Physiological Mechanisms Controlling Cerebral Blood Flow

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SUMMARY. The major conceptions of cerebral blood flow (CBF) control developed in the 19th and 20th centuries are listed. The systems of CBF regulation are considered from the viewpoint of automatic control. In the classification of CBF regulation mechanisms, 4 types are identified. The effectors of CBF regulation, i.e. the specific arterial segments through which each type of regulation is accomplished, were found to be mainly the major arteries of the brain and the small pial arteries rather than the intracerebral arterioles. Review of controlling influences on these effectors of regulation, (myogenic, humoral and neurogenic), show that priority should be given to neurogenic mechanisms. Several criteria governing efficiency of CBF regulation are proposed. Review of interactions of different types of CBF regulation shows that there may be both synergistic and antagonistic relationships. Information about the processes is important for medical practice.

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SEVERAL CONCEPTIONS of the physiological mechanisms controlling cerebral blood flow (CBF) regulation were developed during the 19th and 20th centuries. The earliest was the Monro-Kelly doctrine, which postulated that there are 3 incompressible constituents inside the skull: cerebral tissue, cerebrospinal fluid, and blood. Therefore, the amount of blood and, hence, the CBF, should remain constant under any physiological and pathological conditions. The doctrine actually meant an absence of active control of CBF.

By the end of the 19th century evidence had accumulated to show that CBF may, nevertheless, change. According to this new concept, although the diameter of cerebral blood vessels remained unchanged, CBF could be altered and was thus controlled by changes of the systemic arterial and/or venous pressures.

The next concept concerning regulation of CBF was developed in the 1930s when studies by Forbes and associates showed that the pial arteries may actively contract and dilate. During the 1940s and 1950s further evidence accumulated for an active role of the cerebral blood vessels in regulation of CBF. Investigators, being unaware of which blood vessels were responsible for CBF regulation, speculated that arterioles were responsible as arterioles were the smallest precapillary arteries with one layer of smooth muscle cells. The control of dilatation or constriction of cerebral blood vessels was believed to be the direct effect of metabolic agents, e.g. CO₂ and O₂.

In the 1960s specific responses of particular portions of cerebral arteries (i.e. of the major, pial and intracerebral arterioles) were found to be under different control. In this period experimental evidence accumulated on the important role of neurogenic control of CBF.

The conceptions of the physiological mechanisms regulating CBF mentioned above are schematically summarized in the figure.

Regulation of CBF: Automatic Control

The physiological mechanisms for regulation of CBF are triggered by disturbances such as a primary decrease in cerebral blood flow or by increase in cerebral blood volume. In response to such disturbances, a regulatory mechanism becomes active and adjusts CBF to the new conditions within possible limits. The mechanisms consist of 3 links: 1) afferent information indicating the type of disturbances in
19th CENTURY:

CBP = constant

PRIOR TO 1930s:

CBP → Systemic arterial pressure

1940s - 1950s:

CBP

Systemic arterial pressure

Cerebrovascular resistance (arterioles), humoral control only

1960s - 1970s:

CBF

Systemic arterial pressure

Major arteries, neurogenic control

Small pial arteries, neurogenic control

FIGURE. Schematic presentation of essential conceptions of CBF regulation of the 19th and 20th centuries.

regulation; 2) the controlling mechanism originating in specific nervous centers and, 3) the effector mechanisms of regulation. These links together provide for a feed-back mechanism.

The afferent information may be of various kinds, including the degree of stretch of vascular smooth muscles resulting from changes of the intravascular pressure, which may be caused by diffusion of vasooactive metabolites accumulated in the tissue, or it may be from specific nervous receptors located in the vessel wall, or in the surrounding tissue such as baro- and chemoreceptors.

In response to the afferent information, the controlling effects occur. They may be either direct reactions of the arterial smooth muscles to stretch (myogenic mechanism), the direct effect of metabolites or other active substances upon the vessel walls (humoral mechanism), or efferent vasomotor effects upon the particular blood vessels (neurogenic mechanism). In the last, the controlling signals are generated in specific neuron association centers whose function is also concerned with the coordination of changes in regulation with other processes, i.e. the hemodynamics of the systemic circulation.

The effectors of regulation include the blood vessels in the circulatory bed which respond to the controlling signals and the hemodynamic events occurring in the vascular bed as a result of regulation. These parts of the regulatory mechanism make up control loops which start from the subject of regulation, the arterial tree, and terminate on it.

The efficiency of CBF regulation has gradually developed during the processes of phylogeny and ontogeny. The known basis for efficiency of CBF regulation will be considered below.

