Vascular Mechanisms Controlling a Constant Blood Supply to the Brain ("Autoregulation")

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Abstract: The segmental resistance in the major arteries of the brain and the respective smaller cerebral arteries carrying blood from the circle of Willis was computed (with a mathematical method developed recently) using the inlet and outlet pressures of the internal carotid arteries, as well as the venous pressure in the brain sinuses of dogs. Under the conditions of stepwise changes of the perfusion pressure the following localization of "autoregulatory" responses of the cerebral arteries has been found: changes in the inlet pressure of the internal carotid artery produced corresponding changes of its vascular resistance resulting in a relative constancy of the outlet pressure of the artery, i.e., pressure in the circle of Willis; resistance changes in the smaller brain arteries were evident only when the alterations of the perfusion pressure were too big and the major arteries were unable to eliminate the disturbance. The responses of the internal carotid arteries were eliminated when their muscular layer was maintained normal, but deprived of the nervous control (when the arteries were continuously perfused with blood or oxygenated Ringer-Krebs bicarbonate solution shortly after the death of the animal). Thus, evidence was obtained that the vascular responses were brought about by a nervous and not by a purely muscular mechanism, as is usually assumed.

Additional Key Words: regulation of CBF cerebral arterial responses myogenic Bayliss effect systemic arterial pressure hypotension computer technique in CBF studies

Introduction

The mechanism operating to maintain the constant blood supply to the brain in the face of changes in the perfusion pressure, i.e., so-called "autoregulation," was rejected until the 1950s. This resulted, first, from the wide acceptance of Hill's concept that the systemic arterial pressure itself is the main regulating variable of cerebral blood flow (CBF) and, second, from the poor experimental technique of that period. However, in the last two decades the existence of a well-functioning "autoregulation" of CBF has been shown by many researchers in animal experiments and in human experiments as well. Simultaneously, evidence was accumulated that the regulatory mechanism may easily be disturbed by different kinds of cerebral hypoxia, an increase of CO₂ in blood, or brain trauma. It has been observed that a drop of the arterial pressure regularly was followed by dilatation of the pial arteries and vice versa. However, it was shown recently that vasodilatation appears after such a long delay (two to three minutes) that a causal relationship between the intravascular pressure changes and the vascular responses is unlikely. On the other hand, there was some indirect evidence that the major arteries of the brain (internal carotids and vertebrals) also took part in the control of the constant blood supply to the brain and that smaller variations of the arterial pressure seemed to be primarily eliminated by these arteries. The feedback loop controlling the cerebrovascular responses regulating the blood supply to the brain was thought to be brought about either by a myogenic Bayliss effect, i.e., by immediate response of the arterial muscular layer to a different degree of distention by the intraluminal pressure, or to be triggered by a change in the blood supply to the cerebral tissue.

The present study was designed to provide direct evidence concerning which mechanism is responsible for a constant blood supply to the brain in the face of changes of perfusion pressure, and possibly to detect the presence of a control loop for the regulation of CBF.
Methods

The experiments were carried out with 33 mongrel dogs of both sexes weighing 15 to 25 kg under nembutal anesthesia (about 0.4 gm per kilogram of body weight intraperitoneally).

The vascular resistance was determined both in the hemodynamically isolated internal carotid artery (all connections of the latter with the branches of the external carotid artery being previously interrupted) and in respective smaller arteries located to the periphery of the circle of Willis in the following four series of experiments: (a) under “normal” conditions, (b) when the responses of the muscular layer of the internal carotid artery were preserved, but it was completely deprived of the nervous control, (c) under conditions of perfusion of the artery which was quite recently excised from the organism and possessed preserved elastic properties of the vascular walls, and (d) the same after fixation of the vascular walls with formaldehyde.

