A Study of Regional Autoregulation in the Cerebral Circulation to Increased Perfusion Pressure in Normocapnia and Hypercapnia

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Abstract:
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- Catheterization of Labbé's vein and of a pial branch of the middle cerebral artery has been performed on anesthetized baboons. Closure of the skull has enabled the reaction of the venous outflow from Labbé's vein to be monitored in response to pressure step increases in the pial arterial pressure induced by gas compression of a perfusion mixture connected to the arterial line. Rapid changes in cerebrovascular resistance with swift emergence of regulatory constancy have been shown, and the time characteristics of the resistance changes strongly suggest that they are primarily myogenic in origin. Induction of hypercapnia did not interfere with this autoregulatory mechanism to increased perfusion pressure, which indeed appeared to be more effective at raised arterial $P_{CO_2}$, but the mechanism was abolished by the induction of ischemia from middle cerebral occlusion.

Additional Key Words
- myogenic mechanisms
- venous outflow
- cerebrovascular resistance

Autoregulation of the cerebral circulation, noted as early as 1900,1 was observed in more detail in the work of Fog2,3 and Forbes et al.4 in classical studies in the thirties, and has been demonstrated in numerous studies under normal circumstances5-7 since then. The term "autoregulation" in its restricted sense describes the intrinsic ability of cerebral circulation to maintain a constant blood flow in the face of changing perfusion pressure. Autoregulation usually has been tested by stepwise reduction of arterial pressure, and almost constant CBF has been shown only recently during induced hypertension.8

The mechanism of autoregulation in the cerebral circulation is still a matter of debate. The studies of Bayliss8 and Folkow10,11 in the peripheral vascular system led to the consideration of a myogenic mechanism in the cerebral circulation, and nervous or humoral factors12-16 also have been suggested. The myogenic theory assumes a basal tone of vascular smooth muscle, which is affected by changes of perfusion or transmural pressure, resulting in constriction to rising intravascular pressure and dilatation to falling intravascular pressure. Studies in vascular smooth muscle have demonstrated rhythmical spontaneous activity of muscle cells, probably corresponding to the basal tone, which increases at an augmented transmural pressure.17-19 as also has been shown electrophysiologically.20

In previous experiments the effect on cerebral blood flow (CBF) of different forms of perfusion pressure (nonpulsatile, normally pulsatile and augmented pulsatile perfusion) has been studied.21-24 The
increased flow resistance observed in these experiments seemed to indicate a changing response to altered pressure mediated by myogenic mechanism. These studies further demonstrated that pressure-induced changes of cerebrovascular resistance (CVR) contained two components: a slower reaction to changes of mean pressure, and another sensitive to pressure pulsations. The latter has been predicted to be the initial fast component of cerebral autoregulation. Up to this time, however, it has been difficult to assess fast responses to acute changes of perfusion pressure in the cerebral circulation. The preparation recently developed has enabled us to study hemodynamic reactions to rapid pressure changes in a regional vascular area of the cerebral circulation. The effect of factors which are well known to impair cerebral autoregulation, such as hypercarbia and ischemia, also has been tested in this study.

**Methods**

Twelve baboons in the 10 to 12 kg weight range were studied under general anesthesia induced as previously described, using a sleep dose of thiopentone followed by alpha chloralose 50 to 60 mg/kg, I.V. The animals were then immobilized with gallamine triethiodide (1 mg/kg, I.V., repeated as necessary) and artificially ventilated to control the arterial PCO₂ to a normal level between 35 and 45 mm Hg. A small parietal craniectomy was performed, the dura opened, and Labbe's vein cannulated. The effluent from Labbe's vein was led through an electromagnetic flowmeter (Statham Type SP2200) and returned to the right atrium by means of one femoral vein. A convenient adjacent parietal or temporal branch of the middle cerebral artery was cannulated, the dura was then coapted, and the skull closed with acrylic. Where the middle cerebral artery was to be occluded, the skull was opened through a separate small anterior temporal craniectomy, the dura opened over the Sylvian fissure, the middle

![Figure 1](http://Stroke.ahajournals.org/)

