The Effects of Arterial Blood Pressure on the Regional Cerebral Blood Volume by X-Ray Fluorescence

BY ROBERT L. GRUBB, JR., M.D.,* MICHAEL E. PHELPS, PH.D.,† MARCUS E. RAICHLE, M.D.,‡ AND MICHEL M. TER-POGOSSIAN, PH.D.†

Abstract:
The Effects of Arterial Blood Pressure on the Regional Cerebral Blood Volume by X-Ray Fluorescence

Cerebral blood flow (CBF) remains constant over a wide range of arterial blood pressure. This is thought to be accomplished by changes in the diameter, and therefore the volume, of the cerebral resistance vessels. To test this hypothesis, regional cerebral blood volume (rCBV) was measured in vivo in Rhesus monkeys over a range of mean arterial blood pressures (MABP) of 35 to 200 torr. Multiple measurements were made in each animal by the method of stimulated x-ray fluorescence. A significant linear relationship of \( rCBV = 6.26 \pm 0.47 \text{ SD} - 0.015 \pm 0.004 \text{ SD} \times \text{MABP} \) was found. For each one torr change in the MABP, there is a change in rCBV of 0.015 cc/100 gm of brain tissue over a range of MABP of 35 to 200 torr. An additional observation of this investigation was that autoregulation of the cerebral blood flow (CBF) is perturbed for a period lasting up to 15 minutes after the intravenous injection of Renografin-76R.

Additional Key Words
autoregulation contrast agents

Introduction

It is well known that cerebral blood flow (CBF) remains constant over a wide range of arterial blood pressure. More than 35 years ago both Forbes and Fog, using cranial windows in cats, observed that the diameter of the pial vessels varied with changes in the MABP. A rise in the MABP produced a vasoconstriction of the pial arterioles and a fall in the MABP induced a vasodilation of the same vessels. Fog observed that the smaller pial arterioles (12 to 14\( \mu \)) were much more reactive than the larger (>100\( \mu \)) arterioles. These experiments, and those of Bayliss, showing that the blood flow in the hind limb of dogs, cats, and rabbits was kept constant by changes in the volumes of the limb in response to changes in the blood pressures, formed the basis of the concept that autoregulation in the brain is accomplished by changes in the diameter, and therefore the volume, of the cerebral resistance vessels.

The lack of an accurate method of measuring cerebral blood volume (CBV) has precluded, to date, the validation of this hypothesis.

The purpose of this study was to determine the degree to which CBV is involved in the autoregulation of CBF. Using the method of stimulated x-ray fluorescence, regional cerebral blood volume (rCBV) was measured in Rhesus monkeys over a wide range of arterial blood pressures.

Methods

The system used for the measurement of rCBV by means of stimulated x-ray fluorescence has been described previously in detail. The apparatus consists of an x-ray unit of conventional design and of a solid state Si(Li) x-ray spectrometer. A beam of x-rays, about 1 cm in diameter, is passed through the head of the subject. The field of acceptance of the collimated spectrometer intersects the x-ray beam at a 90° angle within the brain of the subject. The “common volume” formed by the intersection of the x-ray beam and the collimated field of view of the detector is typically 1 cm\(^3\). A nondiffusible indicator labeled with iodine (meglumine [66%] and sodium [10%] diatrizoate, Renografin-76R) is injected intravenously over a period of four minutes. When the iodinated contrast material...
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**FIGURE 1**

Diagram of x-ray fluorescence system.

equilibrates in the vascular pool, the x-ray tube is activated, which excites the iodine in the common volume, and the characteristic K shell fluorescence of iodine, consisting of 28.5 and 32.4 kev x-rays, is emitted and detected by the x-ray spectrometer. The intensity of the iodine fluorescent radiation is proportional, within limits, to the amount of indicator in the common volume. Samples of the subject’s blood drawn simultaneous to the cerebral measurement are later “fluoresced” in a suitable brain phantom. The rCBV is then calculated from the ratio of the fluorescence signal in the brain to that of the blood. About one minute is required to make a measurement of rCBV with this method. Several measurements can be made until the level of contrast material has fallen to a nondetectable level, due to its clearance from the blood by the kidneys. Because Renografin-76K is a plasma tag, all of the rCBV values obtained in this experiment were corrected for a cerebral hematocrit of 85% of the large vessel hematocrit.