Types of Cerebral Blood Flow Regulation

Review of investigations of CBF regulation shows that there are several types. The characterization of types is based on differing circulatory and metabolic disturbances which bring about the operation of respective regulatory mechanisms as well as the central regulatory centers. Four types of CBF
regulation are recognized, each having particular tasks:

**Systemic Arterial Pressure**

1. The regulation of CBF during changes of the systemic arterial pressure is the first type. This mechanism of maintenance provides a relatively constant CBF in spite of changes in the perfusion pressure, and is called "autoregulation." This is not exact since all of the presently known types of CBF regulation may be called autoregulatory to some extent. This type of regulation was identified in the 1950s both from animal experiments and studies on humans.\(^2\)\(^3\)\(^4\)\(^5\) Evidence has accumulated showing that CBF is comparatively independent of the systemic arterial pressure level. Since changes of the arterial pressure result in alterations of the perfusion pressure (arteriovenous pressure difference) for the brain, the comparative constancy of CBF indicates that it is regulated by active changes of vessel lumina and, thus, of resistance in the cerebral blood vessels.

2. The regulation of CBF in response to changes of \(O_2\) and \(CO_2\) content of arterial blood has been the subject of many experimental and clinical investigations which showed that a decrease of arterial \(Po_2\), as well as an increase of \(PCO_2\), results in a rise of cerebral blood flow.\(^17\)\(^20\)\(^24\) but hyperoxia and a decrease of arterial \(PCO_2\) results in a decrease of CBF.\(^25\)\(^26\)

**Adequate Blood Supply**

3. The assurance of an adequate blood supply to brain tissue is the most important type of regulation. Adequate in this case means a correspondence between the actual rate of capillary blood flow and the metabolic demands of the surrounding cerebral tissue. Regulation provides an active change of CBF as soon as this balance is disturbed because of a primary increase in metabolic rate or a decrease in blood supply to the tissue. The existence of this type of CBF regulation was assumed as far back as the end of the 19th century,\(^28\)\(^29\)\(^30\) but only during the 1930s it was proved by many investigators using different experimental procedures.\(^13\)\(^15\)\(^31\)\(^32\)

**Restriction of Blood Volume**

4. The regulation of cerebral blood volume implies elimination of superfluous accumulation through an active restriction of blood inflow through the arteries. This regulation of CBF, first demonstrated at the end of the 1950s, starts to operate under conditions of blood outflow restriction and/or following superfluous arterial inflow.\(^33\)\(^34\) Regulation consists of restriction of blood inflow to the brain resulting in normalization of cerebral blood volume.

**Effectors of Cerebral Circulation Regulation**

In the peripheral vascular bed, the effectors of blood flow regulation are the resistance vessels, i.e. the arteries. Though the precapillary arterioles have the greatest resistance under resting conditions, regulation is accomplished by means of those arterial branches which are most strongly affected by controlling influences and change their lumen and, hence, resistance within wide limits.\(^31\) Thus, to elucidate which of the cerebral arteries represent the actual effectors for each type of CBF regulation, the functional behavior of different portions of the cerebral arterial system (the major arteries, pial arterial ramifications and the intracerebral arteries and arterioles) was studied.

**Systemic and Pial Arterial Changes**

With changes in the systemic arterial pressure, active changes in the pial arterial diameter were observed as early as the 1930s.\(^2\)^\(^3\)\(^4\)^\(^5\) Further studies showed that both constriction and dilatation of the small pial arteries appeared with a considerable and variable delay lasting from 25 seconds to 4 minutes.\(^41\) Thus, the diameter changes were proven not to be a direct response of intraluminal pressure changes. The diameter of the cortical arteries was also observed to change insignificantly during hypotension.\(^42\) As the result of these observations, small pial and cortical arterioles are not believed to be concerned primarily with regulation of a constant CBF during changes in the systemic arterial pressure.

Resistance in the major arteries of the brain, both the internal carotid and vertebrals, as judged from the pressure gradient in them, increases with rising systemic arterial pressure which results in an almost constant pressure level at the circle of Willis.\(^43\)\(^44\) It has been recently shown that the larger pial arteries (with a diameter more than 200 \(\mu\)m) respond to an increase in systemic arterial pressure.\(^45\) Thus, it may be concluded that the principal effectors for CBF regulation in response to blood pressure changes are the major arteries of the brain and the large pial arteries. The small pial arteries (diameter less than 200 \(\mu\)m) play a secondary role, since they act only when the response of the larger arteries is insufficient, i.e. when the adequate blood supply of cerebral tissue is disturbed (see below).

