Cerebral Blood Flow is Regulated by Changes in Blood Pressure and in Blood Viscosity Alike

J. Paul Muizelaar, M.D., Ph.D., Enoch P. Wei, Ph.D., Hermes A. Kontos, M.D., Ph.D., and Donald P. Becker, M.D.

SUMMARY There is still considerable controversy regarding the influence of blood viscosity upon cerebral blood flow (CBF). One factor in this controversy is the report of some authors that changes in blood viscosity lead to changes in CBF, or that CBF is inversely correlated with blood viscosity, while others have been unable to find any relation between the two. It has also been reported that decreasing blood viscosity leads to a large increase in CBF in ischemic brain, but to a lesser increase in nonischemic brain, if at all. Another factor leading to uncertainty is that it remains unknown whether or not blood viscosity as measured in vitro, even at different shear rates, correlates well with viscosity as it prevails in vivo.

In an earlier paper we found a very good correlation between changes in blood viscosity, brought about by the intravenous administration of mannitol, and changes in pial arteriolar diameter observed through a cranial window in the cat. With decreased viscosity vasoconstriction occurred; with increased viscosity the pial arterioles dilated. We assumed that these vessel diameter responses were autoregulatory in nature, similar to responses to blood pressure alterations. In those experiments, however, CBF was not measured, blood pressure changes were not induced and only normal cats with normal CO2 responsivity and, presumably, normal autoregulation were used. In the left caudate CBF decreased 21% with hypotension and 18% with higher viscosity, more than on the right (p < 0.01 and p < 0.2, respectively). CBF increased in the left caudate 56% with hypertension and 47% with lower viscosity, again much more than on the right (p < 0.001 and p < 0.01, respectively). In the other area which is (nearly) exclusively supplied by the middle cerebral artery of the cat, i.e., the ectosylvian cortex, results were similar to those in the caudate nucleus. These results show that viscosity changes must result in compensatory rearrangements of vessel diameter, but that these adjustments do not occur where autoregulation to pressure changes is known to be defective. The adjustments to viscosity changes might be called blood viscosity autoregulation of CBF. We hypothesize that pressure autoregulation and blood viscosity autoregulation share the same mechanism.
the string tightened. The wound was closed in two
layers. CBF was measured by the radioactive micros
phere technique,11 using 15 ± 5 microspheres with
four or five different radioactive labels, injected into
the left atrium. Blood reference samples were drawn
from the left femoral and brachial arteries. Two control
CBF measurements were taken if five isotopes were
available, one before and one after the induction of
hypotension or hypertension. The mean of these two
values was considered the control value. If only four
differently labeled microspheres were available, the
control measurement was done after the blood pressure
manipulation. At the completion of the experiment,
catheters were placed in both carotid arteries and the
cardiac catheter opened. Normal saline was infused
into the carotid arteries with 150 cm of hydrostatic pres
ture until the effluent fluid from the heart was clear.
Fixative, consisting of 2% glutaraldehyde an 2.5%
paraformaldehyde in 0.1 M phosphate buffer, was in
fused into the carotid arteries. The brain was removed
and kept in formaldehyde at least two days and then
each hemi-brain was cut into frontal pole, marginal
gyrus, caudate nucleus, suprasylvian gyrus, dien
ccephalon, ectosylvian gyrus, hippocampus, occipital
pole, midbrain, pons, medulla and cerebellum. How
ever, it has been shown that in the cat occlusion of the
middle cerebral artery leads to infarction most consis
tently in the caudate nucleus and ectosylvian cortex,
while in the rest of the supratentorial brain collateral
circulation varies widely from one animal to the oth
er.12 Therefore, we concentrate here on CBF in the
caudate nucleus and ectosylvian cortex, and contrast
these two regions with an area that is exclusively sup
plied by the basilar artery, i.e., the pons.

Samples of arterial blood were drawn prior to each
blood flow measurement for determination of PO2,
PCO2, pH and hematocrit, and before and 75 minutes
after mannitol administration also for blood viscosity
measurements. Blood viscosity was measured in a
Wells-Brookfield LVT½ viscosimeter. For this pur
pose, 1.5 ml of arterial blood were immediately mixed
with a small amount of dry ethylenediaminetetraacetic
acid and poured into the beaker of the viscosity meter.
Measurements were then performed at 37°C at 60, 30
and 12 rpm, representing shear rates of 450, 225, and
90 seconds⁻¹, respectively.

Hypotension was induced by the intravenous infu
sion of ATP to values approximately 40% below base
line in 10 animals. Hypertension was induced by infu
sion with angiotensin, aiming at a blood pressure 30%
higher than baseline in 13 animals. Mannitol was ad
ministered as a 25% solution in water at 37° in a dose
of 1 gm/kg body weight in one minute.

