Autoregulatory Capacity and the Effect of Isovolemic Hemodilution on Local Cerebral Blood Flow

Rüdiger von Kummer, MD, Johann Scharf, MD, Tobias Back, Harald Reich, MD, Hans G. Machens, and Brigitte Wildemann, MD

The effect of isovolemic hemodilution with dextran 40 on local cerebral blood flow was measured in eight cats by means of the hydrogen clearance technique. Under normotension the decrease of hematocrit from 35% to 25% causes a sudden increase of up to 30% in local cerebral blood flow. After lowering the mean arterial blood pressure from 140 to 80 mm Hg, hemodilution did not alter cerebral blood flow significantly. From this observation it is concluded that the increase of cerebral blood flow following hemodilution is caused by compensatory vasodilatation and not by reduction of blood viscosity. This could imply that hemodilution cannot improve blood flow in areas of impaired autoregulation. (Stroke 1988;19:594-597)

Since it was shown that lowering the hematocrit (Hct) improves cerebral blood flow (CBF), hemodilution has been widely accepted as a treatment for acute cerebral ischemia. However, it is questionable whether hemodilution can increase CBF where cerebral blood vessels have lost their capacity for pressure autoregulation.

Hemodilution may increase CBF by reducing either the viscosity or the oxygen carrying capacity of blood, resulting in compensatory vasodilatation. The latter mechanism requires the ability of vessels to dilate, which is not the case when maximal dilatation has already occurred due to low perfusion pressure. The effect of differing viscosity on CBF should be detectable even in regions where vessel radius is maximal. Thus, we measured CBF before and after hemodilution under physiologic as well as hypotensive conditions (mean arterial blood pressure [maBP] down to 80 mm Hg). To record changes of the microcirculation within the brain tissue, we used implanted microelectrodes of high spatial resolution and the hydrogen clearance method.

Materials and Methods

Ten cats with implanted hydrogen-sensitive electrodes were monitored for sequential local CBF. Up to four experiments were performed per cat to determine the effect of hemodilution with dextran 40 (D-40), hydroxyethyl starch, and Ringer's solution. Hemodilution with D-40 under hypotension was also investigated. Intervals between experiments were not less than 1 week. This article presents the results of the hemodilution experiments with D-40 under normotension and hypotension only.

Animal preparation. This series of experiments was carried out in eight cats of either sex within the weight range of 2.8-4.4 kg 1-5 weeks after electrode implantation. In four cats the effect of hemodilution on local CBF could be observed under normal as well as under decreased maBP. Two cats underwent hemodilution under normotension, another two under hypotension only. Between two experiments (1-4 weeks), the cats were housed in cages and observed carefully. After surgery, 40 mg ampicillin/kg body wt was routinely given.

Electrode implantation. Epoxy-and-glass-insulated platinum wire electrodes with a bare conical tip of 0.2 mm length and 0.2 mm diameter were prepared as described previously. For implantation the cats were anesthetized with 30 mg sodium pentobarbital/kg. After fixation of the cat's head in a stereotactic frame, six electrodes per cat were introduced through 0.5-mm diameter burr holes and inserted into the cortex, subcortical white matter, and caudate nucleus of both hemispheres, with subsequent fixation to the skull using dental cement.

Determination of local cerebral blood flow. For the experiments, anesthesia was induced with 30 mg sodium pentobarbital/kg body wt and maintained with 70% N2O-30% O2 gas via an endotracheal tube. After paralyzing with i.v. pancuronium bromide, the cats were artificially ventilated with a respirator. Local CBF was measured at six sites of each cat's brain by means of the hydrogen clearance method. An Ag-AgCl reference electrode was inserted subcutaneously before each series of local CBF measurement so that the measuring circuit consisted of six electrodes, one reference electrode, six separate amplifiers (Nanoamperemeter, Knick, Berlin, F.R.G.) and a ten-channel pen recorder. H2 gas was administered into the input of the respirator for 1 minute. H2 concentration of the inhaled gas was 5-10%, while the O2 concentration was unaltered. Local CBF was calculated during the 2-3 minute interval of the recorded clearance curves.
using the initial slope index according to Risberg et al."

Experimental design. A catheter was inserted in one femoral artery to monitor arterial blood gases, hemoglobin, Hct, and maBP. One or two femoral venous catheters were inserted for infusions. Simultaneous with the local CBF measurements, 1 ml arterial blood was taken for analysis. In each experiment local CBF was measured 14 times during 5–6 hours. During this time an electric blanket maintained body temperature.