Ten adult Rhesus monkeys weighing 12 to 14 lb were anesthetized with phencyclidine HCl, and given atropine. The monkeys were paralyzed with gallamine triethiodide, and passively ventilated on 100% oxygen with a Harvard respirator. Arterial blood pressure was monitored with a catheter placed in the aorta through the femoral artery and connected to a Statham P23aa transducer. A femoral vein catheter was used for infusion of drugs and withdrawal of blood when the blood pressure was lowered. The end tidal CO₂ was monitored with a Beckman Model LB-1 capnograph. pH, P<sub>CO₂</sub>, and P<sub>O₂</sub> were determined on multiple arterial and venous blood samples with an IL-113 gas analyzer. The animal was maintained at a constant temperature of 37 to 38°C with a heating pad. Superior sagittal sinus blood samples were obtained from several animals through direct puncture of the superior sagittal sinus via a Teflon appliance chronically implanted through a small craniectomy directly over the sinus. This appliance allows repeated superior sagittal sinus blood samples to be obtained without disruption of the sinus.

The anesthetized and paralyzed monkeys were positioned on the fluorescence table so that the target volume was located in the midportion of the posterior frontal lobe. The position of the target volume was verified by making a skull film of the monkey and a double exposure of the collimated x-ray beam. The position of the field of acceptance of the collimated detector was determined by external measurement. The P<sub>PaCO₂</sub> was maintained at a constant level within the normal range of 32 to 46 torr throughout the experiment. The animals were infused with 0.75 cc per pound of Renografin-76 over a four-minute period. A measurement of rCBV was obtained at the animals’ baseline MABP. The MABP was then increased by a constant intravenous infusion of either metaraminol or angiotensin. When the MABP was stabilized at an elevated level, one or two measurements were made. The infusion of pressor agent was then stopped and the MABP was allowed to return to baseline values. Again, rCBV was measured at the baseline MABP level. When the MABP had stabilized, a third baseline rCBV value was obtained. The MABP was then lowered and stabilized by the rapid withdrawal of approximately 80 to 100 cc of blood from the femoral vein catheter. One or two measurements were made before the MABP was elevated by the re-infusion of the withdrawn blood (infusion period of one to two minutes). Within three to four minutes after the re-infusion of the blood, a measurement of rCBV was obtained. The sequence of changes in the MABP was varied in some experiments with an initial lowering of the MABP, followed by elevation of the MABP. In other experiments, the MABP was raised two to three times in sequence and several rCBV measurements were obtained. A total of five to ten measurements of rCBV were made in each experiment. In some of the experiments the arterial P<sub>O₂</sub> and superior sagittal sinus P<sub>O₂</sub> were determined during the rCBV measurements. The reciprocal of arteriovenous oxygen difference across the brain was then used as an index of CBF. The values of rCBV obtained were corrected to a common Pa<sub>CO₂</sub> of 40 torr using a CO₂ responsiveness of 0.046 cc per 1 torr of Pa<sub>CO₂</sub>. Throughout this experiment it was assumed that the intracranial pressure was small as compared to the MABP, and therefore the MABP was assumed to be approximately equal to the perfusion pressure.
**Results**

The values of rCBV at the corresponding MABP are listed in Table 1. The values selected for the table were obtained at baseline pressures and at stable elevated and lowered pressures. Excluded were values of rCBV obtained during the initial 20 minutes after intravenous infusion of Renografin-76, rCBV values obtained immediately after restoration of MABP following induced hypotension, and rCBV values obtained immediately after the discontinuation of a pressor agent infusion. The relationship between rCBV and MABP is depicted in Figure 2. The equation of the regression line is:

\[ rCBV = 6.26 (\pm 0.47 \text{ SD}) - 0.015 (\pm 0.004 \text{ SD}) \text{ MABP} (1) \]

rCBV is in units of cc blood/100 gm tissue and MABP is expressed in torr. This equation indicates that for each torr change in the MABP there is a change opposite in direction in rCBV of 0.015 cc/100 gm of brain tissue over a range of MABP of 35 to 200 torr.

