Optimum degree of hemodilution for brain protection in a canine model of focal cerebral ischemia

SUN HO LEE, M.D., ROBERTO C. HEROS, M.D., JOHN C. MULLAN, M.D., AND KAZUYOSHI KOROSUE, M.D.

Department of Neurosurgery, University of Minnesota Medical School, Minneapolis, Minnesota

The ability of hemodilution to lower blood viscosity and increase cerebral blood flow has been proven experimentally; however, the optimum hematocrit for maximum oxygen delivery to ischemic brain tissue is not known, and a study was designed to determine this. Fifty dogs were selected for inclusion in the study using criteria based on changes in somatosensory evoked potentials at the time of arterial occlusion, which were found in a previous study to predict the development of a moderate infarction of relatively constant size. Infarctions were induced by permanent occlusion of the left middle cerebral artery and the azygous anterior cerebral artery. The animals selected for inclusion were divided into five groups of 10 dogs each: 1) a control group; 2) a group with 25% hematocrit; 3) a group with 30% hematocrit; 4) a group with 35% hematocrit; and 5) a group with 40% hematocrit. Ischemic hemodilution was accomplished 1 hour after occlusion of vessels using dextran infusion and blood withdrawal. The animals were sacrificed after 6 days and infarction volume was determined from fluorescein-stained sections. Statistical analysis was performed using Student's t-test and one-way analysis of variance.

Mean infarction volume for each group, expressed as a percentage of total hemispheric volume ± 1 standard error of the mean, was 28.3% ± 2.8% for the control group, 33.6% ± 3.4% for the 25% hematocrit group, 17.1% ± 2.2% for the 30% hematocrit group, 29.2% ± 4.3% for the 35% hematocrit group, and 29.9% ± 2.1% for the 40% hematocrit group. The 30% hematocrit group showed the smallest average infarction size and this size differed significantly (P = 0.02) from the average infarction size in the control animals. These results show that, in this model of focal ischemia, a hematocrit of approximately 30% is optimum for protecting the brain.

Key Words: hemodilution, cerebral ischemia, hematocrit, infarction, dog

In the wake of cerebral ischemia, one approach to increase cerebral blood flow (CBF) and protect the brain is to improve the rheological properties of blood by lowering its viscosity. Since the most important determinant of viscosity is the hematocrit, hemodilution is a practical and effective way to reduce viscosity. Hemodilution increases CBF and generally there is an inverse relationship between CBF and hematocrit.11,46 Recent work from our laboratory has suggested that the improvement in CBF seen after hemodilution is a result of the decrease in viscosity per se, as opposed to being a compensatory mechanism in response to the decrease in oxygen-carrying capacity that accompanies hemodilution.34 There is considerable evidence that hemodilution is an effective way to increase perfusion in the ischemic brain.34,54,55

Although hemodilution does increase perfusion in ischemic brain, it also decreases the oxygen-carrying capacity of blood. In normal brain, where autoregulation is intact, oxygen delivery remains constant within a certain range of hematocrit values because CBF changes in such a way as to compensate for the changes in oxygen-carrying capacity.1,35 However, in ischemic brain, where autoregulation is lost and resistance vessels are already maximally dilated, hemorheological factors may play a major role in determining CBF and oxygen transport to ischemic tissue. The available data have not clearly defined the optimum hematocrit for maximum oxygen transport to ischemic cerebral tissue. In particular, there has been no experimental study correlating the degree of hemodilution after ischemia with outcome. This study was designed to elucidate the optimum hematocrit for protection of ischemic cerebral tissue, using infarct size and neurological condition as outcome measures.

Materials and Methods

General Protocol

Sixty-two conditioned adult mongrel dogs, each weighing 15 to 20 kg, were used for this study. National Institutes of Health standards were met or exceeded in
the preparation, surgical and anesthetic techniques, and housing of the animals. Twelve animals were excluded because of technical error or because they did not meet the selection criteria based on somatosensory evoked potential (SSEP) monitoring as described below. The remaining 50 animals were randomly allocated to one of five groups of 10 animals each: controls, 25% hematocrit, 30% hematocrit, 35% hematocrit, and 40% hematocrit. The average hematocrit of the control group (no hemodilution) was 50.1 ± 1.4% (± standard error of the mean (SEM)).