**Recording from an anesthetized baboon.** ETCO₂ = end-tidal CO₂ concentration from the trachea; CVF = cerebral venous flow monitored from Labbe's vein; CVP = central venous pressure monitored from the right atrium; SBP = systemic blood pressure. Between the arrows, inhalation of 3% CO₂ or slow infusion of Aramine 50 gamma per ml was carried out. ZC = occlusive zero check of the flowmeter. The black squares represent the points of withdrawal of arterial blood for arterial PCO₂ and the figures associated with them the arterial PCO₂ values so obtained. Autoregulation to increased SBP with preserved reactivity to CO₂ inhalation is shown.
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cerebral artery clipped, the dura coapted, and the skull reconstituted once more with acrylic. Continuity between arterial input and venous outflow was demonstrated in all cases by injection of small volumes of saline into the arterial catheter. This low viscosity injection produced a prompt transient rise in venous outflow just following the injection. Increases in middle cerebral arterial pressure were produced by an adaptation of the method of Basar and Weiss. Constant gas compression of 5 or 10 lb/sq in (psi) was used to drive a perfusion mixture into the middle cerebral arterial catheter, and the effect on cerebral venous outflow was monitored by the flowmeter. Input pressure was measured with a strain gauge, and input flow measured with a second electromagnetic flowmeter. The constitution of the perfusion mixture was two-thirds 10% dextran 40 in saline and one-third "perfudex," that is, 5% dextran 40 in balanced physiological solution. The solution was continuously saturated with any desired concentration of CO$_2$ and oxygen. CO$_2$ of the perfusion solution could be varied between 32 and 150 torr. The CO$_2$ content of the solution was 6.05 vol % at a P$_{CO_2}$ of 40 torr and 9.20 vol % at a P$_{CO_2}$ of 80 torr. The P$_O_2$ of the solution was approximately 440 to 460 torr. The fluid behaved as a Newtonian fluid with a viscosity of 4.6 centipoises (cp) (by the same method of estimation, blood gave a viscosity of 4.0 cp). The osmolality of the solution measured by the technique of depression of the freezing point was 322 mOsm/kg. pH of the solution as prepared was 5.4 (Astrup), but as this could be elevated to normal levels by small amounts of phosphate buffer, adjustment seemed unnecessary. The animals were continuously ventilated with oxygen and the P$_{CO_2}$ kept around 450 torr. P$_{CO_2}$ was controlled at normal levels between 35 and 45 torr by adjustment of the ventilation. P$_{CO_2}$ could be lowered by increasing the ventilatory volume or raised by adding enrichments of CO$_2$ to the input of the pump. Calculation of the added pressure in the bed was made in vitro following the experiment, by recreating the same conditions of input pressure and flow in the same catheterization system and measuring the pressure immediately distal to the small arterial catheter after its withdrawal from the middle cerebral artery. This technique was used in preference to catheterization of a further branch of the middle cerebral since it was found that increasing the handling of the preparation decreased the effectiveness of autoregulation, as one might have expected. The 5 psi injection was found to add about 80 mm Hg pressure to perfusion distal to the catheter; 10 psi gave about 140 mm Hg added pressure. The output of the various devices was recorded on a mechanical recorder with curvilinear ordinates (Beckman Type R).

**Results**

The condition of the preparation was evaluated prior to the experiments by testing the autoregulatory and CO$_2$ responses of CBF (fig. 1). Hypercarbia from inhalation of 3% CO$_2$ increased cerebral venous outflow considerably, whereas hypertension induced by Aramine infusion led to an insignificant flow augmentation only, demonstrating well-preserved autoregulation.

**NORMOCAPNIA**

The acute pressure rise in the vascular bed of the middle cerebral artery resulted in an initial spike of arterial input flow (I/PF), which then fell to a constant elevated level (fig. 2). Following the "pressure step," cerebral venous flow (CVF) exhibited some oscillating variation within the first 1 to 1.5 seconds, and thereafter reached a steady state, at or even below the control value, despite sustained pressure elevation (fig. 3). Faster recording (fig. 4) demonstrated a small initial flow augmentation at the beginning of the pressure step, which then fell within 0.8 to 1 second below the control value, and reached a steady state in from 10 to 90 seconds in different experiments.

The flow resistance calculated from the curves of figure 4 demonstrates the fast changes in the pressure/flow relation (fig. 5). Following an initial peak reached after 0.5 second, flow resistance rose again to a second peak, thereafter returning slowly to lower values and eventually approaching a steady state after 10 to 12 seconds. Slight variations of this principal flow reaction to acute "pressure steps" were observed in individual experiments.
The oscillation of cerebral venous flow produced by the pressure step. Recordings as in figures 1 and 2.