A similar rise in MABP was induced by both metaraminol and angiotensin. Angiotensin, however, gave a faster and more pronounced elevation of the MABP. When the reciprocal of the arterial and superior sagittal sinus oxygen difference was used as an index of flow, CBF was noted to remain constant at an elevated MABP with both metaraminol and angiotensin. On one occasion with metaraminol the CBF initially rose with the MABP elevation before stabilizing again at the baseline value.

**Table 1**

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<th>MABP (torr)</th>
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<th>rCBV†</th>
<th>P_{CO_2} (torr)</th>
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* rCBV values corrected for a cerebral hematocrit of 85% of the large vessel hematocrit. 10 11
† rCBV values corrected for a cerebral hematocrit of 85% of the large vessel hematocrit 10 11 and corrected to a common P_{CO_2} of 40 torr using a CO_2 responsiveness of 0.046 cc/1 torr of P_{CO_2}. 11
typical response of the rCBV after the MABP has been elevated. The rCBV is seen to decrease in response to the rise in MABP, and then increase slightly as the MABP falls slightly. Figure 4 illustrates the increase of the rCBV to a rapid and marked lowering of the MABP. A measurement obtained three minutes after the re-infusion of the withdrawn blood indicated that the rCBV was considerably higher than the rCBV before and during the period of hypotension, although the MABP at this time was close to the baseline MABP.

Occasionally autoregulation was briefly superseded during a rapid rise in the MABP. This is seen in figure 5. In this experiment a 55 torr rise in the MABP was achieved in a period of 30 seconds with metaraminol. A measurement made one minute later showed an increase in rCBV instead of the expected decrease. The reciprocal of the arterial-superior sagittal sinus oxygen difference obtained at the same time indicated an increase in the CBF. Five minutes later a repeat measurement while the metaraminol infusion was continued showed the expected decrease in rCBV when the CBF had returned to its baseline value. The MABP was now stabilized and lower than the peak value obtained, but still considerably higher than the baseline MABP.

An intravenous infusion of iodinated contrast material in the quantity used in this experiment (1 cc per pound of body weight) can disturb autoregulation in the Rhesus monkey for as long as 15 minutes after the injection is started. These effects of Renografin-76° on autoregulation are shown in figure 6. An intravenous metaraminol infusion was started eight minutes after the injection of the contrast agent was begun. Instead of the decrease in rCBV that is seen with intact autoregulation, there was a marked increase in rCBV when the MABP was elevated. Repeated intravenous infusions of metaraminol (not illustrated) given later than 20 minutes after the Renografin-76° injection demonstrated the expected decrease in rCBV in response to an elevation of MABP.

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The response of rCBV to an elevation of MABP. (The dashed lines are not meant to indicate values of rCBV, but are only for continuity.)

Discussion
The autoregulation of the cerebral circulation is now well accepted. This concept implies that the CBF remains constant over a wide range of perfusion pressures.\textsuperscript{1-4} It had previously been thought that the CBF remained constant at extreme elevations of the MABP, but recent evidence indicates that autoregulation may fail with an increase in CBF at MABP greater than 200 torr.\textsuperscript{13} On the opposite end of the autoregulation curve the lower limits of the MABP at which autoregulation is intact vary in different species of animals and in different experiments using the same species of animals. Harper\textsuperscript{1} found that the CBF in dogs decreased when the MABP was less than 80 to 90 torr. In humans, Lassen\textsuperscript{3} found that autoregulation failed at an MABP lower than 60 torr. Häggedahl et al.\textsuperscript{14} and Zwetnow\textsuperscript{15} found that the perfusion pressure in dogs could be reduced to 30 to 50 torr before a reduction in CBF was seen. Rapela and Green\textsuperscript{4} found that CBF was constant down to an MABP of 40 to 50 torr in dogs. It is felt that vasoconstriction and vasodilation, and hence changes in the volume of the cerebral resistance vessels, play a major role in the maintenance of a constant CBF over a wide range of MABP. However, only indirect measurements of CBV have been made in response to changes in MABP.