Animal Preparation

All animals were splenectomized 1 week prior to craniotomy in order to abolish the volume reservoir function of the spleen and to maintain an isovolemic condition during the study. On the day of craniotomy, anesthesia was induced with intravenous thiamylal sodium (25 mg/kg) and maintained with 0.5% to 2% halothane. The animals were intubated with auffed endotracheal tube and ventilated with a Harvard ventilator. Arterial PCO₂ was determined hourly and ventilation was adjusted to keep the PaCO₂ between 30 and 35 mm Hg. A heating blanket was used to maintain rectal temperature at 37.5°C. Pancuronium (1 mg/kg, given intramuscularly) and bicolin (600,000 U subcutaneously) were administered at the beginning of the procedure. In all animals the left femoral artery was cannulated with a No. 16 catheter for blood pressure monitoring and blood gas determination, as well as for hemodilution and blood sampling. A 2 × 2-cm craniectomy was made over the left frontoparietal cortex and a Silastic leaflet with three electrodes (4-mm diameter platinum disc electrodes with 6-mm separation) was positioned beneath the dura for SSEP measurement. The electrodes were moved until a SSEP waveform characteristic of placement over the somatosensory cortex (C3 position) was obtained. The Silastic leaflet was then fixed to the dura and the surrounding skull. The left middle cerebral artery (MCA) and the azygous anterior cerebral artery (ACA) were exposed through a small left retro-orbital craniectomy. The animals then underwent permanent occlusion of the left MCA at a point before its bifurcation, followed by occlusion of the azygous ACA with a single 4 × 0.75-mm Scoville-Lewis clip, while SSEP’s were monitored to select animals with moderate-sized infarcts as described below. Serum glucose and hematocrit were measured after induction of anesthesia, immediately after hemodilution, 6 hours after occlusion, and on postoperative Days 1, 4, and 6.

The animals were kept alive for 1 week after surgery and a daily neurological assessment was performed. Somatosensory evoked potentials were recorded before and after vessel occlusion and on postoperative Day 6.

Monitoring of SSEP’s

Platinum needle electrodes were placed in the distribution of the second division of the right trigeminal nerve and stimuli were given as 10-msec square waves at 1/sec, with the voltage adjusted to twice the threshold (8 to 10 V) required for facial twitch. The SSEP’s were recorded from an electrode on the above-mentioned subdural Silastic strip, with another electrode in the ipsilateral temporal muscle serving as reference. Averaging over 50 responses was performed. The amplitude was measured from the top of the major positive peak to the bottom of the major negative peak. The selection criteria for dogs likely to have moderate-sized infarctions, determined in a previous study in our laboratory, are as follows: after MCA occlusion, SSEP amplitude should not fall below 25% of baseline amplitude and, after subsequent azygous ACA occlusion, the amplitude should fall below 15% of baseline amplitude. In our previous study, animals in which the SSEP amplitude fell below 25% of baseline value after MCA occlusion alone had massive infarctions and did not survive. On the other hand, animals in which the SSEP amplitude did not fall below 15% of baseline value after MCA and subsequent azygous ACA occlusion had either no infarct or only minimal infarction. We postulated that, by using these criteria a priori, animals could be selected that would have a relatively uniform infarct size, thus reducing the overall number of animals required for meaningful comparison studies. This in fact was confirmed in a separate group of animals in which these criteria were used a priori.

Isovolemic Hemodilution

Isovolemic hemodilution was accomplished immediately after occlusion of the vessels by the withdrawal of 50 ml of blood and the simultaneous infusion of 35 ml of low-molecular-weight dextran. This procedure was repeated until the designated hematocrit level was reached. Since low-molecular-weight dextran is a hypotonic and hyperoncotic solution, it attracts water from the extravascular space and expands blood volume by about 1.5 times the volume of dextran infused. Thus, the infusion volume of this agent required to maintain isovolemia in our several previous studies was found to be only 70% of the volume of blood withdrawn.

Postoperative Care and Monitoring

The animals were cared for in a postoperative recovery facility for 6 days. During this period they were given free access to food and water. On any day that an animal could not drink, 50 ml normal saline was administered subcutaneously. Neurological assessment was performed daily according to the following modification of the criteria of Crowell and Olsson:~ Grade 1: normal; Grade 2: mild hemiparesis, stands without assistance, able to walk, may circle toward operated side; Grade 3: stands without assistance but does not walk, no impairment of consciousness; Grade 4: cannot stand and/or decreased level of consciousness; and Grade 5: dead.

