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.

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Key Words • cerebral blood flow • hemodilution • tomography, emission computed

Blood flow increases as hematocrit decreases, and this forms the theoretical foundation of hemodilution therapy for cerebral ischemia.\(^1\)-\(^4\) However, this increased blood flow does not necessarily improve oxygen transport and oxygenation of cerebral tissue because it may be due to reduced blood viscosity or reduced arterial oxygen content.\(^5\)-\(^11\) In fact, the effect of hematocrit reduction on tissue oxygenation is still uncertain, even in the normal brain.\(^4\)-\(^13\) Clinically, unintended hemodilution can easily occur in many of our postoperative neurosurgery patients because we usually do not transfuse erythrocytes when a patient's hematocrit is >30%.\(^14\) This is particularly important in patients with subarachnoid hemorrhage because of the possibility of delayed vasospasm. We used positron emission tomography (PET) to study the effect of hemodilution on cerebral hemodynamics and oxygen metabolism in the normal human brain.

Subjects and Methods

Subjects comprised eight normal volunteers of mean age 25.3 (range 20–35) years from whom informed consent was obtained before the study. The PET scans were performed with a Headtome III PET scanner (Shimadzu Co., Kyoto, Japan) with an image resolution of 8 mm in full width at half maximum and a slice thickness of 11–13 mm. Regional cerebral blood flow (CBF), oxygen extraction fraction (OEF), and oxygen metabolic rate (CMRO\(_2\)) were measured by an oxygen-15-labeled gas steady-state inhalation technique,\(^15\) and regional cerebral blood volume (CBV) was measured by a \(^{15}\)O-labeled carbon monoxide bolus inhalation technique,\(^16\),\(^17\) with correction for overestimation of OEF and CMRO\(_2\) by CBV.\(^18\) The product of CBF and total oxygen content of arterial blood (CaO\(_2\)) was computed as an index of oxygen delivery to cerebral tissue,\(^5\),\(^8\),\(^14\),\(^15\) and CBF/CBV was used as an index of regional cerebral perfusion pressure.\(^19\),\(^20\) CaO\(_2\) was calculated as \((1.39 \times Hb \times SaO_2) + (0.0031 \times PaO_2)\), where Hb is the hemoglobin concentration, SaO\(_2\) is the arterial oxygen saturation, and PaO\(_2\) is the arterial oxygen tension.\(^21\) All studies were performed in a dark room, and mean arterial blood pressure, heart rate, and blood gases were monitored. Subjects underwent phlebotomy of 400 ml and drip infusion of 500 ml low molecular weight dextran for hemodilution for 80–100 minutes. The PET studies were then repeated.

We set contiguous 14×14-mm (49 pixels) regions of interest on the CBF images to encompass the entire cortical gray matter, periventricular white matter, and basal ganglia. Mean PET values were calculated from these data for three regions: overall cortical gray matter, periventricular white matter, and basal ganglia, including the putamen and thalamus. The values measured before and after hemodilution were compared by the paired Wilcoxon two-sample rank test, and the criterion for significance was \( p < 0.05 \).

Results

Physiological data collected before and after hemodilution are shown in Table 1. Hemodilution reduced mean hematocrit from 42.5% to 37.2% \(( p < 0.005 )\), hemoglobin concentration from 14.3 to 12.6 g/dl \(( p < 0.005 )\), and CaO\(_2\) from 19.1 to 16.9 ml/dl \(( p < 0.005 )\).
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<0.025) and CBF/CMRO2 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<0.025) and CBF×Cao2 from 8.7 to 8.0 ml/100 ml/min (p<0.05). 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%. 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 1. Physiological Data From Eight Volunteers Before and After Hemodilution

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ht (%)</td>
<td>42.5±1.5</td>
<td>37.2±1.9</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>14.3±0.6</td>
<td>12.6±0.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PacO2 (mm Hg)</td>
<td>42.3±3.7</td>
<td>41.2±4.2</td>
<td>...</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>88.5±8.6</td>
<td>89.8±5.9</td>
<td>...</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>95.5±1.1</td>
<td>95.9±0.8</td>
<td>...</td>
</tr>
<tr>
<td>Cao2 (ml/dl)</td>
<td>19.1±1.0</td>
<td>16.9±1.0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>pH</td>
<td>7.40±0.02</td>
<td>7.40±0.03</td>
<td>...</td>
</tr>
<tr>
<td>MABP</td>
<td>79.4±11.5</td>
<td>81.9±8.0</td>
<td>...</td>
</tr>
</tbody>
</table>

Values shown are mean±SD, compared by the paired Wilcoxon two-sample rank test.

### Table 2. Positron Emission Tomographic Values of Eight Volunteers Before and After Hemodilution

<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/CMRO2 (ml/100 ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical gray matter</td>
<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>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td>Basal ganglia</td>
<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>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td>White matter</td>
<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>
</tr>
<tr>
<td></td>
<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>
</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.
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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