**HYPERCAPNIA**

Typical results of pressure elevations at raised PaCO₂ are demonstrated in figures 6 and 7. The well-known flow augmentation in hypercapnia is seen in the left part of figure 6. An acute pressure step did not result in any further flow increase, but rather reduced CVF considerably for the duration of the pressure step. CVF returned to the initial level when the added pressure was discontinued. Fast recording (fig. 7) showed that initial oscillatory flow changes passed into a lower steady state during sustained hypertension. The calculated changes of CVR (fig. 8) differed distinctly from those in normocapnia. Two peaks are hardly distinguishable, although their time relationships are identical.

**ISCHEMIA**

In contrast to the consistent pressure/flow relationship described in hypercapnia above, ischemia resulted in a flow augmentation which closely paralleled the pressure curve (fig. 9). It appeared that autoregulation was abolished during ischemia.

**Discussion**

The relatively long latency between variation in perfusion pressure and reactive change in CVR, confirmed by many others in the literature, has up to now militated against acceptance of a myogenic mechanism of cerebral autoregulation. Recent studies in isolated organs and renal circulation in situ have demonstrated the fast onset of pressure-induced changes of flow resistance.
Mainly for technical experimental reasons it has so far been difficult to assess rapid changes of CBF to acute alterations of perfusion pressure. 37

When monitoring arterial inflow, flow spikes occurring during "pressure steps" may be mistaken for sudden changes in CVR. These spikes, however, do not reflect changes in peripheral resistance, but rather the arterial capacitance which is momentarily increased during an acute rise in intracranial pressure. The suddenly increased flow volume passing the flow probe is "stored" by a distended vascular bed and thereafter released in a fairly constant flow when elasticity reverses the acute distention. 25, 38-40

To study acute changes in CVR, therefore, cerebral venous outflow has to be measured. There are, however, technical difficulties in applying rectangular pressure steps to the total cerebral circulation because of the special vascular supply to the brain. An acute pressure step applied to the aortic arch will be "damped" by the "storing" effect of the four great extracranial arteries before reaching the resistance vessels. 41 These difficulties also are evident in the experiments of Yoshida et al., 42 where acute hypertension was induced by clamping the thoracic aorta.

A solution to this problem is offered by a preparation recently developed 28, 29 which permits measurement of arterial inflow and venous outflow from the regional vascular area supplied by the middle cerebral artery. Conditions in this preparation differ from isolated organs, since the outflow from Labbe's vein does not cover the entire area of the middle cerebral artery and varies from animal to animal. Slight variations in individual experiments therefore must be expected. Since the small venous outflow demanded high amplification, only low frequency response could be used. The rapid venous

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FIGURE 6

The result of pressure step increase in pial arterial pressure under hypercapnic conditions. In this figure, cisternal pressure (Cist. P) and extradural pressure with a strain gauge pressure transducer (E-DP) also have been recorded. The other recordings are as in figures 1 and 2. The reduction in cerebral venous outflow to the pressure step is obvious.
outflow spikes observed in isolated organs therefore could not be detected in this preparation.

In spite of these methodological difficulties, our experiments have shown reactive changes of CVR, which are evident as fast flow changes as early as 0.8 to 1 second after the acute step increase of pressure.

Calculations of flow resistance that are admissible in a steady state are somewhat questionable in dynamic conditions because physical factors, such as the inertia of the accelerated volume, the capacity of yielding tubes, pressure and flow waves and their reflection, etc., become effective besides biologically active regulatory mechanisms. From the experiments of Basar and Weiss, however, it can be assumed that these hydrodynamic and physical forces have passed after 0.4 second. Because of the somewhat delayed response in our preparation, the first peak reached within 0.5 second may be attributed to these factors, but the second rise of calculated resistance beginning after one second or less corresponds to the reactive changes in resistance which occur within 0.3 to 0.7 second in isolated organs.

The initial wavelike flow pattern after an acute "pressure step," with short "overshooting" reactions, suggests that the pressure-induced changes in resistance are an oscillatory process complete in our experiment within 10 to 90 seconds, thereby confirming adjustment times of "seconds,"42 "40 to 50 seconds,"43 "30 to 60 seconds,"33 and "20 to 50 seconds,"44 which had been obtained by different methods.