Measurement of Infarct Size

The animals were sacrificed on Day 6 for determination of infarct volume. They were given an intravenous injection of 15 ml (100 mg/ml) fluorescein and were sacrificed 30 minutes later by intravenous injection of 20 mEq potassium chloride. The brains were
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**TABLE 1**

*Serum glucose levels in a canine model of cerebral ischemia*  

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Posthemodilution*</th>
<th>Postop Day 1</th>
<th>Postop Day 4</th>
<th>Postop Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>125.2 ± 12.6</td>
<td>117.0 ± 9.2</td>
<td>99.7 ± 10.2</td>
<td>90.7 ± 7.8</td>
<td>79.0 ± 5.0</td>
</tr>
<tr>
<td>Hct 25%</td>
<td>98.6 ± 7.8</td>
<td>130.3 ± 8.0</td>
<td>122.1 ± 8.2</td>
<td>102.0 ± 5.0</td>
<td>98.1 ± 4.6</td>
</tr>
<tr>
<td>Hct 30%</td>
<td>114.5 ± 9.7</td>
<td>138.2 ± 9.8</td>
<td>115.2 ± 6.3</td>
<td>103.7 ± 5.3</td>
<td>92.7 ± 9.3</td>
</tr>
<tr>
<td>Hct 35%</td>
<td>132.0 ± 6.4</td>
<td>161.4 ± 8.3</td>
<td>117.1 ± 5.9</td>
<td>104.5 ± 6.5</td>
<td>111.6 ± 8.1</td>
</tr>
<tr>
<td>Hct 40%</td>
<td>108.4 ± 4.7</td>
<td>114.1 ± 4.5</td>
<td>101.0 ± 6.9</td>
<td>111.8 ± 11.2</td>
<td>96.7 ± 8.6</td>
</tr>
</tbody>
</table>

* Hct = hematocrit. Data are presented as mean ± standard error of the mean, in mg/100 ml. There were 10 dogs in each group.  
† Levels measured immediately following hemodilution.  

**TABLE 2**

*Mean systemic arterial blood pressure in a canine model of cerebral ischemia*  

<table>
<thead>
<tr>
<th>Group</th>
<th>2 Hrs Preop</th>
<th>1 Hr Preop</th>
<th>At MCA/ACA Occlusion</th>
<th>1 Hr Postop</th>
<th>2 Hrs Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>129.6 ± 6.2</td>
<td>125.1 ± 7.5</td>
<td>122.5 ± 6.5</td>
<td>119.1 ± 5.8</td>
<td>115.7 ± 14.0</td>
</tr>
<tr>
<td>Hct 25%</td>
<td>122.5 ± 5.5</td>
<td>122.0 ± 6.3</td>
<td>127.3 ± 5.6</td>
<td>119.9 ± 11.5</td>
<td>118.2 ± 12.0</td>
</tr>
<tr>
<td>Hct 30%</td>
<td>119.9 ± 7.9</td>
<td>119.0 ± 7.2</td>
<td>113.8 ± 5.9</td>
<td>112.4 ± 4.9</td>
<td>116.3 ± 5.0</td>
</tr>
<tr>
<td>Hct 35%</td>
<td>129.8 ± 7.0</td>
<td>126.9 ± 5.7</td>
<td>127.2 ± 6.2</td>
<td>128.0 ± 6.5</td>
<td>122.2 ± 7.4</td>
</tr>
<tr>
<td>Hct 40%</td>
<td>122.6 ± 3.7</td>
<td>117.5 ± 4.2</td>
<td>118.4 ± 5.2</td>
<td>115.8 ± 4.7</td>
<td>109.8 ± 4.9</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± standard error of the mean, in mm Hg. There were 10 dogs in each group. Hct = hematocrit; MCA = left middle cerebral artery; ACA = azygous anterior cerebral artery.  