All data are expressed as the mean ± SEM and were
analyzed utilizing paired t-tests. Values of p < 0.05
were considered significant.

Results

Table 1 contains a number of physiological data
obtained at the moment of the CBF measurements.
Throughout the course of the study temperature, pH,
PaO2, and PaCO2 remained essentially constant. The
changes in blood pressure, hematocrit and viscosity
were naturally intentional, except the small increase
in MABP at 15 minutes post-mannitol. It should be
noted that at 75 minutes in 5 animals the viscosity and
hematocrit were still lower than baseline and the data
obtained at 75 minutes in these animals have been
discarded.

CBF values of the two areas supplied most custom
arily by the middle cerebral artery exclusively in the
cat, i.e., the caudate nucleus and ectosylvian cortex,
are shown in table 2. For comparison, we have also
included the CBF values of the pons in this table and
have performed all the statistical calculations on these
values. Flow data from all other areas are shown in
table 3. The CBF values at control were lower in the
left caudate than in the right caudate nucleus (t =
7.22, d.f.22, p < 0.001). CBF in the left ectosylvian
cortex was also lower than in the right side (t = 3.45,
d.f.22, p < 0.005). In the pons flows were equal, left
and right.

With hypotension all CBF values except those in the
left caudate nucleus, ectosylvian cortex, suprasylvian
cortex, and occipital pole were not much different
from baseline or even increased. The mean CBF de
crease of 21% in the left caudate was not significantly
different from control (t = 1.85, d.f.9, p < 0.1). The

| TABLE 1 Effect of Hypotension, of Hypertension, and of Mannitol Bolus on Physiological Parameters |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| MABP (torr) | Control | Hypotension | Hypertension | Time (minutes) post-Mannitol |
| Viscosity (shear rates) | | | | |
| 90 sec⁻¹ | 121 ± 5 | 83 ± 5* | 150 ± 7* | 130 ± 4* |
| 225 sec⁻¹ | 2.67 ± 0.10 | 2.19 ± 0.11* | 3.08 ± 0.15* |
| 450 sec⁻¹ | 2.42 ± 0.10 | 2.03 ± 0.09* | 2.70 ± 0.14* |
| Hematocrit (%) | 2.32 ± 0.07 | 1.97 ± 0.07* | 2.53 ± 0.09* |
| PaCO2 (torr) | 30 ± 2 | 30 ± 2 | 29 ± 2 | 24 ± 1* |
| PaO2 (torr) | 31 ± 1 | 31 ± 1 | 30 ± 1 | 29 ± 1 |
| pH | 82 ± 6 | 82 ± 10 | 78 ± 6 | 77 ± 7* |
| | | | | |
| *p < 0.05, compared to control value. |
Table 2  CBF (ml/100 g/min) ± SEM Under Various Conditions in Areas Exclusively Irrigated by the Middle Cerebral Artery (Caudate Nucleus and Ectosylvian Gyrus) and, for Comparison, in an Area Completely Outside the Middle Cerebral Artery Territory (Pons). Left Middle Cerebral Artery Occluded

<table>
<thead>
<tr>
<th></th>
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<th>Hypertension</th>
<th>Decreased viscosity</th>
<th>Increased viscosity</th>
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<td>90 ± 18</td>
<td>104 ± 9*</td>
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<td>30 ± 9</td>
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<td>55 ± 18*</td>
<td>56 ± 7*</td>
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<td>43 ± 4</td>
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<tr>
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<td>40 ± 7†</td>
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<td>20 ± 4</td>
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<tr>
<td>Pons</td>
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<td>41 ± 5</td>
<td>47 ± 5</td>
<td>39 ± 4</td>
<td>45 ± 5</td>
</tr>
<tr>
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<td>42 ± 5</td>
<td>38 ± 3</td>
<td>40 ± 4</td>
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</tbody>
</table>

*p < 0.05, compared to control value.
†p < 0.05, change from baseline value left compared to change from baseline value right.

Mean decrease in the left ectosylvian cortex (32%) was also not significantly different from control (t = 1.74, d.f.9, p < 0.1). However, comparing the percentage changes from baseline between left and right during hypotension, the difference is highly significant (t = 3.93 and t = 3.69, respectively, d.f.9, p < 0.01). This means that with hypotension in the left caudate nucleus and ectosylvian cortex, with the occluded middle cerebral artery, a sizeable drop in CBF occurred compared to the right side. In the pons no significant change

Table 3  CBF (ml/100 g/min) ± SEM in the Other Areas. No Calculations Were Made as to Whether the Differences Were Statistically Significant

