurs. In focally ischemic regions, the gradient of shear rates within vessels is depressed as the blood flow slows distal to a narrowed or occluded segment of cerebral artery. A vicious cycle results as the elevated blood viscosity within the region of slow blood flow further compromises perfusion and ischemia deepens. The irreversibility of this neuronal insult is dependent upon both the depth and duration of the ischemia as well as the ability of conductance vessels to provide adequate collateral circulation to maintain neuronal metabolism within the ischemic region.

Experimental studies have demonstrated significant elevations in regional cerebral blood flow in focally-ischemic brain following the acute reduction of hematocrit employing hypervolemic infusions of autologous plasma or low-molecular-weight dextran. In one animal study, the size of hemispheric infarction following distal internal carotid and proximal middle cerebral arterial clipping was decreased by 60% after the administration of two serial infusions of low-molecular-weight dextran, each equal to 20% of the total blood volume. Experimental demonstrations of significant elevations in regional cerebral blood flow in ischemic but not in non-ischemic brain imply that the effect of hypervolemic hemodilution on brain perfusion is greater in regions of low flow and may be related to infusion-induced alterations in blood viscosity. This hypothesis is supported by experimentally-demonstrated inverse correlations between cerebral blood flow within ischemic regions and fresh blood viscosity at low shear rates following hypervolemic hemodilution with autologous plasma. This inverse relationship between cerebral perfusion and fresh blood viscosity occurs following low-molecular-weight dextran or autologous plasma infusions even in the absence of ischemia. Although the oxygen content of the blood is reduced as the hematocrit is decreased, the relative oxygen transport capacity has been calculated to increase as
FIGURE 2. Influence of hematocrit on the relative oxygen transport capacity of blood. Note the increase in relative oxygen transport capacity as the hematocrit decreases to approximately 30–33% despite the reduction in blood hemoglobin. As the hematocrit is reduced below 30%, the relative oxygen transport capacity falls. (Modified with permission from Hint H: The pharmacology of dextran and the physiological background for the clinical use of Rheomacrodex and Macrodex. Acta Anaesthesiol Belg 19: 119–138, 1968)

the hematocrit is lowered to approximately 30% or (fig. 2). Accordingly, the optimal hematocrit for the survival of critically-ill postoperative patients has been reported to be 33%. Our own experimental studies have supported this concept by demonstrating a favorable inverse relationship between regional cortical oxygen transport and hematocrit in ischemic, but not in normal, brain after hypervolemic hemodilution to a mean hematocrit of 33% with autologous plasma. Other experimental and clinical evaluations have calculated optimal oxygen transport to the brain to occur at hematocrit of 35% and 40–42%, respectively. Recently, the reduction of hematocrit by venesection has also been shown to elevate oxygen transport to the brain in patients with high hematocrits.

Contrarily, hyperexpansion of the intravascular volume without hemodilution does not appear to improve cerebral blood flow. Whole blood infusions administered to dogs with focal ischemia secondary to cerebral arterial occlusions do not elevate cortical blood flow within the area of focal ischemia in the presence of unaltered blood pressure, despite significant elevations in cardiac output. In addition, no correlation was observed between cardiac output and cerebral blood flow following nonhemodilutional hypervolemia. Decreased velocity of blood flow through superficial cortical vessels and enhancement of cerebral infarction has been observed in animals transfused with packed erythrocytes. This unfavorable influence of nonhemodilutional hypervolemia with secondary hemoconcentration has been attributed to elevations in blood viscosity and cellular aggregation.

In general, alterations in blood flow and viscosity resulting from manipulations of erythrocyte aggrega-
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... tors. Increased platelet aggregation has been observed in young stroke patients when compared to young control individuals.