**TABLE 3**

*Body (rectal) temperature in a canine model of cerebral ischemia*  

<table>
<thead>
<tr>
<th>Group</th>
<th>2 Hrs Preop</th>
<th>1 Hr Preop</th>
<th>At MCA/ACA Occlusion</th>
<th>1 Hr Postop</th>
<th>2 Hrs Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>37.9 ± 0.2</td>
<td>38.1 ± 0.1</td>
<td>38.1 ± 0.1</td>
<td>38.1 ± 0.0</td>
<td>38.8 ± 0.5</td>
</tr>
<tr>
<td>Hct 25%</td>
<td>37.7 ± 0.2</td>
<td>37.8 ± 0.2</td>
<td>37.8 ± 0.2</td>
<td>37.7 ± 0.1</td>
<td>38.3 ± 0.1</td>
</tr>
<tr>
<td>Hct 30%</td>
<td>37.6 ± 0.2</td>
<td>37.8 ± 0.3</td>
<td>37.9 ± 0.2</td>
<td>38.7 ± 0.3</td>
<td>38.0 ± 0.2</td>
</tr>
<tr>
<td>Hct 35%</td>
<td>37.7 ± 0.2</td>
<td>38.1 ± 0.2</td>
<td>38.1 ± 0.2</td>
<td>38.1 ± 0.1</td>
<td>38.2 ± 0.3</td>
</tr>
<tr>
<td>Hct 40%</td>
<td>37.9 ± 0.2</td>
<td>37.9 ± 0.3</td>
<td>38.1 ± 0.1</td>
<td>38.0 ± 0.1</td>
<td>38.1 ± 0.1</td>
</tr>
</tbody>
</table>

* Data are presented as the mean ± standard error of the mean, in °C. There were 10 dogs in each group. Hct = hematocrit; MCA = left middle cerebral artery; ACA = azygous anterior cerebral artery.  

placed in 10% formalin for 24 hours, then coronally sliced in 3-mm sections. Each slice was examined under ultraviolet light at a wavelength of 366 μm and the areas of fluorescence were considered to be infarcted. This method of infarct determination has been found to be highly reliable when compared to histological sections in our previous studies. The infarct volume of a single slice was calculated from the average of the infarcted areas on both sides of the slice multiplied by the thickness of the slice. The percent of the hemisphere infarcted was determined by comparing the volume of infarct to the entire volume of the ipsilateral hemisphere. The fraction of the hemisphere infarcted was calculated using the Jandel PC3D computer system. Statistical Analysis All values are expressed as mean ± SEM. Comparison among three or more groups was accomplished using one-way analysis of variance with Tukey post hoc comparisons of each group with each of the other groups for each postoperative day. Student's t-test analysis for unpaired data was performed for comparisons involving only two groups. The changes in physiological parameters within the groups were analyzed by Student's two-tailed paired t-test.  

**Results**

**General Physiological Parameters**

The mean intraoperative pCO₂, body temperature, blood pressure, preischemic serum glucose and hematocrit levels, and the mean postoperative body temperature and serum glucose levels were not statistically different (p > 0.05) between the various groups (Tables 1, 2, and 3). The hematocrit did not change significantly
throughout the study after induction of the designated hematocrit level (Table 4).

**Infarct Volume**

The mean infarct volume, expressed as a percentage of the total hemispheric volume ± SEM, was as follows (Table 5): control group (mean hematocrit about 50%): 28.3% ± 2.8%; 25% hematocrit: 33.6% ± 3.4%; 30% hematocrit: 17.1% ± 2.2%; 35% hematocrit: 29.2% ± 4.3%; and 40% hematocrit: 29.9% ± 2.1%. The 30% hematocrit group showed a statistically significant decrease in size of infarct volume when compared to the control group (p = 0.02) and to each of the other groups (p < 0.05). The average infarct volume of the other groups did not differ significantly from the control group or from each other, although the 25% hematocrit group showed a trend toward more severe infarction (Table 5 and Fig. 1).

**Neurological Assessment**

The daily mean neurological grades of the animals are shown in Table 6. Animals in the control group had a mean grade of 2.8 on postoperative Day 1, which improved to a grade of 1.7 by postoperative Day 3. The neurological grade of the 25% hematocrit group was significantly worse than in the control group on postoperative Days 3, 4, 5, and 6. Other than that, there was no significant difference between the groups in terms of neurological status.