<table>
<thead>
<tr>
<th>Suprasylvian cortex</th>
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<td>50 ± 5</td>
<td>28 ± 5</td>
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<td>Frontal pole</td>
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<tr>
<td>Right</td>
<td>51 ± 5</td>
<td>57 ± 15</td>
<td>65 ± 7</td>
<td>60 ± 4</td>
<td>50 ± 5</td>
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<td>27 ± 2</td>
<td>28 ± 4</td>
<td>36 ± 4</td>
<td>35 ± 3</td>
<td>26 ± 3</td>
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<tr>
<td>Occipital pole</td>
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<tr>
<td>Right</td>
<td>36 ± 3</td>
<td>37 ± 7</td>
<td>46 ± 4</td>
<td>44 ± 3</td>
<td>35 ± 3</td>
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<td>22 ± 4</td>
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<td>33 ± 3</td>
<td>26 ± 3</td>
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<td>Marginal gyrus</td>
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<td>26 ± 5</td>
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<td>42 ± 3</td>
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<tr>
<td>Left</td>
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<td>44 ± 7</td>
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<td>Right</td>
<td>47 ± 4</td>
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<td>Left</td>
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<tr>
<td>Medulla oblongata</td>
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<tr>
<td>Right</td>
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</table>
occurred, neither compared to baseline, or comparing left and right.

With hypertension an increase in CBF was found in all areas examined. In the right caudate nucleus the mean increase was 32% (t = 3.55, d.f. 12, p < 0.05); on the left side it was 56% (t = 6.09, d.f. 12, p < 0.01). Comparing the percentage increases in the left and right caudate nucleus, we find a significantly larger increase on the left (t = 6.39, d.f. 12, p < 0.001). In the right ectosylvian cortex the mean increase was 30% (t = 3.22, d.f. 12, p < 0.01); in the left side it was 60% (t = 3.29, d.f. 12, p < 0.01). The percentage increases in the left were, however, not significantly larger than on the right (t = 0.96, d.f. 12, p < 0.21). None of the changes in the pons were statistically significant.

With decreased blood viscosity CBF increased in the right caudate nucleus by 10% (t = 3.58, d.f. 22, p < 0.01) and in the left caudate by 47% (t = 5.15, d.f. 21, p < 0.001). The percentage changes in the left caudate nucleus were much larger than in the right (t = 3.16, d.f. 22, p < 0.01). In the ectosylvian cortex no CBF increase occurred on the right side, but a 44% increase was recorded on the left side (t = 3.2, d.f. 22, p < 0.01). The 5% increases bilaterally in the pons were not significant.

At 75 minutes post-mannitol we have taken into account only those experiments in which viscosity as measured in vitro was higher than baseline. In five cats this was not the case, so these CBF data were discarded. Another two experiments were prematurely terminated because of continuously decreasing blood pressure, so that their 75-minute data also could not be used. This leaves 16 cats in which viscosity was higher than baseline with valid measurements of CBF at 75 minutes. With higher blood viscosity CBF remained the same or even increased by up to 22% in nearly all areas. A sizeable decrease in CBF occurred only on the left side in the caudate nucleus (18%, t = 0.98, d.f. 15, p < 0.2), ectosylvian cortex (20%, t = 1.42, d.f. 15, p < 0.1) and suprasylvian cortex (22%, t = 2.32, d.f. 15, p < 0.015).

Discussion

The present paper shows that, in areas of the brain presumed to be normal, CBF is fairly constant despite changes in blood pressure or changes in blood viscosity. The adjustments in response to blood pressure or intracranial pressure changes occur through changes in vessel diameter. This well-known phenomenon is termed pressure autoregulation. Considering the classic Hagen-Poiseuille equation for blood flow through vessels, 

\[ Q = k \times P \times r^4/L \times n, \]

where Q is blood flow, k is a constant, P is pressure gradient, r is vessel diameter, L is length of the vessels and n is viscosity, it is clear that when viscosity alterations do not change CBF, this must be caused by vessel diameter adjustments. In earlier experiments it was shown that, in normal brain vessel constriction occurred with decreased viscosity and vasodilation with increased viscosity. When autoregulation is abolished, as was done in the left caudate nucleus and ectosylvian cortex through left middle cerebral artery occlusion in the present experiments, CBF passively falls with hypotension or with increased viscosity and passively rises with hypertension or with decreased viscosity. In this sense, "blood viscosity autoregulation" is comparable to "pressure autoregulation."

The comparability of blood viscosity autoregulation and pressure autoregulation may also shed some light on the controversy regarding the mechanism responsible for pressure autoregulation, i.e., the myogenic, Bayliss mechanism or the metabolic mechanism. With blood viscosity changes no (great) alterations occur in trans-mural pressure or the amount of stretch of the smooth muscles in the vessel wall, but vessel diameter adjustments nevertheless take place. Thus, blood viscosity autoregulation is probably metabolically mediated. We have not made any measurements to identify this mediator (e.g., local O2 delivery or local adenosine concentration), nor can we state that the mediators in both types of autoregulation must be the same. However, our findings are certainly not at variance with the view that the two types of autoregulation share the same mechanism and may serve as a stimulus to further test the hypothesis that pressure autoregulation is also metabolically mediated.

