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 prehe-  
during the experiment and to avoid hypovolemia. How-  
mml dextran to account for the natural water depletion  
used in this study. We replaced 400 ml blood with 500  
42.5% to 37.2% over 80-100 minutes. This is considered  
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±3.7</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. Ht, hematocrit; Hb, hemoglobin concentra-  
tion; PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen  
tension; SaO₂, saturation of oxygen in arterial blood; CaO₂, total  
oxxygen content of arterial blood; MABP, mean arterial blood  
pressure.

There were no significant differences between prehe-  
modilution 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/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<0.025) 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. How-  
ever, 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 con-  
sidering 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 reduc-  
tion 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 he-  
modilution 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>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical gray matter</td>
<td></td>
<td></td>
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</tr>
<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>Basal ganglia</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<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>White matter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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; CaO2, total oxygen content of arterial blood; CBV, cerebral blood volume.

been maximum to compensate for the tissue hypoxia.19,20 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.14 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.24 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.19,20 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.16,17 We used a value of 0.85 for this ratio, which is conventionally accepted in most PET measurements.16,17 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%.23 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.26

Acknowledgments

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