**TABLE 4**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Post-Hemodilution†</th>
<th>6 Hrs Postop</th>
<th>Postop Day 1</th>
<th>Postop Day 4</th>
<th>Postop Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>50.1 ± 1.4</td>
<td>52.8 ± 1.6</td>
<td>49.9 ± 2.0</td>
<td>46.4 ± 1.4</td>
<td>44.3 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Hct 25%</td>
<td>46.7 ± 2.5</td>
<td>25.1 ± 0.1</td>
<td>28.3 ± 1.2</td>
<td>28.3 ± 0.7</td>
<td>27.1 ± 0.7</td>
<td>29.0 ± 0.9</td>
</tr>
<tr>
<td>Hct 30%</td>
<td>46.1 ± 1.2</td>
<td>30.0 ± 0.2</td>
<td>32.3 ± 1.2</td>
<td>32.0 ± 0.7</td>
<td>31.9 ± 0.7</td>
<td>32.3 ± 1.0</td>
</tr>
<tr>
<td>Hct 35%</td>
<td>47.8 ± 1.6</td>
<td>34.8 ± 0.1</td>
<td>35.5 ± 0.7</td>
<td>34.2 ± 0.6</td>
<td>33.9 ± 0.8</td>
<td>34.4 ± 0.7</td>
</tr>
<tr>
<td>Hct 40%</td>
<td>46.6 ± 0.8</td>
<td>40.0 ± 0.2</td>
<td>42.8 ± 2.8</td>
<td>39.3 ± 0.8</td>
<td>39.4 ± 0.6</td>
<td>37.8 ± 0.8</td>
</tr>
</tbody>
</table>

*Hct = hematocrit. Data are presented as mean ± standard error of the mean, in percent. There were 10 dogs in each group.
† Measured immediately following hemodilution.

**TABLE 5**

**Infarct Volume in a canine model of cerebral ischemia**

<table>
<thead>
<tr>
<th>Group</th>
<th>Infarct Volume (% of hemisphere)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>28.3 ± 2.8</td>
</tr>
<tr>
<td>Hct 25%</td>
<td>33.6 ± 3.4</td>
</tr>
<tr>
<td>Hct 30%</td>
<td>17.1 ± 2.2†</td>
</tr>
<tr>
<td>Hct 35%</td>
<td>29.2 ± 4.3</td>
</tr>
<tr>
<td>Hct 40%</td>
<td>29.9 ± 2.1</td>
</tr>
</tbody>
</table>

*Hct = hematocrit. Data are presented as mean ± standard error of the mean. There were 10 dogs in each group.
†Significance of difference: p < 0.05 vs. control group.

**Discussion**

**Rationale for Hemodilution in Ischemia**

The rationale for using hemodilution in the treatment of cerebral ischemia is based on the well-known Hagen-Poiseuille equation which indicates that, if other factors remain constant, flow is inversely proportional to viscosity. Blood viscosity is determined by several factors including hematocrit, erythrocyte aggregation, erythrocyte flexibility, platelet aggregation, plasma viscosity, and the viscosity of cellular components determined by their membrane and intracellular composition. Of these factors, hematocrit is overwhelmingly the single most important determinant of blood viscosity under ordinary circumstances.

In normal conditions in healthy brain, the pressure gradient and radius of conductance vessels are the major factors that determine blood flow. However, in areas of focal cerebral ischemia in which vessels are maximally dilated and the capacity for pressure autoregulation is impaired, blood viscosity becomes a major determinant of blood flow, and hematocrit is a particularly important determinant of flow at low-velocity gradients (shear rates) in the microcirculation. With ischemia these velocity gradients decrease further and hematocrit becomes an even more important fac-
Optimum hematocrit for brain protection