If one defines autoregulation as the tendency of the brain to keep its CBF constant despite changes in perfusion pressure or in blood viscosity, we find that this mechanism does not always function perfectly. The increase in CBF with hypotension in all the areas with normal autoregulation is somewhat puzzling. It has been reported by Farrar and coworkers that in patients in whom hypotension was induced during surgery for intracranial aneurysms, CBF often increased until a certain, very low blood pressure (average MABP 29 mmHg) was reached; only then CBF fell passively with further reduction of blood pressure. The explanation is that in normal brain the drugs used to induce hypotension also cause vasodilation. In ischemic brain, however, there is already maximal vasodilation and CBF follows blood pressure passively. The increase in CBF in the areas with intact autoregulation during hypertension was fairly large and statistically significant in the right caudate nucleus and ectosylvian cortex. Sizeable increases of CBF were also found with lower blood viscosity in the right caudate and a number of other normal regions. This is compatible with the finding that adjustments in vessel diameter with hypertension or lower viscosity are smaller than with hypotension or higher viscosity. Apparently, the brain is tuned to prevent a decrease in CBF and accept some increase in CBF above normal needs.

The mean decrease in blood viscosity as measured by us 15 minutes post-mannitol was 18.1% at 90 sec⁻¹, 16.2% at 225 sec⁻¹ and 14.9% at 450 sec⁻¹. The mean increase in CBF in the left caudate was 47%; according to the Hagen-Poiseuille equation, this CBF increase should be obtained with a viscosity change of 32%, provided other variables remain the same. Similarly, the 18% CBF decrease at 75 minutes can be explained
with an increase in viscosity of 22%, much larger than the viscosity increase actually found. It is clear that at higher shear rates the percentage changes are smaller than at lower shear rates and other data might be taken to indicate that even much lower shear rates than those which we have measured prevail in vivo. It has been shown that at shear rates above approximately 150 sec⁻¹ blood starts to behave like a Newtonian fluid and viscosity does not change much anymore with different shear rate.¹⁶ The in vitro viscosity measurements do not take into account, however, an important denominator of blood viscosity in vivo, i.e., erythrocyte deformability. Although it has been shown that mannitol reduced blood viscosity probably at least in part by enhancing erythrocyte deformability,¹⁷ it is not known how much this effect contributes to the in vivo viscosity decrease. Similarly, it is unknown whether the "rebond" increase of blood viscosity at 75 minutes post-mannitol is accompanied by a decrease in erythrocyte deformability, which would result in a larger blood viscosity increase in vivo than we have measured in vitro. It appears to us that the effect of mannitol on erythrocyte deformability may be much larger than on whole blood viscosity and therefore the effects on in vivo viscosity are much larger than on in vitro viscosity. Measurements of CBF or vessel diameter in a species in which erythrocyte deformability is less important because the erythrocytes are already smaller than the capillary diameter, such as is the case in the dog, may throw more light upon this question.

Another explanation for the imperfect match between calculated values and theoretical values is the great difference between in vivo conditions and those which apply to the Poiseuille equation in the strictest sense (Newtonian fluid in a tube of uniform bore!). But, assuming that the Hagen-Poiseuille equation is indeed operable in the brain with defective autoregulation, it is justifiable to compare the percentage changes between left and right in the caudate and ectosylvian cortex. The fact that the differences in percentage, both with blood pressure alterations and with blood viscosity changes, are much greater on the left side than on the right side, leads us to the conclusion that a compensatory mechanism has been operable in the right side. Whether the mechanism for these compensations is the same with blood pressure changes and blood viscosity alterations remains unknown as yet. The effect on CBF of these compensations is, however, the same: pressure autoregulation and blood viscosity autoregulation.

Blood viscosity autoregulation explains why CBF increases only when hematocrit is reduced from very high to normal values.² ³ At supra-normal hematocrit values there is maximal vasodilatation so CBF passively follows viscosity changes, but once CBF has become normal further reduction of hematocrit and blood viscosity is compensated for by vasoconstriction. It also serves to explain that, with intact autoregulation, mannitol decreases intracranial pressure much better than with defective autoregulation. With intact autoregulation the lower viscosity leads to vasoconstriction, thus keeping CBF constant but decreasing cerebral blood volume with an ensuing decrease in intracranial pressure, while with defective autoregulation the lower viscosity only leads to an increase in CBF without effect on vessel diameter, cerebral blood volume and intracranial pressure.¹⁸

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References

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