The preparatory surgical procedure involved: (1) hemodynamic isolation of one (usually the right) internal carotid artery in situ, or (2) complete isolation of the artery from the body. Furthermore, (3) catheters were inserted to measure (a) the inlet pressure of the internal carotid artery, (b) its outlet pressure in the region of the circle of Willis, (c) the pressure of the venous sinuses of the brain, and (d) the pressure within the thoracic aorta. (4) A large glass or plastic cannula was inserted to connect the animal’s arterial system with a pressurized reservoir arrangement. The detailed preparatory surgical procedure and the experimental techniques applied were the following:

1. The technique of hemodynamic isolation of the internal carotid artery, i.e., the interruption of all its connections with the branches of the external carotid artery, was the following: The incision was made along the midsagittal line of the neck under the mandible. All the branches of the right common carotid artery except the internal carotid artery were ligated at their first portions, so that all the nervous connections of the carotid sinus and the arterial branches would be carefully preserved. After this, dissection was made between the digastric and mylohyoid muscles to reach the pterygoid muscle. The latter was separated from the bone by means of a diathermocautery and pushed aside until the internal maxillary artery was reached. Separating the artery carefully in the direction of its peripheral branches, the external ophthalmic artery was reached, thus enabling occlusion of the anastomosis. The latter was then ligated and, where that proved impossible, coagulated and dissected. Since the middle meningeal artery branches off from the internal maxillary artery inside the pterygoid canal, the latter had to be ligated at both ends of the canal, resulting in interruption of flow in the middle meningeal artery. The whole procedure was carried out very carefully with minimum damage to the tissues. The area under operation was always additionally anesthetized with 0.5% novocain.

2. The technique for complete isolation of the internal carotid artery for investigation outside the body was the following: Both common carotid arteries were exposed, including their bifurcations, the external carotid arteries about 2 cm long and the internal carotid arteries for the entire length to the carotid canal of the temporal bone. After this the dog was sacrificed by bleeding from a large artery and simultaneously the carotid arteries started to be continuously perfused with oxygenated Ringer-Kreb’s bicarbonate solution through rapidly inserted catheters into their cranial direction. The brain then was removed as fast as possible through a large trepanation hole (which had been made previously when the dog was still alive), so that the entire circle of Willis with the first portions of the anterior, middle and posterior cerebral arteries 3 to 5 mm long were left intact on the base of the skull. After this all the skull bones were removed except those parts where the internal carotid arteries pass inside the bone canals and the cavernous sinuses. Through an incision in the dura mater, which covered the cavernous sinuses, all the branches of the internal carotid arteries (anastomoses with the ramifications of the external carotid arteries) were ligated at their first portions. Such an isolation of the internal carotid arteries lasted approximately 30 minutes after the animal had been sacrificed, but because of the continuous perfusion of the artery its smooth muscle elements remained alive, and the vascular wall normally reacted to, e.g., 1 to 2 µg of intra-arterially administered serotonin. The experiments were carried out both with the living internal carotid artery isolated from the organism and after fixation of the vascular walls with 5% formaldehyde (prepared with 0.85% NaCl) for 20 to 24 hours.

3. The recording of blood pressure was performed with electromagnetic and Minograf 81 (Elaema-Schönander, Sweden). The four pressure transducers (type EMT 35) were set at the level of the animal’s heart auricle. The mean pressures were recorded by electrical integration. To eliminate blood clotting during the experiments, heparin (2,000 to 2,500 units per kilogram of body weight) was given intravenously after completing the preparatory surgical procedure. The following blood pressures have been measured:

(a) The inlet pressure of the internal carotid artery (P_in) was determined by the constant output pump through which the artery was perfused with blood from the respective common carotid artery either in the same animal or from a donor dog. The inlet pressure of the artery was measured through a catheter inserted into the external carotid artery and led backward almost until the bifurcation of the common carotid artery, whose branches except for the internal carotid artery were previously ligated (fig. 1).