**TABLE 6**

*Postoperative neurological grade in a canine model of cerebral ischemia*

<table>
<thead>
<tr>
<th>Group</th>
<th>Postop Day 1</th>
<th>Postop Day 2</th>
<th>Postop Day 3</th>
<th>Postop Day 4</th>
<th>Postop Day 5</th>
<th>Postop Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>2.8 ± 0.4</td>
<td>2.3 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Hct 25%</td>
<td>3.2 ± 0.2</td>
<td>2.6 ± 0.3</td>
<td>2.3 ± 0.2*</td>
<td>2.2 ± 0.2‡</td>
<td>2.2 ± 0.2‡</td>
<td>2.2 ± 0.2‡</td>
</tr>
<tr>
<td>Hct 30%</td>
<td>2.9 ± 0.3</td>
<td>2.1 ± 0.3</td>
<td>2.0 ± 0.3</td>
<td>1.7 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>Hct 35%</td>
<td>2.8 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>1.9 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td>Hct 40%</td>
<td>3.0 ± 0.0</td>
<td>2.4 ± 0.2</td>
<td>2.0 ± 0.0</td>
<td>2.0 ± 0.0</td>
<td>2.0 ± 0.0</td>
<td>2.0 ± 0.0</td>
</tr>
</tbody>
</table>

* Hct = hematocrit. Data are presented as mean ± standard error of the mean. There were 10 dogs in each group. See Materials and Methods section for explanation of grading system.

† Significance of difference: p < 0.05 vs. control group.

for repeated infusions, as has been discussed by us and others.30,46

The rationale for using colloid as opposed to crystalloid infusions has also been discussed in our previous publications.20,23 In brief, crystalloids tend to exacerbate cerebral edema and increase intracranial pressure in the presence of cerebral ischemia; this problem is not encountered with colloids.20,25 In addition, the infusion volume required for an equivalent degree of hemodilution is about four times larger with crystalloids.25,47

**Optimum Hemodilution**

It should be noted that the issue of “optimum hematocrit” is far from settled and that considerable controversy continues.1,10,27 In addition, tissue ischemia undoubtedly alters normal conditions and no study has resolved satisfactorily the question of what is the optimum hematocrit to improve viability of ischemic brain. Sunder-Plassmann, et al.43 have suggested that in the experimental animal a hematocrit of 30% is optimum for improvement in blood flow and maximum oxygen delivery. Wood and Kee39 concluded from their review of this issue that a hematocrit of 33% is ideal, although Kusunoki, et al.27 have suggested that the optimum level is nearer 40%. Other experimental and clinical studies have suggested that optimum oxygen transport to the brain occurs at hematocrits of 35% and 40% to 42%, respectively.27 In the current study, a hematocrit of about 30% was optimum and a lower hematocrit appeared to be detrimental. This confirms theoretical considerations which indicate that below a hematocrit of about 30% the loss in oxygen-carrying capacity due to the dilution of hemoglobin exceeds the benefits of the improvement in CBF brought about by a decrease in viscosity resulting from hemodilution. Ideally, the issue of what is the optimum hematocrit for delivery of oxygen to ischemic tissue could be best settled by directly measuring tissue oxygen content. However, these measurements are extraordinarily difficult to obtain and to interpret, as was extensively discussed in one of our recent publications.24 For this reason we decided to use as outcome measurement the more clinically relevant parameters of infarct size and neurological condition.

Grotta and colleagues.11,12 emphasized the importance of viscosity in low blood flow states. Under these circumstances, shear rates will fall and viscosity may increase manifold. This will tend to slow blood flow even further, favoring sludging and thrombus formation. Conversely, any improvement in flow results in an increase in shear rates and a reduction in viscosity.

Hemodilution improves CBF and final neurological outcome in animal models of cerebral ischemia.23,48,55-57 Experimental studies have demonstrated significant elevations in regional CBF in focal ischemic brain following the acute reduction of hematocrit via hypervolemic or isovolemic infusion of autologous plasma or low-molecular-weight dextran. In one animal study, the size of hemispheric infarction following distal internal carotid artery and proximal MCA clipping was decreased by hypervolemic hemodilution with low-molecular-weight dextran.55,56 The experimental demonstration of significant elevations in regional CBF in ischemic but not in normal brain implies that the effect of hypervolemic hemodilution on brain perfusion is greater in regions of low blood flow.23,47

**Experimental Model and Method of Hemodilution**

Several previous hemodilution studies in our laboratory utilized a temporary occlusion model.20,25,48,49 In the current experiment a permanent occlusion model, recently developed in our laboratory, was used.52 We believe that a permanent occlusion model is more relevant to the clinical situation where reperfusion is less likely to occur after stroke. In addition, permanent occlusion reduces the possibility of deleterious cerebral edema secondary to reperfusion.

