Hemodilution Increases Cerebral Blood Flow in Acute Ischemic Stroke

Sissel Vorstrup, MD, Allan Andersen, MD, Marianne Juhler, MD, Birgitte Brun, MD, and Gudrun Boysen, MD

We measured cerebral blood flow in 10 consecutive, but selected, patients with acute ischemic stroke (<48 hours after onset) before and after hemodilution. Cerebral blood flow was measured by xenon-133 inhalation and emission tomography, and only patients with focal hypoperfusion in clinically relevant areas were included. Hemodilution was done according to the hematocrit level: for a hematocrit ≥42%, 500 ml whole blood was drawn and replaced by the same volume of dextran 40; for a hematocrit between 37% and 42%, only 250 ml whole blood was drawn and replaced by 500 cc of dextran 40. Mean hematocrit was reduced by 16%, from 46±5% (SD) to 39±5% (SD) (p<0.001). Cerebral blood flow increased in both hemispheres by an average of 20.9% (p<0.001). Regional cerebral blood flow increased in the ischemic areas in all cases, on an average of 21.4±12.0% (SD) (p<0.001). In three patients, a significant redistribution of flow in favor of the hypoperfused areas was observed, and in six patients, the fractional cerebral blood flow increase in the hypoperfused areas was of the same magnitude as in the remainder of the brain. In the last patient, cerebral blood flow increased relatively less in the ischemic areas. Our findings show that cerebral blood flow increases in the ischemic areas after hemodilution therapy in stroke patients. The marked regional cerebral blood flow increase seen in some patients could imply an improved oxygen delivery to the ischemic tissue. (Stroke 1989;20:884-889)

Our study was performed as a spin-off of the Scandinavian Multicenter trial of hemodilution in acute ischemic stroke1,2 to evaluate the acute cerebral blood flow (CBF) changes induced by hemodilution. The theory behind hemodilution in acute ischemic stroke is to improve tissue oxygenation by increasing blood flow in the collaterals via a reduction in blood viscosity.3 Earlier clinical studies on this therapy yielded controversial results.4-7 One reason could be that the pathophysiology of ischemic stroke varies considerably and that not all subtypes or stages of a stroke may benefit from flow-increasing maneuvers. In vascular occlusions causing larger infarcts, a border zone of potentially viable tissue surrounding the dense ischemic core has been observed in some patients early after onset.8 In these areas defined as regions having a low CBF with increased oxygen extraction, changes in collateral flow and hence oxygen delivery may be critical. Consequently, we included in our study only patients having a cortical/subcortical low-flow area at the initial CBF measurement and excluded patients with normal flow maps (probably representing patients with small cortical/subcortical or lacunar infarcts, or brainstem strokes). Likewise, patients in whom lysis of the arterial occlusion had taken place resulting in focal hyperemia were not included.

Subjects and Methods

Cerebral blood flow was measured by the atraumatic xenon-133 inhalation technique and single photon emission computer tomography (SPECT) (Tomomatic 64, Denmark), a method previously described in detail.9,10 Three horizontal slices of brain tissue are studied simultaneously, each slice being 2 cm thick with an interslice distance of 2 cm. The level of the lowest slice was placed corresponding to the plane 1 cm above the orbito-meatal (OM) plane. Repositioning of the patient during repeated studies was secured by the use of slit beamed positioning lights and external markings on the patient's face.

End-expiratory CO₂ fraction (FeCO₂) was measured by a capnograph before, during, and after termination of the study. The arterial blood pres-
sure was measured by auscultation immediately after each flow study. The hematocrit (Hct) was measured before the first CBF study and repeated after the third study.

We calculated regional CBF by using the double integral method as proposed by Kanno and Lassen.\textsuperscript{11} In this calculation, scaling of CBF is done using the pixels with the highest flow values assumed to correspond to gray matter with a partition coefficient (\(\lambda_{gray}\) value) equal to 85 ml/g. No adjustment is normally made for the interindividual variations in Hct. In our study, however, a correction for the Hct was applied as a considerable decrease in Hct was induced. This scaling was done according to the data of Yeh and Peterson,\textsuperscript{12} calculating the \(\lambda_{gray}\) values for each given Hct at a temperature of 37\degree C. Mean hemispheric CBF was calculated by delineation of the brain contour on the nonaffected side. By use of a midsagittal axis of symmetry, the contralateral hemispheric CBF value was obtained. CBF was calculated in the focal low-flow area and the symmetrically placed area in the contralateral, healthy hemisphere. The difference in CBF between these symmetrical areas taken as a percentage of the higher value indicated the degree of side-to-side asymmetry (\(D\)). Based on calculations in an age-matched normal group, a significant low flow (>11 cm\(^2\)) has been defined as a \(D\) value >10%\textsuperscript{10}