(b) The outlet pressure of the internal carotid artery under investigation (P_out) was measured directly at the end of the artery, i.e., at the site of its connection with the circle of Willis through a thin polyethylene catheter inserted through the middle cerebral artery. For this purpose the region had to be surgically approached through the temporal bones. The incision was made vertically to the middle of the cheekbone. The latter and the coronal process of the mandible were chipped off and the temporal muscle removed. That made it possible to make a large trepanation in the temporal and parietal bones. After dissection of the

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circle of Willis was performed using a mathematical smaller blood vessels located peripherally from the systemic arterial pressure when necessary during the investigation—R_m and in the peripherally located smaller arteries—R_p was determined. In this case it was assumed that the relative viscosity of blood in the vessels remained constant during the experiment, and thus the resistance might be altered only due to changes of vascular lumina. To determine the above relationship special experiments were carried out with the internal carotid arteries isolated from eight dogs (as has been described above). The following data were obtained: (1) The relationship between P_out and P_in was linear under conditions when the R_m and R_p were constant (fig. 2A); the angles of the slope of the linear responses (i.e., the ratios P_out/P_in) changed depending on the fixed values of R_m and R_p. (2) The changes of the ratio P_out/P_in related to changes of both R_m and R_p, were nonlinear, and saturation zones (where changes of R_m and R_p did not cause any considerable changes of the ratios P_out/P_in) were present (figs. 2B and C); similar data were obtained by other researchers by perfusion of a "small isolated vascular region." The error of the present experiments expressed in terms of standard deviation was ~ 0.002. The accuracy of all the experiments was controlled and substantiated according to the Cochran criterion.25

For elucidation of the relationship of the three parameters P_out/P_in, R_m and R_p, the method of least squares was used that allowed to obtain the following regression equation:

\[ P_{\text{out}}/P_{\text{in}} = 0.742 - 0.04R_m + 0.0149R_p + 0.000093R_mR_p + \]
\[ + 0.00713R_m^2 - 0.0001779R_p^2 - 0.0000041R_m^3 + 0.0000007R_p^3 \]

(1)

A statistical evaluation of equation (1) according to the regressive and correlative analysis showed its high accuracy: the correlation relationship was ~ 0.99.

To find the two unknown quantities R_m and R_p from equation (1), it was necessary to have one more equation. According to the continuity law the volume velocity of blood flow in the major arteries of the brain (in this case, in the internal carotid artery) \( V_m \) must be the same as in the respective smaller blood vessels which carry blood from the artery, i.e., \( V_m = V_v \), or, expressing the volume velocity of blood flow as ratios of pressure gradients to resistances, it is possible to write:

\[ P_{\text{in}} = P_{\text{out}} \]
\[ R_m = \frac{P_{\text{out}} - P_v}{R_p} \]

(2)

Both equations show the relationship of \( P_{\text{in}}, P_{\text{out}}, P_v, R_m \) and \( R_p \). However, equation (1) obtained from quantitative experimental results implies the peculiarities of the hemodynamics in the major arteries of the brain of dogs and yields information which is not included in equation (2), based on Poiseuille's law and the principle of continuity of blood flow. Thus, it is

\[ \text{FIGURE 1} \]

A schematic presentation of measurements of the inlet and outlet pressures in the dog internal carotid artery hemodynamically isolated in situ. P_in and P_out are pressure transducers measuring the pump dependent perfusion pressure (inlet pressure) and the pressure of the circle of Willis (outlet pressure), respectively.
possible to solve both equations (1) and (2) and compute the values of $R_m$ and $R_p$ from $P_{in}$, $P_{out}$, and $P_v$ without having measured directly the blood flow in the respective vasculature.