**Increased Cerebral Blood Volume**

With increased cerebral blood volume, caused by the simultaneous occlusion of the jugular veins or rapid injection of blood into the venous sinuses of experimental animals, a drop in blood pressure in the circle of Willis occurred while the systemic arterial pressure remained unchanged. This proved that an increased resistance in the major arteries of the brain had occurred.\(^30\)^\(^44\) These vascular responses (along with the collateral blood outflow from the skull) compensate for the circulatory disturbances which reduce blood outflow from the brain. In this situation, there was no venous stagnation in the brain as the blood pressure dropped in the pial arteries. The capillaries of the cortex did not dilate, and the pressure in the venous sinuses increased only for a short period and insignificantly.
An analogous situation was observed when an increased cerebral blood volume was caused by an increased arterial inflow to the brain (e.g. following recovery of CBF after 1–2 minutes stoppage). Under these conditions a post-ischemic (reactive) hyperemia simultaneously appeared with an increase in resistance in the major arteries. 99 

A similar constrictor response of the major arteries of the brain was also observed during asphyxia 47, 48 when hyperemia appears in the whole brain because of dilatation of the pial arteries 47, 48 and following an intra-arterial injection of strychnine causing seizures and functional hyperemia throughout the cerebral hemispheres. 46 Consequently, with a superfluous increased cerebral blood volume this disturbance is eliminated by a constrictor response of the major arteries to the brain (the pial arteries may be either constricted or dilated under these conditions depending upon the adequacy of blood supply to cerebral tissue).

Changes in O2 and CO2

During asphyxia O2 decreases and CO2 increases, causing dilatation of the pial arteries. 47, 48 The major arteries of the brain behave differently. Their reaction was investigated by measuring both the pressure gradient along them and the perfusion pressure in a circulatory-isolated carotid artery in dogs. 49 With asphyxia, these measurements showed evidence of constriction. The intracortical arteries also behave differently from the pial blood vessels, showing a pronounced tendency to constrict. 48 Thus, the effectors of CBF regulation which cause CBF to increase under conditions of hypoxia and hypercapnia seem to be the pial arteries which undergo considerable dilatation. Neither the small cortical, nor the major cerebral arteries take part in this regulation. The constrictor responses in these vessels are a manifestation of regulation of cerebral blood volume.

Regulation of Adequate CBF

There are several experimental models for the study of the role of effectors in the regulation of adequate CBF. These include deficient CBF caused either by a primary decrease in blood supply to the cerebral tissue (occlusion of isolated vessels), or a considerable increase in the metabolic demands of the brain (seizure activity, etc.). Under these conditions the pial arteries regularly dilate, especially the smallest ramifications with a diameter of 30–100 μm (in rabbits), and the specifically active microvessels, i.e. the sphincters of their offshoots, the precortical arteries and the interarterial microanastomoses which control blood supply to the smallest areas of the cerebral cortex. 47, 50, 51 The functional behavior of the smallest cortical arteries and arterioles under these experimental conditions was distinctive in that their external diameter never showed an increase but the internal one, on the contrary, decreased regularly, though the CBF in the same areas (measured by the krypton or hydrogen clearance method) showed a considerable increase. Hence, the luminal contraction of the cortical arterioles with a diameter up to 40 μm did not interfere with the acceleration of CBF in the respective areas of the cerebral cortex. This may be explained, at least partially, by an increase in blood fluidity as noted by the Fährnus-Lindqvist rheological phenomenon. The experimental evidence seems to allow the conclusion that the smallest pial arterial ramifications and specific microvascular effectors located on the brain surface are the principal vascular effectors of regulation of adequate CBF.

Feedback Mechanisms Controlling CBF

Knowledge of the physiological feedback mechanisms regulating CBF was neither complete nor conclusive for many years. A considerable advance in understanding occurred during the last 2 decades and was, at least partly, due to discovery of the effectors of CBF regulation, i.e. of the specific function of the cerebral arteries which are responsible for various kinds of regulation.

In studies of CBF regulation it was shown that feedback was accomplished by: a) the myogenic mechanism which occurs at the level of arteries, b) the humoral mechanism which is believed to have direct effect upon the vascular walls through humoral factors either circulating in the blood (CO2 and O2) or accumulated in the tissue (acid metabolites, K+, etc); c) the neurogenic mechanism which has materialized as a true vasomotor reflex or a simplified variation like an axon reflex. These feedback mechanisms may operate not only isolated from each other but also in various combinations.