Although numerous investigators have attempted to enhance cerebral perfusion by manipulating rheologic factors in the treatment of acute cerebral ischemia, most early retrospective studies which either supported or refuted the beneficial effect of low-molecular-weight dextran infusions in the treatment of acute ischemic stroke were all compromised by various problems in design, methodology and assessment. Subsequent prospective evaluations of low-molecular-weight dextran or 5% serum albumin solutions in patients with ischemic stroke have demonstrated diffuse improvement in regional cerebral blood flow, as well as significant increases in mean power frequency or reductions in the slowing of the quantitative electroencephalogram. The induced augmentation of regional cerebral perfusion correlated inversely with hematocrit (Fig. 4). More recently, a prospective randomized clinical trial in Sweden has verified the beneficial effect of the acute reduction in hematocrit (via venesection and low-molecular-weight dextran infusions) on the neurologic deficit in patients with acute cerebral ischemia less than 48 hours in duration. That study found 85% of 52 hemodiluted and 64% of 50 control patients improved in neurological scoring over the first 10 days. At 3 months of follow-up, both groups had similar mortality rates, however the surviving group of hemodiluted patients had 3 times fewer patients remaining in the hospital and 3.8 times fewer patients unable to walk than did the surviving group of control patients. Thus, hemodilution therapy improved the overall clinical outcome over the first 3 months.

Attempts at clinically manipulating rheologic factors other than hematocrit have thus far been limited in number. Infusions of hydroxyethyl starch, a synthetic plasma volume expander, have been reported in preliminary trials to decrease erythrocyte aggregation, but only at concentrations of greater than 4%. Contrary to discouraging reports of the experimental lowering of serum fibrinogen levels, a recent clinical trial employing pentoxifylline, an inhibitor of fibrinogen synthesis, found significant reductions in blood viscosity and in plasma fibrinogen concentration, as well as improved platelet disaggregation and erythrocyte filterability, in patients with cerebrovascular disease, treated for 6 weeks. These pentoxifylline-treated patients experienced significantly fewer ischemic episodes than did control patients.

Current Application and Future Investigation

Presently, incremental venesection with intravascular volume replacement with colloid solutions (isovolemic hemodilution) is used to increase cerebral blood flow in patients after cerebral arterial bypass surgery during the period in which the anastomosis undergoes dilatation. Isovolemic hemodilution may be useful in augmenting cerebral perfusion distal to an obstructed or a severely stenotic carotid artery in patients with acute cerebral infarcts who are waiting 3–6 weeks to undergo cerebral arterial bypass surgery or carotid endarterectomy.

Intravascular volume expansion by the infusion of hemodiluting colloid solutions (hypovolemic hemodilu-
Experience with hypervolemic hemodilution in the treatment of patients with vertebrobasilar ischemia is limited. Encouraging results have been observed in those patients with documented basilar artery stenosis; however, no improvement has occurred in patients with basilar artery occlusion (Wood JH, unpublished data). Since hypervolemic hemodilution elevates collateral perfusion to ischemic brain regions which have anatomic anastomoses between major vascular territories and since the augmented collateral flow is proportional to the degree of collateralization, hypervolemic hemodilution is not likely to benefit ischemia in poorly-collateralized brain regions supplied by occluded functional end-arteries. Therefore, ischemic patients with occluded lenticulostriate, thalamoperforate, or penetrating basilar arterial branches would not be considered good candidates for this type of rheologic treatment.