Data analysis. For each electrode a regression line was calculated from the six CBF measurements in each cat before hemodilution and the simultaneously measured PaCO₂. All electrodes with a correlation coefficient of <0.65 were discarded. The individual absolute CO₂ reactivity was used to correct local CBF values for CBFₜₙ where PaCO₂ differed from 35 mm Hg. Due to the impaired CO₂ reactivity, under hypotension CBF was not corrected for PaCO₂. We were thus able to analyze the data from 24 electrodes in normotension experiments and 27 electrodes used for CBF measurement under hypotension. To assess the effect of hemodilution on local CBF, each cat served as its own control. The mean of the last four Hct or CBF values before the first step of hemodilution was compared with each value after hemodilution using D-40. The paired Wilcoxon test was used for statistical analysis. The 0.05 level was accepted as significant.

Hemodilution under normotension. To determine baseline CBF and CO₂ reactivity, CBF was measured six times in each cat before hemodilution under hypercapnia (PaCO₂ of 50 mm Hg) and normocapnia (PaCO₂ of 35 mm Hg). PaCO₂ was adjusted by varying the breathing volume of the respirator. All six cats then underwent isovolemic hemodilution in two steps within 40 minutes by replacing 18 ml blood with 18 ml D-40 after the sixth and eighth CBF measurements. Following hemodilution local CBF was measured intermittently every 15–30 minutes during 3–4 hours while PaCO₂ was held constant.

Hemodilution under hypotension. In anticipation that CBF would not respond to hypercapnia, PaCO₂ was held at comparable levels during the measurements. CO₂ reactivity at the electrodes’ location in the brain was defined in another experiment 1 week later or earlier. maBP was decreased and kept at 80 mm Hg after the second CBF measurement by a constant infusion of sodium nitroprusside (Nipride, Roche Laboratories, Nutley, New Jersey) until CBF was measured the last time. During the hypotensive experiments hemodilution was performed after the eighth and tenth measurements as under normotension.

Results

Hemodilution under normotension. As shown in Figure 1 the stepwise replacement of blood with D-40 causes a sudden drop of Hct from 35% to 25% and simultaneously a significant increase of local CBF from 0.45 to 0.59 ml/g/min. During the next 200 minutes, Hct increased slightly, whereas local CBF decreased but remained significantly elevated. No interregional differences in CBF change were registered. The exact linear correlation between mean Hct and local CBF is shown in Figure 2.

Hemodilution under hypotension. Figure 3 shows the simultaneous recording of the mean local CBF, PaCO₂, Hct, and maBP. During 330 minutes, mean local CBF was not altered significantly, varying between 0.37 and 0.43 ml/g/min. There was no influence of the maBP decrease to 80 mm Hg or the Hct decrease from 38% to 28%, which indicates normal autoregulation to changes in maBP but not a further reaction to the reduction of blood viscosity achieved by hemodilution with D-40 under hypotension. The slight increase of mean PaCO₂ before hemodilution was nonsignificant.

Discussion

The significance of factors determining blood flow within the microvasculature of the brain is very complex and cannot simply be described by the Hagen-Poiseuille equation. An increase of the vessel diameter will lead to an increase of flow (volume per time) only if flow velocity does not decrease. With low perfusion pressure, cerebral blood volume increases to maintain appropriate CBF, whereas flow velocity decreases. As described by Fahreus and Lindquist, blood viscosity apparently decreases in vessels of progressively smaller diameter. This reduction in blood viscosity ceases when the vessel diameter approaches

![Figure 1](http://example.com/f1.png)

**Figure 1.** Effect of isovolemic hemodilution with dextran 40 on local cerebral blood flow (CBF) and hematocrit (Hct). Each point represents mean of 24 microelectrodes implanted in cortex, caudate nucleus, and subcortical white matter of 6 cats. * Significantly different from mean of the last 4 CBF measurements before hemodilution (p<0.05).

![Figure 2](http://example.com/f2.png)

**Figure 2.** Correlation between mean of 24 cerebral blood flow (CBF) measurements in 6 cats and corresponding mean hematocrit (Hk). \( Y = -85.8X + 73.8; r = -0.90 \) (p<0.05).
Arterial carbon dioxide tension (PaCO₂), hematocrit (Hct), and blood flow (CBF) is mean of 27 measuring microelectrodes in areas of autoregulation by sodium nitroprusside (Nipride). Cerebral cortex, caudate nucleus, and subcortical white matter of 6 cats. Lowering mean arterial blood pressure (ma BP) to lower limit of well-defined, small brain regions. It was previously demonstrated that electrodes implanted over long periods of time do not alter local CBF. Variations in mean PaCO₂ were nonsignificant.

The diameter of the erythrocyte (5-7 μm). Viscosity in the microcirculation is also affected by the Hct of blood entering the capillary, by the flow velocity within the capillary, by erythrocyte flexibility and aggregation, by platelet aggregation, and by plasma viscosity. All these factors might influence each other so that the in vivo conditions of blood viscosity in the cerebral microcirculation can hardly be predicted. From this it is obvious that the interdependence of blood viscosity and cerebral microflow cannot be quantified by in vitro studies or with methods of CBF measurement that are not able to differentiate between flow in large and small vessels.