Measurements of CBV using the x-ray fluorescence method indicate that the rCBV increases 0.051 cc/100 gm tissue with a 1 torr decrease in the MABP between the range of 35 to 200 torr. To understand the magnitude of the change, it is first profitable to consider the relationship of flow, pressure, and volume in a rigid tube as expressed by Poiseuille's law:
\begin{equation}
\text{Flow} = \frac{\pi D r^4}{8 \eta}
\end{equation}
where $\Delta p$ is the net pressure across the tube, $r$ and $l$ are the radius and length of the tube, respectively, and $\eta$ is the viscosity of the fluid flowing through the tube. Using the volume of a tube, $\pi r^2 l$, substituting...
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FIGURE 4

The response of rCBV to a decrease of MABP. Also seen is a period of hyperemia following the return of the MABP to control levels. (The dashed lines are not meant to indicate values of rCBV, but are only for continuity.)

into equation 2 and rearranging, we find the volume is inversely related to \((\Delta p)^{\frac{1}{2}}\) as follows:

\[
v = \left(\frac{F\eta l^2\pi}{\Delta p}\right)^{\frac{1}{2}} \quad (3)
\]

If one considers the vessels that are responsible for autoregulation and that \(F, I, \) and \(\eta\) are constant, then a 50% increase in \(\Delta p\) would require a 20% decrease in the volume, and conversely a 50% decrease in \(\Delta p\) would require a 41% increase in the volume. Using a mean value of rCBV of 4.6 cc blood/100 gm tissue at an MABP of 110 torr, equation 1 would indicate that a 50% reduction of MABP to 55 torr would produce only an 18% increase in rCBV. Also a 50% increase in MABP would produce an 18% reduction in rCBV. (Tissue pressure is assumed to be small as compared to the MABP, and thus \(\Delta p = \text{MABP}\).) The variation in the CBV change calculated from Poiseuille's law, which depends upon whether the MABP is raised or lowered 50%, is accounted for by the square root dependence between MABP and CBV, whereas equation 1 shows a linear relationship. Thus, a regression analysis was performed on the data from table 1 as rCBV versus \((\text{MABP})^{-\frac{1}{2}}\), but the correlation was much less significant than equation 1. This discrepancy between the predicted results for a rigid tube system and the actual results can be explained by three reasons. (1) The vascular structure of the brain does not behave as a rigid tube. (2) The central volume principle (flow = volume/mean transit time [T]) shows a direct relationship between flow and volume but this direct relationship is actually modified by changes in the mean transit time. Because of this factor, large changes in the CBF can be accompanied by relatively small changes in the CBV. (3) The CBV measured in this experiment may include the volume of vessels other than the cerebral resistance vessels. The cerebral resistance vessels have been thought to be the terminal pial arteries and arterioles,\(^7,16,17\) but
recent evidence indicates that a larger portion of the pressure-decrement in the cerebral vascular bed is across larger arteries of the brain proximal to the terminal arteries and arterioles. Shapiro et al., using a modified Wiederhielm servo-micropipet system, found a 39% pressure-decrement proximal to the largest (200 to 455μ) pial arteries, a 10% decrement between the largest (200 to 455μ) and smallest (25 to 40μ) pial arteries, and a 46% pressure drop distal to the smallest (25 to 40μ) pial arteries. A 1 cm³ target volume in the monkey brain will include the vascular volume of arteries, capillaries, and veins. Because of this the rCBV changes seen in response to MABP changes with this method may be less than the volume changes occurring in the actual cerebral resistance vessels.