Based upon these experimental and clinical observations which suggest that acute reductions in hematocrit may favorably modify the course of acute cerebral ischemia, the necessity of a prospective, randomized clinical trial involving large numbers of patients emerges. Such an investigation would require accurate assessment of the nature of the cerebrovascular event and assure comparable control and treatment groups by excluding patients in whom hemodilution therapy is likely to be of no benefit such as those with intracerebral hemorrhage and increased intracranial pressure, as well as those with brainstem or lacunar infarctions. In patients with higher baseline hematocrits, venesec tion would be required in addition to the infusion of plasma volume expanding colloids, because infusion alone cannot rapidly or sufficiently reduce high hematocrits. Pulmonary capillary wedge pressure monitoring in an intensive care unit setting is needed for patients with marginal cardiac reserve, to ensure effective and safe hemodilutional therapy. The goal of therapy in all patients is the rapid reduction of hematocrit to a level of approximately 33% as soon as possible following the onset of acute cerebral ischemia. Although all of the treated patients would be maximally-hemodiluted within safe limits, those patients whose baseline hematocrits were higher at the time of admission would be expected to experience greater augmentation in cerebral blood flow, and, possibly, be more apt to demonstrate neurologic improvement following hemodilution. Therefore, the statistical analyses should include stratifications based upon the hematocrit prior to treatment. One such protocol strategy is presented in table 1. Our experience (Wood JH, Prats AR, unpublished data) suggests that hemodilution therapy that does not result in a hematocrit reduction of

### Table 1. Clinical Guidelines for Hypervolemic Hemodilution

**Initial patient evaluation**

- Establish baseline motor and speech function for subsequent comparisons during therapy.
- Detect altered level of consciousness, which may indicate increased ICP and thereby preclude use of hypervolemic hemodilution.
- Examine cranial CT for evidence of acute structural cerebral damage (hypodensity, enhancement, hemorrhage, and/or mass effect), etiology of present insult, and presence of previous cerebral infarctions.
- Examine cerebral angiogram for etiology of present insult and degree of collateralization.
- Determine baseline hematocrit, central venous pressure, and, in case of elderly or cardiac patients, pulmonary wedge pressure or cardiac output.

**Infusion technique**

<table>
<thead>
<tr>
<th>Baseline hct (%)</th>
<th>Venection*</th>
<th>Colloid replacement†</th>
<th>Expected acute % hct reduction</th>
<th>Adjusted colloid infusion‡</th>
</tr>
</thead>
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<tr>
<td>36–40</td>
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<td>8–18%</td>
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<td>41–46</td>
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</tr>
<tr>
<td>46 or greater</td>
<td>1000 cc</td>
<td>1000 cc</td>
<td>28% or greater</td>
<td>yes</td>
</tr>
</tbody>
</table>

Infusion rate adjusted to maintain hematocrit at approximately 33%.

Infusion rate adjusted to "normalize" intravascular volume (CVP between 8 and 12 cm H₂O).

In patients with marginal cardiac reserve, infusion rate adjusted to keep PCWP less than 20 mm Hg.

Maintain infusion for 72 hours, then attempt taper.

If level of neurologic improvement deteriorates during taper, increase infusion rate and reattempt taper in 48 to 72 hours.

*Calculated for average body weight but may require adjustment for extremes of body weight.

†Note that maximum dose of Dextran-40 given must not exceed 1.5 gm/kg per day so as to avoid coagulation complications. Thus, maximum daily dose of 10% Dextran-40 is 15 cc/kg.

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Abbreviations: CT = computed tomographic scan; ICP = intracranial pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; Dextran-40 = low-molecular-weight dextran.

greater than 15% does not necessarily raise cerebral blood flow and therefore patients with acute cerebral ischemia and relatively low hematocrits (30–38%) may not be expected to improve after hemodilution therapy. Thus, the assessment of cerebral blood flow during hemodilution therapy is crucial in clinical trials of this hemorheologic therapy.

Duration of therapy will vary from a minimum of 72 hours to a maximum depending upon the ability to taper the patient from the infusion while maintaining the level of improvement obtained during the course of treatment. Both short-term and long-term results will be necessary to adequately evaluate any difference between treated and untreated groups.

If further studies of appropriate patient populations support published preliminary experimental and clinical observations, hemorheological manipulation may offer a rapid and relatively simple approach to the treatment of acute ischemic neurologic deficit secondary to cerebral arterial stenosis, thrombosis, embolization or vasospasm. In addition, such therapy should be used routinely to augment cerebral blood flow peripheratively in patients undergoing cerebral revascularization, carotid endarterectomy, carotid ligation and aneurysm surgery.

References