Thus, being assured of the statistical significance of the obtained data, as well as of the equality of the direct and inverse correlative relationships, the system of equations (1) and (2) was written as a program in the algorithmic language "Algol-60" for a digital computer. The comparison of data obtained by computation and by direct experimental measurements showed that (a) the method may be considered as adequate for such experimental conditions when there are no considerable changes in the volume of blood flow (and, thus, in resistance changes caused by them), (b) the values of the segmental resistances obtained by calculations cannot be considered as absolute values, since, first, they are based on the averaged responses (regression curve) and, second, they do not take into account the effect of such factors as flow velocity, the composition of blood, etc., and (c) the coefficient of correlation between resistance changes, obtained from direct experimental measurements and calculations on a computer, is 0.96, thus proving a high degree of accuracy of the method for solving problems of the respective class.

If the above-mentioned method was used for a single internal carotid artery in the present study, previously, it had been applied to all the major arteries of the brain (both carotids and vertebrais) while the systemic arterial pressure, pressure in the circle of Willis, and pressure in the venous sinuses of the brain were simultaneously recorded. Although the method makes it possible to obtain the values of the resistance changes in smaller blood vessels located peripheral to the circle of Willis, this is to be interpreted as resistance changes in the smaller arteries, since the responses of the walls of both capillaries and veins most probably do not participate actively in the regulation of the cerebrovascular resistance under normal conditions.

**Results**

Twenty-five experiments were carried out with the dog's internal carotid arteries hemodynamically isolated from the extracranial arterial system and whose nerve supply, including the carotid sinus region, was carefully preserved. The arteries were continuously perfused with the arterial blood from the common carotid arteries of the same animals. The following pressures were simultaneously recorded: the inlet pressure of the isolated carotid artery ($P_{in}$), the outlet pressure of the artery ($P_{out}$), the pressure in the venous sinuses of the contralateral side ($P_v$), and the systemic arterial pressure of the aorta ($P_a$).

By changing the output of the pump the inlet pressure of the internal carotid artery was altered stepwise in a total range of $110 \pm 12$ mm Hg, so that its values were always higher than the systemic arterial pressure; when necessary the latter was artificially changed by means of a pressurized reservoir system. Figure 3A shows that the stepwise changes in the inlet pressure of the artery in ranges of 90 to 180 mm Hg resulted in a considerably smaller change of the outlet pressure of the artery, i.e., in the circle of Willis, while the venous pressure in the brain sinuses remained unaltered. The computed resistance in the internal carotid artery ($R_m$) changed proportionally to the level of the inlet pressure of the artery (fig. 3B). However, when the inlet pressure sur-
passed a certain level, usually 190 mm Hg, this resulted in respective change of the outlet pressure of the artery, i.e., within the circle of Willis. The resistance changes in the smaller blood vessels located peripherally from the circle of Willis ($R_p$) were negligible when the pressure changes in the latter were small, and became considerably greater when they were pronounced.

The elimination of change of the inlet pressure of the internal carotid artery (i.e., of an analog of the systemic arterial pressure) along the artery, resulting from resistance changes in the artery, was not identical in different experimental animals. This was probably due to impairment of the mechanism responsible for the constancy of blood supply to the brain by surgical trauma.

To find whether the feedback loop for the vascular responses of the major arteries of the brain is muscular (i.e., similar to the Bayliss effect) or nervous, it was necessary to exclude one of the possible mechanisms. However, since the major arteries of the brain have an abundant nerve supply from different sources, it was impossible to succeed in their complete surgical denervation. To study whether the "autoregulatory" responses of the internal carotid artery would be preserved after the vascular wall was deprived of nervous control, though having a normal muscular layer, the same animals (as in the above experiments) were sacrificed at a given time (by bleeding from the femoral artery), but the perfusion of the artery under investigation was continued with blood from a donor dog whose systemic arterial pressure was made constant by means of a pressurized reservoir system. The muscular layer of such arteries responded normally to vasoactive substances, e.g., to 1 to 2 μg serotonin, during several hours. Figure 4 shows that during stepwise variations of the inlet pressure of the artery, its resistance did not change, while the outlet pressure, i.e., that in the circle of Willis, followed the changes of the perfusion pressure. The negligible changes of the resistance were probably due to alterations of the blood flow rate in the artery which had a complicated geometrical form. Furthermore, quite similar results were obtained when the internal carotid arteries were perfused with oxygenated Ringer-Krebs bicarbonate solution either under the same conditions of a living muscular layer (the arterial wall normally reacted to locally administered vasoactive substances), or after the certain death of the arterial wall, being previously fixed with 10% formaldehyde for 24 hours. The values of the parameters investigated after the changed pressure has been stabilized in both kinds of arteries (i.e., newly excised and having the muscular layer preserved alive, and those fixated with formaldehyde) were similar. Some differences were in evidence briefly immediately after the change of $P_{in}$, and this was probably due to the elastic property of the vascular walls.
**Discussion**