Data from this series of experiments suggest that the rate of change of resistance vessel diameter with changes in the MABP is not instantaneous, as illustrated in figure 5. Here a rapid increase in MABP to a peak level in less than a minute with metaraminol produced an increase in rCBV instead of the expected decrease. However, several minutes later with the MABP still elevated, the rCBV was lower than the baseline value, as expected. This implies that on occasion there is a short time lag before autoregulation is re-established after an acute change in the MABP. Concomitantly, the rCBV rises (or falls if the MABP is decreased), and the CBF passively follows the MABP until autoregulation is re-established. Because many studies of CBF are done by monitoring the washout of isotopes over a 10 to 15-minute period, autoregulation has been assumed to be a rapid phenomenon, even with extreme changes in the MABP. Rapela and Green, found by diverting the outflow from the venous sinuses of dogs through an electromagnetic flowmeter probe that up to 90 seconds could be required for autoregulation to be re-established. Ekström-Jodal, using a continuous cuvette oximeter

A variant of the usual rCBV response to an increase in MABP. (The dashed lines are not meant to indicate values of rCBV, but are only for continuity.)
The response of rCBV to an elevation of MABP in the period when autoregulation is still disturbed by the intravenous injection of Renografin-76. (The dashed lines are not meant to indicate values of rCBV, but are only for continuity.)

The recording of the oxygen saturation of the superior sagittal sinus as an index of flow in dogs, noted a 40 to 45-second lag in the autoregulatory response. Other studies, however, have shown that autoregulation is a very rapid phenomenon, occurring in a matter of seconds.

Reactive hyperemia, a phenomenon previously defined as an increased CBF at a normal MABP and PaCO₂ combined with a passive pressure-flow relationship, was observed in this experiment as an increased CBV (fig. 4). This reaction is produced by an antecedent period of reduced perfusion pressure created by either arterial hypotension or increased intracranial pressure. Restoration of a normal perfusion pressure produces the reactive hyperemia. In most reports a reduction of CBF was associated with the low perfusion pressure that preceded the reactive hyperemia. However, Håggen-dahl et al. found that a reactive hyperemia could occur in dogs after the perfusion pressure had been lowered only to 70 to 80 torr, with no associated reduction in CBF. Siesjö and Zwetnow have shown that reduction in the perfusion pressure to this degree is sufficient to produce an accumulation of lactate in the brain, which presumably underlies the reactive hyperemia. In our experiments we found an increased rCBV, as compared to the baseline values, up to ten minutes after the MABP had been restored to a normal level, following a period of hypotension induced by blood withdrawal. The degree of hyperemia varied in different experiments.

Our experiments confirm the observations of others that iodinated contrast materials transiently affect the cerebral circulation. Huber and Handa found that Urografin 60% injected as a bolus directly into the carotid artery produced dilation of the cerebral arteries as measured on serial angiograms, especially those measuring 0.5 to 1.0 mm in diameter on the films. The dilation was seen on late arterial phase films of the initial injection of contrast material and also on series of films taken after a secondary injection of contrast material a few
minutes after the first injection. Potchen et al. found that an injection of 6 cc of Conray 60% as a bolus directly into the carotid artery one minute prior to injection of $^{182}$Xe for a CBF study by the isotope washout method increased the CBF an average of 18.8% over control CBF values in human subjects. It has been shown that an intravenous injection of Renografin-76R over a period of four minutes in a dosage of 1 cc per pound of body weight increased the CBF (as measured in Rhesus monkeys by a Doppler ultrasonic flow probe system) over control levels (M. Hernandez—personal communication). In addition, Hernandez found that the Renografin-76R injection also abolished autoregulation to an elevation of MABP with pressor agents for a period lasting as long as 15 minutes. In our experiments the rCBV increased in response to a rise in the MABP (fig. 6) during the first 15 minutes after the intravenous injection of Renografin-76R over a four-minute period was begun, implying a temporary loss of autoregulation. For this reason, observations of rCBV in the initial 15 minutes after the injection of Renografin-76R were not used in the data showing the relationship of rCBV and MABP.

**Conclusion**

A significant relationship between rCBV and the MABP has been demonstrated. The rCBV responds inversely to changes in the MABP over a range of 35 to 200 torr, thus confirming the role of the CBF in the autoregulation of CBF. The remainder of the autoregulation of the CBF is accommodated by changes in the mean transit time (t). For each 1 torr change in the MABP, there is a change in rCBV of 0.015 cc/100 gm of tissue. Autoregulation of the CBF can be perturbed for as long as 15 minutes after an intravenous injection of Renografin-76R.

**Acknowledgment**

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