Pressure-induced reactive changes of flow resistance are a biphasic process containing a fast and rate-sensitive component and a slower one which, occurring later, is rate independent, longer lasting and actually exerting autoregulation. Previous experiments in cerebral circulation in situ also have shown that cerebral autoregulation can be evoked by nonpulsatile pressure and even by quite slow increases of perfusion pressure.14,21 It was concluded that the first fast component does not seem to be essential for cerebral autoregulation.23 The existence of a fast component in cerebral circulation has been assumed so far only by the observation of a rate sensitive part in cerebral autoregulation,14 but now, in the present experiment,
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Calculation of cerebrovascular resistance from the curves of figure 7 during hypercapnia. The comparison with figure 5 shows that two peaks are more difficult to find.

Calculation of cerebrovascular resistance from the curves of figure 7 during hypercapnia. The comparison with figure 5 shows that two peaks are more difficult to find.

has been demonstrated to become effective after a short latency of one second or less. In smooth muscle of tenia coli, Golenhofen has observed two reactions of different time constant to sinusoidal stretch of varying frequencies. It seems likely, therefore, that the present findings in cerebral circulation are best explained, as those in isolated organs and in renal circulation, by myogenic reactions of the vasculature. According to the original Bayliss concept, myogenic vascular reactions are evoked by stretch of vascular smooth muscle via intraluminal or transmural pressure. This stimulus, however, would become ineffective by a sustained contraction of smooth muscle cells at constant pressure elevations. This difficulty of the Bayliss concept may be solved by the finding of rhythmical spontaneous activity of smooth muscle cells, different frequencies of contraction to pressure change explaining the autoregulatory constancy of CBF.

The mechanism of cerebral autoregulation is quite vulnerable and easily impaired by hypoxia and trauma. Human observation, also, abolished autoregulation has been shown in cerebral infarction, tumors, and trauma of the brain. Abnormal autoregulation was observed in our experiments following ischemia from the close parallel between "pressure step" and the cerebral venous outflow trace.

Ischemia is believed to cause maximal vasodilation via tissue acidosis, thus inhibiting pressure-induced changes of CVR. In this condition, CBF is passively dependent on the perfusion pressure. The ultimate cause of this vasoparalysis is not yet completely understood. A similar condition seems to exist in hypercapnia, where a marked vasodilatation with impaired autoregulation is observed at higher P CO2 levels. Recent studies suggest that pH changes in the perivascular tissue or the vascular wall itself resulting from arterial hypercapnia are the effective factor. The same mechanism also is suspected in vasoparalysis due to ischemia, the first step being tissue lactacidosis.

Clinical and experimental findings, however, cast some doubt on this assumption, since CO2 reactivity may be retained when autoregulation is abolished from ischemia. The present study also shows a distinct difference between ischemic vasoparalysis with abolished autoregulation and CO2-induced vasodilatation which still permits changes of CVR reactive to acute "pressure steps." Maintained or only slightly impaired autoregulation in hypercapnia also has been observed by other authors. The initial oscillatory adjustment of CBF to pressure steps is present in hypercapnia also, although the extent of the oscillations is distinctly smaller than in normocapnia. The constant finding of a full adjustment to a lower level in the steady state, together with the initial oscillatory adaptation, suggests that the mechanism of autoregulation is not paralyzed in hypercapnia. If cerebral regulation in hypercapnia is tested to falling perfusion pressure, the additive effect of two vasodilator factors may well simulate abolished autoregulation. At induced hypertension, on the other hand, there is competition
between the constrictor stimulus of increased pressure and the vasodilator effect of raised $P_{O_2}$. In this situation, changes of CVR may be expected, and have indeed been shown, which are the resultant of these two opposite forces. Our findings therefore support the earlier assumption that different mechanisms are effective in cerebral autoregulation and $CO_2$ reactivity in the cerebral circulation. The myogenic mechanism of cerebral autoregulation, abolished by ischemia, is maintained or only slightly impaired in hypercapnia.

References

2. Fog M: Om Piaarteriernes Vasomotoriske Reaktioner. Munksgaard, Copenhagen, 1934
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41. Held K, Thiemann V: Unpublished data


47. Severinghaus JW, Lassen N: Step hypocapnia to separate arterial from tissue Pco2 in the regulation of cerebral blood flow. Circulation Research 20: 272-278 (Feb) 1967


Correction


The legends to figures 2A and 2B (page 58) should be reversed.
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