Therefore, in our study we used the hydrogen clearance method, which allows repeated CBF measurements within 10-15 minutes by flow several hours in well-defined, small brain regions. It was previously demonstrated that electrodes implanted over long periods of time do not alter local CBF. In our study we tested each electrode for its ability to record CO₂ reactivity. It seems unlikely that the results are influenced by the initial pentobarbital anesthesia because measurements started no sooner than 2 hours after i.v. anesthesia due to the time needed for cat preparation. It was also shown by Häggendal et al. that cortical blood flow remains constant between 1 and 6 hours after an injection of 30-35 mg pentobarbital/kg body wt.

Our data demonstrate an inverse linear relation between blood flow through brain tissues and Hct (between 24% and 37%) of arterial blood taken from the aorta thoracalis. The high correlation coefficient (0.90) is remarkable and suggests a direct relation although considerable differences between Hct of the large vessels and the brain are known. Under normotension, reduction of Hct caused a sudden increase in local CBF in all electrode positions. Whereas Häggendal et al. did not register any CBF change when Hct varied between 30% and 70%, later studies in animals and humans, as well as our results, showed a clear inverse correlation, with an increase in flow of between 19% and 50% when Hct was reduced by 7-14%. All except one study conclude that the oxygen carrying capacity is the more important factor. The possibility, however, that the rheologic properties of blood may become critical under pathologic circumstances could not be excluded. Studies in patients with increased blood viscosity as a result of paraproteinemia or leukemia recently showed no significant correlation between whole blood viscosity and CBF, demonstrating the fundamental importance of arterial oxygen content in the regulation of CBF. These patients, however, showed no impairment of the autoregulatory capacity of the cerebral blood vessels, so the effects of viscosity have probably been dominated by the compensatory vasodilatation due to anemia. We, therefore, tried to exclude the effect of low arterial oxygen content on CBF regulation by decreasing the perfusion pressure to the lower limit of autoregulatory capacity. Under these circumstances the reduction of Hct from 38% to 28% had no influence on local CBF. This might suggest that hemodilution cannot improve CBF in regions of severe ischemia. Contrary to our results, Wood et al (the same data was again published 1 year later) observed a greater effect of hypervolemic hemodilution on CBF in regions of low flow than in nonischemic brain. These experiments, however, were performed by means of the krypton clearance technique, with only one detector. The lowest CBF they recorded was between 30 and 40 ml/100 g/min. From this it can be assumed that regions of normal and impaired vasoreactivity were detected simultaneously. Thus, data obtained from these experiments can provide no conclusions for brain regions of severe ischemia.

Hct is the major factor influencing blood viscosity. The relation between Hct and viscosity is logarithmic, so the effect on viscosity is less when Hct is reduced from 30% to 20% than when it is reduced from 40% to 30%. The curve of the Hct- viscosity relation is shifted to the left when the shear rate is low. In this case, alterations of Hct between 30% and 55% may have profound effects on blood viscosity. When the cerebral blood vessels are maximally dilated, very low shear rates can be assumed. This suggests that the reduction of Hct under hypotension in our experiments may cause a considerable decrease in viscosity in the microvasculature. This change in viscosity, however, did not influence local CBF significantly.

Under these circumstances, hemodilution might decrease the focal oxygen delivery capacity because the decrease of oxygen carrying capacity is not compensated. This has not yet been observed in experimental studies. Both studies, however, could again demonstrate the superior role of oxygen content in CBF.
regulation. Therefore, it may be assumed that the measurements were performed in brain regions with unimpaired autoregulation.

Our findings probably explain the lack of clinical improvement in stroke patients after hemodilution therapy. Using our data we cannot, however, exclude that in polycythemia viscosity can become the major determinant of CBF. In these patients hemodilution will considerably reduce whole blood viscosity, whereas the compensatory vasodilatation due to the reduction of oxygen carrying capacity may be slight. Further studies with local CBF measurements are needed to clarify whether a reduction of viscosity can improve CBF even in the presence of impaired vasomotor function. Only if this would prove to be the case can hemodilution be expected to be effective in the therapy of acute stroke.

Acknowledgments
The authors acknowledge Miss J. Schriever for technical assistance and Dr. E. Wilder-Smith for his review of the manuscript.

References

Key Words • autoregulation • cerebral blood flow • hemodilution
Autoregulatory capacity and the effect of isovolemic hemodilution on local cerebral blood flow.

R von Kummer, J Scharf, T Back, H Reich, H G Machens and B Wildemann

Stroke. 1988;19:594-597
doi: 10.1161/01.STR.19.5.594

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/19/5/594

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/