Effect of Hemodilution on Cerebral Hemodynamics and Oxygen Metabolism

Akihiko Hino, MD; Satoshi Ueda, MD; Norihiko Mizukawa, MD; Yoshio Imahori, MD; and Hiroshi Tenjin, MD

Background and Purpose: To evaluate the effects of hemodilution on cerebral hemodynamics and oxygen metabolism in the normal human brain, we measured regional cerebral blood flow, oxygen extraction fraction, oxygen metabolic rate, and regional cerebral blood volume in eight normal volunteers before and after hemodilution using positron emission tomography and oxygen-15-labeled gas inhalation technique.

Summary of Report: Hemodilution was accomplished by phlebotomy of 400 ml and drip infusion of 500 ml low molecular weight dextran, which reduced hematocrit from 42.5% to 37.2% and arterial oxygen content from 19.1 to 16.9 ml/dl (both \( p < 0.005 \)). It also increased mean cerebral blood flow from 45.2 to 47.7 ml/100 ml/min (\( p < 0.025 \)), but decreased tissue oxygen delivery from 8.7 to 8.0 ml/100 ml/min (\( p < 0.05 \)) and cerebral blood volume from 4.9% to 4.6% (\( p < 0.025 \)) in the overall cortical gray matter.

Conclusions: Our results indicate that hemodilution in the tested range does not improve oxygen transport or tissue oxygenation in the normal human brain, although it increases cerebral blood flow. (Stroke 1992;23:423-426)

KEY WORDS • cerebral blood flow • hemodilution • tomography, emission computed
There were no significant differences between prehemodilution and posthemodilution blood gases, pH, or systemic arterial blood pressure.

Mean PET values are shown in Table 2 and in Figure 1. Hemodilution increased mean CBF from 45.2 to 47.7 ml/100 ml/min (p<0.005) and CBF/CBV from 9.4 to 10.7 (p<0.005) in the overall cortical gray matter. It also reduced mean CBV from 4.9% to 4.6% (p<0.005) and CBF×Cao2 from 8.7 to 8.0 ml/100 ml/min (p<0.005). There were no significant differences in OEF or in CMRO2, although mean OEF increased from 41.7% to 43.3% and CMRO2 decreased from 3.5 to 3.4 ml/100 ml/min.

Similar effects were seen in both the white matter and the basal ganglia, but the differences were not statistically significant.

**Discussion**

It is important to consider the mode of hemodilution used in this study. We replaced 400 ml blood with 500 ml dextran to account for the natural water depletion during the experiment and to avoid hypovolemia. However, this may result in a slight hypervolemia rather than isovolemia because of the high oncotic pressure of dextran. As a result, the hematocrit decreased from 42.5% to 37.2% over 80–100 minutes. This is considered to be a moderate reduction, but it is a somewhat greater and more rapid hemodilution than those used on the first day in recent clinical trials. In the Scandinavian Stroke Study group, the dilution was from 44.3% to 37.1% after 5 days; in the Italian Stroke Study Group, the decrease was from 43% to 37% after 2 days. We designed the present hemodilution protocol after considering that the optimal hematocrit reduction in the human brain is not established; that many of our postoperative neurosurgery patients are in a state of moderate hemodilution, similar to that induced in this study; and that the acute effect of hemodilution is most important, but a more aggressive strategy may have adverse effects if it is applied to patients with ischemic stroke. We thus studied the immediate effect of slightly hypervolemic, moderate hemodilution in normal human brains.

It is widely accepted that hemodilution can raise CBF under normal circumstances by increasing blood fluidity. Nonetheless, it may decrease oxygen delivery to cerebral tissue because it decreases the blood oxygen content. Recent experiments have shown that the CBF increase brought about by hemodilution is no more than a physiological response, compensating for the reduction in Cao2. Our data indicate that oxygen delivery to cerebral tissue may decrease despite a significant increase in CBF. In other words, given the level of hemodilution that we studied, the reduction in Cao2 had a greater effect on cerebral oxygen transport than did the increase in blood fluidity: the increased CBF did not totally compensate for the reduced Cao2. Although we did not evaluate oxygen delivery over a wide range of hematocrit, our data support the view that the optimal hematocrit in the human brain is that normally found at sea level, although the optimum was previously reported to be 30–33%, 1,2,12

Despite numerous investigations, the effect of hemodilution on tissue oxygen transport in the ischemic brain remains controversial. Our results, as well as some recent studies, suggest that the increased CBF is merely a physiological response to compensate for the reduced blood oxygen content in the normal brain. However, in acute ischemia, such a compensatory mechanism would probably not be active because both vasodilatation and the increase in OEF should have