The variance of \(D\) for a focal low-flow area in acute ischemic stroke was assessed from two CBF studies done 1 hour apart in 12 patients (including seven of the cases presented here), all studied within 7 days after onset of an ischemic stroke. The mean value of the individually obtained variances was then used to estimate if a significant (\(p<0.05\), \(t\) test) change in \(D\) was induced by hemodilution in individual patients in our series.

\(P_{50}\), the Po\(_2\) at which the hemoglobin is half saturated with \(O_2\), was calculated in six patients to exclude any possible effect of dextran 40 on the oxygen dissociation curve. \(P_{50}\) was obtained from the following equation:

$$\log P_{50} = \log P_{O_2} + \frac{100-O_2 \text{ sat } \%}{O_2 \text{ sat } \%}$$

where \(P_{O_2}\) and \(O_2 \text{ sat } \%\) are the corresponding values measured in the venous blood.\textsuperscript{13} No corrections were made to standard pH and PCO\(_2\).

Ten patients presenting with their first ischemic stroke (eight men and two women) with a mean age of 65±14 years (SD) were included. Informed consent was given by all participants, and the study design had been approved by the local ethical committee. CBF measurements were done as soon as possible, at an average of 31 hours (range 6–48 hr) after the onset of clinical symptoms. Two baseline CBF studies were performed 20 minutes apart and repeated once after hemodilution, approximately 1 hour later.

Hemodilution was done according to the protocol:\textsuperscript{1} For Hct ≥42\%, 500 ml of whole blood was drawn and replaced by a similar volume of dextran. For Hct between 37\% and 42\%, only 250 ml whole blood was drawn but still replaced by 500 ml dextran (i.e., actually leading to a hypervolemic hemodilution). The patients were premedicated with a monovalent hapten for binding of preexisting antibodies to reduce the risk of anaphylactoid reactions.

Neurologic examination was done before and just after the CBF studies, without prior knowledge of the result of the CBF measurements. Grading was done using a scoring system previously described.\textsuperscript{1} All patients had suffered a moderate to severe stroke at onset, in one case resolving to only slight hemiparetic/hemisensory symptoms at the time of the CBF study. Five of the six patients with infarcts in the left hemisphere had aphasic symptoms in

### Table 1. Clinical Data and Effect of Phlebotomy on Hematocrit

<table>
<thead>
<tr>
<th>Pt/sex/age</th>
<th>Clinical symptoms</th>
<th>Location of infarct (CT scan)</th>
<th>Phlebotomy (ml)</th>
<th>Hematocrit (before/after)</th>
<th>CBF study done (hours after stroke)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/75</td>
<td>Moderate R hemiparesis</td>
<td>L temporoparietal</td>
<td>500</td>
<td>49/37</td>
<td>48</td>
</tr>
<tr>
<td>2/M/77</td>
<td>Slight L hemiparesis, moderate sensory impairment</td>
<td>R parietal (posteriorly)</td>
<td>500</td>
<td>49/37</td>
<td>6</td>
</tr>
<tr>
<td>3/F/65</td>
<td>Slight L hemiparesis</td>
<td>R temporoparietal</td>
<td>400</td>
<td>54/50</td>
<td>40</td>
</tr>
<tr>
<td>4/M/47</td>
<td>Slight paresis of R face and arm, aphasia</td>
<td>L subcortical</td>
<td>500</td>
<td>41/37</td>
<td>48</td>
</tr>
<tr>
<td>5/M/71</td>
<td>Severe R hemiparesis, global aphasia</td>
<td>L temporal horn</td>
<td>500</td>
<td>46/37</td>
<td>23</td>
</tr>
<tr>
<td>6/M/45</td>
<td>Severe R hemiparesis</td>
<td>L parietal</td>
<td>420</td>
<td>48/40</td>
<td>11</td>
</tr>
<tr>
<td>7/M/76</td>
<td>Moderate R hemiparesis, global aphasia</td>
<td>No infarct</td>
<td>500</td>
<td>50/40</td>
<td>23</td>
</tr>
<tr>
<td>8/M/53</td>
<td>Moderate aphasia</td>
<td>L temporoparietal</td>
<td>500</td>
<td>46/37</td>
<td>36</td>
</tr>
<tr>
<td>9/M/59</td>
<td>R facial palsy, moderate aphasia</td>
<td>L subcortical</td>
<td>500</td>
<td>47/41</td>
<td>30</td>
</tr>
<tr>
<td>10/F/86</td>
<td>L homonymous hemianopsia</td>
<td>R occipital</td>
<td>300</td>
<td>37/32</td>
<td>40</td>
</tr>
</tbody>
</table>