Myogenic Mechanism

The myogenic mechanism was believed to operate by the well known Bayliss-effect which is an increase in vascular tone in response to muscle stretch, and vice versa. Theoretically, this mechanism may participate in the regulation of CBF when it is to be maintained constant under conditions of changes in systemic arterial pressure. It is assumed that changes in the stretch of the arterial walls cause changes in the level of depolarization of muscle cell membranes and result, in turn, in their constriction. 53, 54 It was also believed that the myogenic mechanism is responsible for vasodilatation during the development of collateral blood flow and post-ischemic (reactive) hyperemia, since the drop of the intravascular pressure during ischemia is believed to cause a decrease of vascular tone during the period of CBF recovery. 55

The myogenic responses of vascular smooth muscles have been experimentally observed. Stretching the wall of caval vein results in an increase in both spike and contractile activity of smooth muscle cells. However, a problem remains as to whether regulation of CBF can be achieved only by the myogenic effects of cerebral arteries. It seems that vascular responses dependent only on a myogenic effect would never control CBF as well as it actually is controlled during changes in the systemic arterial
pressure. There is an increasing accumulation of experimental evidence that the responses of the major and pial arteries during changes of the systemic arterial pressure are not myogenic. First, the arterial smooth muscles respond only to a stretch having specific characteristics while CBF is maintained virtually constant, independently of the rate and duration of the arterial pressure changes. Second, the smaller pial arteries dilate earlier and more than the larger arteries during arterial hypotension. The drop in intravascular pressure, and, thus, decrease in stretch of vascular muscles, should be more pronounced in the larger vessels. Third, the comparatively long and considerable variations of latency in dilatation and constriction of the pial arteries during changes in arterial pressure is a further argument against a major myogenic mechanism. Thus, it might be conjectured from these observations that the myogenic responses of both the major and pial arteries play a secondary role in CBF regulation during changes of the systemic arterial pressure, but they may favor the initial changes in vascular tone which respond to quick changes in intravascular pressure.

Humoral Mechanism

The humoral mechanism may operate during the following 2 types of regulation of CBF. It may operate when changes are caused by primary alterations in the content of blood gases and when adequate blood supply to cerebral tissue is maintained. Under these conditions the sources of afferent input are changes in the arterial PCO₂ and PO₂, or changes in metabolic content (e.g., acids, K⁺ or other substances) actually occurring in cerebral tissue. This humoral mechanism for CBF regulation implies that the afferent information directly reaches arterial walls without participation of neural structures but by diffusion of gases, metabolites or other substances.

In the 1950s and early 1960s the most important humoral factor was believed to be carbon dioxide. This is the final product of metabolism and is believed to be the most potent vasodilating substance for cerebral blood vessels. The speculation is that CO₂ accumulates in the cerebral tissue (e.g., during deficiency of blood supply), diffuses to the arterial walls, and causes vasodilatation. Another hypothesis suggests that vasodilatation is a result of the pH changes which, in turn, are caused by accumulations of CO₂ or other acid products (e.g. lactate) in the environment of vessel walls. Finally, as CBF increases during hypoxia, it has been speculated that vasodilatation may be caused by a decrease of PO₂ in the environment of arterial walls. Evidence has accumulated indicating the absence of a direct effect of blood gases on cerebral blood vessels. Possible humoral factors which could trigger functional vasodilatation in the cortex have been under extensive study in recent years. It has been shown that an increase in the concentration of K⁺ within physiological limits causes dilatation of pial arteries. Estimation of K⁺ and H⁺ concentration by selective microelectrodes within the cerebral cortex have supported the hypothesis that functional hyperemia may be triggered by K⁺ increase and then maintained by H⁺. Other possible humoral factors causing dilatation of the pial arteries included adenosine. This is an activator of adenylcyclase, producing cyclic AMP in the vascular smooth muscle. These humoral factors affecting the cerebral vessels may be interactive.

There is evidence for a role of several humoral factors in the regulation of adequate blood supply to the brain, but under some experimental conditions there has been no correlation between the mentioned metabolic factors and functional hyperemia, which suggests that they could not be its immediate cause.

It is possible that humoral factors may be the trigger of local vasomotor reflexes and may participate in the neurogenic regulation of CBF. It could be conjectured that when they are not independent controlling mechanisms, changes of the chemical environment in vessel walls may contribute to those other vascular regulators like the neurogenic ones.