The above experimental findings give direct evidence that changes in the inlet pressure of the internal carotid artery result in such alterations of the resistance along the artery that its outlet pressure (i.e., that of the circle of Willis) remains either constant or changes insignificantly. This suggests that under normal circumstances the major arteries of the brain are the vascular mechanisms which primarily control the constancy of blood supply to the brain, in spite of changes of the systemic arterial pressure, as had been supposed previously as a result of some indirect experimental evidence. The smaller cerebral arteries begin to participate in this control of CBF only when the effect of the major arteries of the brain becomes insufficient.

The main source of error in the above experiments could be a relatively low inlet pressure of the internal carotid artery resulting in the dependence of its outlet pressure on the systemic arterial pressure —through the collateral pathways of the three remaining major arteries of the brain. However, this was excluded in the present experiments, since (1) the perfusion pressure of the internal carotid artery was maintained always higher (sometimes very considerably) than the systemic arterial pressure, and (2) the fluctuations of the outlet pressure showed that they reflected the fluctuations of the perfusion pump and not those of the systemic arterial pressure. The major arteries of the brain seem to be involved in maintaining a constant blood supply to the brain mostly under the conditions of the rise of the systemic arterial pressure and less when it is decreasing, since the resistance in the arteries is not very great under normal conditions (about 3 to 5 mm Hg per milliliter per minute, i.e., some 20% to 25% of the cerebrovascular resistance in dogs) and thus it cannot be decreased considerably; but the possibility of increasing the resistance is very great. Consequently, if there is a large increase of the systemic arterial pressure, the arteries are able to restrict the blood supply to the brain as much as necessary.

The described functional behavior of the major arteries of the brain, i.e., their constriction with ensuing increase in resistance under conditions of rise of the inlet pressure and vice versa, might be due either to functioning of a nervous mechanism (reflex constriction or dilatation of the arteries) resulting from stimulation of some baroreceptors of arterial walls, or only to direct responses of the smooth muscle cells of the vascular walls brought about by their extension to different degrees, as it has been supposed by some researchers. As to the major arteries of the brain, the metabolic mechanism of their responses (i.e., the direct effect of any metabolic substances on the vascular walls) could certainly be excluded because of their anatomy.

The fact that blood flow to the brain remains constant after dissection of the sympathetic fibers and vagus nerves (in spite of changes in systemic arterial pressure) is an argument against the nervous system control mechanism. This is not conclusive, since the reflex might be performed (either always or only under conditions of dissection of the nerves) through nerve fibers which pass in other nerves, as the internal carotid arteries have an abundant nerve supply from different sources. It has been concluded that the mechanism is a myogenic one.

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*Figure 4*

The same as in figure 3, but when the arterial wall is deprived of any nervous control and has a preserved muscular layer.
because the vascular responses seem to be resulting from changes in the inlet pressure of the brain vasculature, since those were present only when pressure changes took place in the arterial but not the venous system, and the vascular responses appeared relatively rapidly (within 15 seconds) and disappeared after the administration of vasoactive substances affecting the muscular layer (e.g., papaverine). However, this does not exclude a nervous mechanism for the vascular response.