In this experiment we used isovolemic hemodilution. The rationale for this has been discussed in detail in several previous publications from our laboratory.15,20, 28-29,46,47 In brief, isovolemic hemodilution offers as much protection as hypervolemic hemodilution in experimental models of ischemia and avoids the increases in cardiac output, brain edema, and intracranial pressure that can accompany hypervolemia in the presence of cerebral ischemia.15,20,47,62 In addition, with isovolemic hemodilution, which requires blood removal and induction of an anemic state, isovolemia can be maintained for longer periods of time without the need for repeated infusions, as has been discussed by us and others.46,47

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The rationale for using colloid as opposed to crystalloid infusions has also been discussed in our previous publications.20,23 In brief, crystalloids tend to exacerbate cerebral edema and increase intracranial pressure in the presence of cerebral ischemia; this problem is not encountered with colloids.20,25 In addition, the infusion volume required for an equivalent degree of hemodilution is about four times larger with crystalloids.25,47

**Optimum Hemodilution**

It should be noted that the issue of “optimum hematocrit” is far from settled and that considerable controversy continues.1,10,27 In addition, tissue ischemia undoubtedly alters normal conditions and no study has resolved satisfactorily the question of what is the optimum hematocrit to improve viability of ischemic brain. Sunder-Plassmann, et al.43 have suggested that in the experimental animal a hematocrit of 30% is optimum for improvement in blood flow and maximum oxygen delivery. Wood and Kee39 concluded from their review of this issue that a hematocrit of 33% is ideal, although Kusunoki, et al.27 have suggested that the optimum level is nearer 40%. Other experimental and clinical studies have suggested that optimum oxygen transport to the brain occurs at hematocrits of 35% and 40% to 42%, respectively.27 In the current study, a hematocrit of about 30% was optimum and a lower hematocrit appeared to be detrimental. This confirms theoretical considerations which indicate that below a hematocrit of about 30% the loss in oxygen-carrying capacity due to the dilution of hemoglobin exceeds the benefits of the improvement in CBF brought about by a decrease in viscosity resulting from hemodilution. Ideally, the issue of what is the optimum hematocrit for delivery of oxygen to ischemic tissue could be best settled by directly measuring tissue oxygen content. However, these measurements are extraordinarily difficult to obtain and to interpret, as was extensively discussed in one of our recent publications.24 For this reason we decided to use as outcome measurement the more clinically relevant parameters of infarct size and neurological condition.

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Clinical Application

The value of hemodilution by volume expansion with colloid solution in the treatment of vasospasm is well established. However, the role of hemodilution in patients with cerebral infarction is less certain. It is likely that for hemodilution to be effective in the setting of acute stroke, it must be carried out much earlier and to a more profound degree than was accomplished in the two large randomized published clinical trials. In the initial single-institution Scandinavian trial, significant improvement in outcome was noted in stroke patients treated by venesection and colloid infusion (isovolemic hemodilution). However, when this trial was extended to include several centers, these results were not sustained. The latter trial has been criticized because hemodilution was very slowly achieved over a 3- to 5-day period, the hematocrit was lowered only to an average of 37%, and patients were entered into the study relatively late (up to 48 hours) after the onset of stroke; only 28% were entered within 12 hours. The Italian trial also showed no improvement in the short-term prognosis of acute stroke; again, in this trial, hemodilution was carried out slowly and only to a modest degree. On the other hand, in a study of 35 stroke patients in whom hemodilution was achieved by venesection and plasma administration within 72 hours of the onset of symptoms, a substantial increase in CBF and an improvement in evoked potentials and clinical condition was noted in most patients without complications from the therapy.

How quickly after the onset of ischemia must hemodilution be undertaken to have a significant clinical effect has to be studied; this issue of timing and the "window of opportunity" after ischemia is presently being intensively addressed in our laboratory. Clinically, it is likely that hemodilution will be most beneficial when used early and in conjunction with other potentially beneficial therapies such as calcium channel blockers, antagonists of excitatory amino acids, and free radical scavengers. The current study indicates that, when hemodilution is used, a hematocrit of about 30% appears to be a reasonable goal; however, care must be exercised in extrapolating the results obtained in this well-controlled experiment to the clinical situation, where the potential for variability (such as premorbid hematocrit, severity of ischemia, and coexistent medical morbidity) is unlimited.

References

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