Pt, patient; CT, computed tomographic; CBF, cerebral blood flow; M, male; L, left; R, right; F, female.
addition to their motor deficits. To exclude a hemorrhagic component, computed tomographic (CT) scans were done on Days 1 to 4 in eight patients and Days 6 and 14 in the remaining two. All but one revealed single hypodense lesions in agreement with the clinical symptoms. The remaining patient studied on Day 3 revealed cortical atrophy only. In three of the youngest patients, angiography was performed within the first week for consideration of reconstructive vascular surgery. Two patients showed occlusion, one had a severe stenosis of the relevant internal carotid artery. The clinical data are given in Table 1.

Results

Mean Hct was reduced by 16%, from 46±5% (SD) to 39±5% (SD) (p<0.001, t test). Mean CBF increased in both the affected and nonaffected hemispheres, by 19.3±9.6% (SD) and 22.5±8.2% (SD), respectively (p<0.001, t test). Regional cerebral blood flow (rCBF) increased in all cases in the ischemic areas, on average by 21.4±12.0% (p<0.001, t test). The rCBF increase in the symmetrically placed region in the nonaffected hemisphere was 19.7±3.8% (p<0.001). Figure 1 shows the increase in rCBF induced by hemodilution.

Regional CBF was evaluated by calculation of D, the degree of side-to-side asymmetry as outlined above. In three patients, significant redistribution of flow in favor of the hypoperfused area was noted. Two of these three patients were the only ones to show clinical improvement after the last CBF measurement. One such patient (Case 6) is presented as Figure 2, which shows the flow and the flow distribution map (mean CBF=100%). In six patients, no significant changes in regional flow distribution were observed. An example (Case 10) is shown in Figure 3. Finally, one patient showed a significant aggravation in D, but the absolute flow value in the ischemic area still increased.

FIGURE 1. Line graph showing effect of hemodilution on regional cerebral blood flow (rCBF). Region of interest (roi) was selected as hypoperfused area in affected hemisphere (straight line). For comparison, rCBF was calculated in symmetrically placed roi in healthy, unaffected hemisphere (dotted line). In all cases, rCBF increased with decreasing hematocrit (Hct) by an average of 21.4% and 19.7% in affected and nonaffected hemispheres, respectively.

FIGURE 2. Cerebral blood flow (CBF) in 45-year-old man with acute onset of right hemiparesis with aphasial. CBF study was done 11 hours after onset and showed hypoperfusion in left frontoparietal lobes (F1). (Left hemisphere is oriented to left, and scale gives flow from 0–112 ml/100 g/min.) After hemodilution, mean CBF increased by 24%, and significant redistribution of flow in favor of hypoperfused areas was observed (F3). FD1 and FD3 indicate corresponding flow distribution maps, that is, each pixel is expressed as percentage of mean CBF value (scale runs from 0–200%). Improvement of aphasial symptoms and of motor function of lower extremity was noted also. Hematocrit decreased by 17%, from 48% to 40%.
No complications to the hemodilution regimen were observed in this small series.

FeCO₂ and mean arterial blood pressure remained unchanged throughout the procedures.

The calculated values of P₅₀ were 25.7 mm Hg ± 2.9 mm Hg (SD) and 26.3 mm Hg ± 2.5 mm Hg (SD) before and after hemodilution, respectively (NS, Wilcoxon).

Discussion

Under normal circumstances the Hct is the single major determinant of blood viscosity with CBF increasing when Hct is reduced, leaving the oxygen delivery capacity per tissue volume stable both at normal and elevated Hct. The CBF increase after hemodilution is probably achieved both by cerebral vasodilation and by an increase in linear flow. The optimal Hct for brain tissue perfusion is not known, but some studies have shown that the lower values of approximately 30–33% are advantageous.