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>CBF (ml/100 ml/min)</th>
<th>OEF (%)</th>
<th>CMRO2 (ml/100 ml/min)</th>
<th>CBV (%)</th>
<th>CBF×Cao2 (ml/100 ml/min)</th>
<th>CBF/CBV (ml/100 ml/min)</th>
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</thead>
<tbody>
<tr>
<td><strong>Cortical gray matter</strong></td>
<td></td>
<td></td>
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<tr>
<td>Before</td>
<td>45.2±8.0</td>
<td>41.7±5.9</td>
<td>3.50±0.23</td>
<td>4.91±0.35</td>
<td>8.66±1.37</td>
<td>9.4±1.1</td>
</tr>
<tr>
<td>After</td>
<td>47.7±6.7*</td>
<td>43.3±6.7</td>
<td>3.40±0.34</td>
<td>4.62±0.36*</td>
<td>8.04±1.10‡</td>
<td>10.7±1.2‡</td>
</tr>
<tr>
<td><strong>Basal ganglia</strong></td>
<td></td>
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<tr>
<td>Before</td>
<td>39.3±6.7</td>
<td>38.3±5.9</td>
<td>2.84±0.28</td>
<td>4.60±0.47</td>
<td>7.46±1.17</td>
<td>9.0±1.6</td>
</tr>
<tr>
<td>After</td>
<td>43.7±5.1*</td>
<td>40.1±6.5</td>
<td>2.95±0.18</td>
<td>4.59±0.54</td>
<td>7.40±1.04</td>
<td>10.2±1.1</td>
</tr>
<tr>
<td><strong>White matter</strong></td>
<td></td>
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<tr>
<td>Before</td>
<td>24.0±3.0</td>
<td>43.0±5.2</td>
<td>1.94±0.13</td>
<td>2.97±0.16</td>
<td>4.56±0.59</td>
<td>8.2±0.9</td>
</tr>
<tr>
<td>After</td>
<td>26.5±3.8</td>
<td>44.2±6.8</td>
<td>1.86±0.15</td>
<td>2.96±0.24</td>
<td>4.27±0.44</td>
<td>8.7±0.8</td>
</tr>
</tbody>
</table>

Values shown are mean±SD. CBF, cerebral blood flow; OEF, oxygen extraction fraction; CMRO2, cerebral metabolic rate for oxygen; CBV, cerebral blood volume; Cao2, total oxygen content of arterial blood. *p<0.025, ‡p<0.05, †p<0.005 significantly different from baseline by Wilcoxon's paired two-sample rank test.
FIGURE 1. Positron emission tomography values in overall cortical gray matter of eight patients before and after hemodilution. Open circles and vertical bars show mean ± SD of all volunteers. Values were compared by paired Wilcoxon two-sample rank test. CBF, cerebral blood flow; OEF, oxygen extraction fraction; CMRO₂, cerebral metabolic rate for oxygen; \( \text{CaO}_2 \), total oxygen content of arterial blood; CBV, cerebral blood volume.

been maximum to compensate for the tissue hypoxia. In this situation, the ischemic tissue requires a greater increase in the local perfusion pressure or circulating blood velocity to avoid the adverse effect of the reduced blood oxygen content. As far as tissue oxygenation is concerned, this assumption makes us doubt that hemodilution benefits the ischemic brain. However, a similar degree of hemodilution can easily occur in many postoperative neurosurgery patients. This can be tolerated in most patients, but might be dangerous in those with delayed vasospasm after subarachnoid hemorrhage. Further study is needed to determine if that is the case.

It is also noteworthy that this study documents a fall in CBV and an increase in CBF/CBV, as well as an increase in CBF, after hemodilution. This might indicate an increase in perfusion pressure, reduced blood viscosity, or both. However, this interpretation does not explain the reduction in CBV. In addition, previous PET studies have shown that CBF and CBV are coupled in the normal brain. On the other hand, the accuracy of conventional CBV measurement by PET depends on the stability of the ratio of cerebral tissue hematocrit to large peripheral vessel hematocrit. One recent experiment, however, has shown that this ratio decreases after hemodilution, from 0.81 at a hematocrit of 42.5% to 0.48 at a hematocrit of 20%. If this occurred in our subjects, the CBV after hemodilution may in fact have been underestimated. To test this hypothesis, we are now designing an experiment with PET tracers for erythrocytes and plasma to measure the ratio of cerebral tissue to peripheral vessel hematocrit.

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