Our experimental results show that a living internal carotid artery with preserved function of its smooth muscle layer, but completely deprived of the nervous control (as it was also in cases of the certain death of the arterial wall), did not perform “autoregulatory” changes of vascular resistance. This is strong evidence for the nervous mechanism. The loss of constant CBF (i.e., of “autoregulation”) caused by hypoxia, hypercapnia and brain trauma is another argument for a nervous system mechanism for vascular responses, since it is well known that smooth muscle cells are considerably less sensitive to those abnormal conditions than are nervous elements.

The nervous system receptors which trigger the reflex controlling the “autoregulatory” responses of the major arteries of the brain remain unknown. Thorough surgical denervation of the sinus in the present study did not abolish the responses of the respective internal carotid artery. It appears that in addition to the pressoreceptors of the carotid sinus, this function also might be performed by the receptors disseminated along the artery and in the region of the circle of Willis. We were not able to eliminate the above regulatory responses of the internal carotid arteries by blockers of nervous transmission (both adrenergic or cholinergic). This result is difficult to explain as yet; it may be due to the fact that the mechanism is very perfectly adjusted and has probably some reserve arrangements maintaining the reliability of its function.

An evidence against the myogenic mechanism of the regulation of constancy of CBF is the following: for the appearance of the myogenic Bayliss effect a fast stretching of the smooth muscle cells is required, while the regulatory responses of the cerebral arteries appear usually more or less irrespective of the rate of the intravascular pressure changes. Furthermore, if the mechanism of the regulation

FIGURE 5

Schematic presentation of the control loop of regulation of a constant blood supply to the brain in the face of changes of the systemic arterial pressure. $P_{\text{perf}}$ is the perfusion pressure, i.e., the systemic arterial pressure; $MAB$ are the major arteries of the brain, i.e., the internal carotid and vertebral arteries; $P_{\text{carotid}}$ is the pressure in the circle of Willis; CBF is the cerebral blood flow; and PA are the pial arteries.
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would be a purely myogenic one, it would be deprived of a feedback from the processes which were to be regulated, i.e., from the pressure within the cerebral blood vessels as well as from the actual blood supply to the brain tissue, etc.

Thus the major arteries of the brain seem to be the main vascular mechanism maintaining the CBF constant in spite of changes of the level of the systemic arterial pressure, as it is with damping of the arterial pulse and other fluctuations.16 41 Similar changes occur in the smaller brain arteries only when there is a change of blood supply to the cerebral cortex and a decrease in PaO2.15 Such resistance changes in the smaller arteries of the brain may take place when the changes of the systemic arterial pressure are too large, or when the function of the major arteries of the brain is impaired, resulting in abnormal blood supply to the brain.

The resistance in the smaller blood vessels located to the periphery of the circle of Willis is similar to that of the pial arteries; this was observed as early as in the 1930s.11-13 Responses of the smaller pial arteries (up to 100 μ) appeared earlier and were always considerably greater in amount,14 15 as in the case of functional and reactive hyperemia in the cerebral cortex.42 The precortical arteries (i.e., vascular segments between the pial and radial arteries) were proved to constrict during arterial hypotension, but there were no significant responses during hypotension.16 40 The cortical arteries and arterioles did not respond actively to drop of the systemic arterial pressure either.15 Thus the smaller pial arteries (in some cases the precortical arteries as well) constitute a secondary mechanism in maintaining the constant CBF. This mechanism starts to function when the primary mechanism of the major arteries of the brain becomes insufficient to provide a constant blood supply to the brain tissue.

The mechanism for maintaining a constant blood supply to the brain is shown in the block diagram (fig. 5). This regulation of CBF is usually called "autoregulation." Analysis of mechanisms responsible for maintaining a constant blood supply to the brain suggests that the term "autoregulation" is not adequate for the processes which are described here, since it should include only those processes which operate locally in the vascular bed and should exclude extrinsic mechanisms such as reflexes.4

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