In ischemic brain tissue where CBF is decreased, the viscosity and hence the Hct of blood becomes critical, especially in the microcirculation: As the flow decreases, the viscosity increases markedly, at some point even causing a further reduction in flow. The residual flow is dependent on the regional perfusion pressure (determined by the collateral flow capacity) and the regional viscosity. In addition, a complicated interplay of local tissue factors such as metabolic acidosis, calcium ion accumulation, tissue edema, and so forth occur, which influence the degree of dilation of the cerebral vasculature. All these factors make the resulting flow difficult to predict. Attempts to increase the regional perfusion through systemic blood pressure elevation is not without major risks in this generally elderly and atherosclerotic patient group. However, decreasing the Hct under normovolemic or slightly hypervolemic conditions is normally well tolerated. Theoretically, hemodilution would be expected to increase the residual flow, decreasing the extent of permanent tissue damage, provided that treatment is induced early enough after onset of ischemia.

In our study, we generally found that hemodilution increased CBF in the affected and nonaffected hemispheres in a roughly inverse relation to the decrease in Hct. In all cases but one, CBF increased in the hypoperfused areas as well. No distinction could be made between the CBF changes in the infarct area and in the surrounding zones, as CT scanning was done only in the acute phase, and the extent of permanent tissue damage (i.e., neuronal death) as evidenced by CT scan was not available. Although part of the CBF increase may be due to the Compton scattered radiation, it is unlikely that this effect alone can explain the observed changes. Previous studies performed with the same technique using a potent cerebral vasodilator (acetazolamide) have documented that a further decrease in focal CBF can be visualized despite a significant global flow increase. Still, the finding of an increased flow in the low-flow areas does not indicate that the crucial factor, the tissue oxygenation, increases as well. Studies using positron emission tomography have demonstrated that CBF measurements alone do not describe the metabolic status of the tissue in acute focal ischemia, as uncoupling of CBF and oxygen metabolism often occurs. The reduced flow levels may be accompanied by a low, normal, or high oxygen extraction. Only when the oxygen extraction is high, reduced flow and thus reduced O₂ delivery can be expected to restrict local metabolic demands. Only under these circumstances might an induced CBF increase influence...
the outcome. This could indeed have been the case in the two patients who had objective improvement along with a significant redistribution of flow to the hypoperfused area (Figure 2). These patients were studied 11 and 23 hours after onset of their symptoms, that is, intervals not differing from those of some of the other patients.

An open question is still whether flow-improving maneuvers after several hours of clinical symptoms have any impact. It may be speculated that the core of the ischemic area has sustained maximal injury resulting in neuronal death but that the peri-infarct areas within a yet-unknown time limit still have viable and therefore salvageable neurons. Some experimental evidence supports this contention. Pollock et al. showed that lowering the Hct value in gerbils reduced the size of the final infarction. Similar conclusions were reached by Wood et al. in dogs. Previous clinical studies on the effect of hemodilution in acute stroke but with small numbers of patients have yielded controversial results. Two large randomized multicenter studies have recently been published, the Scandinavian Stroke Study and the Italian Acute Stroke Study comprising 373 and 1,267 patients, respectively. Although somewhat differing hemodilutional regimens were applied, the conclusions drawn by both groups were quite similar: Hemodilution does not improve the clinical outcome. This was the case even when detailed subgroup analyses among the 373 Scandinavian patients using parameters such as sex, age, past medical history, Hct at entry, delay of treatment, severity of clinical symptoms, and so forth were done to identify any group of patients where hemodilution might be of benefit. Likewise, in the Italian study hemodilution did not improve the outcome in the large subgroup of patients (n = 269) who were treated within 6 hours after onset of symptoms. It should be noted, however, that a moderate Hct reduction was achieved in both studies in the acute phase (Day 1); mean Hct was reduced by 7.3% (from 42.7% to 39.6%) and by 9.2% (from 44.3% to 40.2%) in the Italian and Scandinavian studies, respectively. None of these studies included CBF measurements, and thus evidence for a tolerable low-flow area was not documented. However, in the Italian study, the large number of patients makes it more likely that a positive effect of hemodilution would have been detected, assuming that the incidence of patients with focal low-flow areas constitute the majority of stroke cases. But it can be argued that adequate hemodilution significantly improving regional CBF in accordance with the theoretic considerations given above has not been tested clinically. A more aggressive regimen in the acute phase could possibly change the clinical outcome.

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**KEY WORDS** • cerebral blood flow • cerebrovascular disorders • hemodilution
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Stroke. 1989;20:884-889
doi: 10.1161/01.STR.20.7.884

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