If the humoral mechanisms have an independent role in the control of vascular responses during regulation of adequate blood supply to the brain, the responses should be diffuse. If this is the case, it would be difficult to explain the very localized reactions in the microvascular effectors (spincters of the offshoots of the pial arteries, precortical arteries and pial arterial microanastomoses) as these appear to be responsible for distribution of blood among the individual radial arteries supplying the smallest areas of the cerebral cortex.

Neurogenic Mechanisms

Neurogenic mechanisms of CBF regulation were previously rejected by many research workers. Since the 1960s, however, experimental evidence has gradually led to general acceptance of the important role of neurogenic control of CBF. The experimental evidence for neurogenic control of CBF during changes of the systemic arterial pressure is: First, the elimination of such regulation by brain trauma, hypercapnia and hypoxia may be used as evidence for a neurogenic, rather than for a myogenic, mechanism as neural elements are more easily damaged than vascular smooth muscle. Second, complete deprivation of the internal carotid arteries of neural innervation eliminates their active reactions responsible for constant blood inflow to the brain. Third, the role of the carotid sinus pressoreceptors for this type of CBF regulation has been demonstrated experimentally. Fourth, the active responses of the pial arteries to changes in the systemic arterial pressure are eliminated following blocking of cholinergic and adrenergic nerves. Changes in CBF which eliminate superfluous cerebral blood volume are brought about by the constrictor responses of the major arteries to the brain, and have been demonstrated to function reflexly following distension of the cerebral venous system. Experimental evidence has gradually accumulated...
indicating that the cerebral arterial responses to changes of Po2 and PCO2 in the blood are in part neurogenic because cholinergic blocking,64 removal of vascular efferent nerves,65 and lesions of the respective parts of the brainstem65 can eliminate or substantially decrease the dilating effect of the blood gases on cerebral blood vessels.

There is also evidence for a neurogenic vasodilatory mechanism responsible for regulation of adequate blood supply to the brain: a) microsurgical removal of nerve fibers connecting the pial arteries with the cerebral cortex stop vasodilatory responses during increase in cortical activity.46 b) the vascular responses with functional hyperemia in the cerebral cortex occur with a very short latency.19

Abundant efferent innervation in the walls of cerebral blood vessels has been demonstrated by histological, histochemical and electronmicroscopical techniques which show both adrenergic and cholinergic nerves in the walls of the major 87 pial98-95 and intracerebral arteries.30, 84

When CBF is regulated by a neurogenic mechanism the necessary afferent information originates from specific nervous receptors located either in the walls of cerebral vessels or in the brain tissue. The following kinds of receptors are believed to be present: a) mechanoreceptors in the vascular walls indicating the intravascular pressure (baro-or pressoreceptors).79, 96 b) mechanoreceptors of the cerebral veins and meninges56, 97 activated by an increase in cerebral blood volume or brain volume changes; c) chemoreceptors in cerebral blood vessel walls and probably in the cerebral tissue. These have not yet been definitely identified. Little is known about the afferent neural pathways carrying information to respective central neurons in specific centers. There is also little knowledge about the localization of specific centers. It can be only conjectured that some are localized in the hypothalamus and medulla oblongata.58, 54, 96 It is possible that the neurogenic mechanism responsible for reactions of the small pial arteries during regulation of cerebral blood supply to the cortex may be local. Afferent input may be from nerve fibers which directly connect the cortex with the pial arteries.96, 100

Efficiency Criteria of CBF Regulation

The regulatory system of blood flow to and in the brain, gradually developed through evolution. The criteria for efficiency depend on anatomical and physiological peculiarities of the cerebrovascular system.

One of the criteria depends mainly on blood vessel structure and is the minimum energy lost by blood when flowing through cerebral blood vessels. This is especially important under unfavorable conditions for blood supply to the brain, such as pronounced arterial hypotension. Evidence for existence of this criterion appears in the size of angles and the relation of radii in arterial ramifications which should provide minimum resistance.101 Studies of the geometry of pial arterial ramifications show that the radii and angles of arterial ramifications with a diameter more than 100 \( \mu m \) in rabbits provides minimum resistance.102 For smaller pial arteries the criteria for function efficiency seem to be different (see below).

Other criteria for efficiency of CBF regulation are related to the function of cerebral blood vessels, as effectors of regulation. This function is the most rapidly operating of the systems. This means that both structure and function of the system should permit a very rapid change in resistance and, hence, provide a rapid redistribution of blood to various parts of the brain. The rapid operation is provided for by the following presently known peculiarities of the cerebral vascular system. There are considerable windings along the course of major arteries to the brain (both in the internal carotid and vertebral arteries) where turbulence can occur in blood flow.103 This should result in a tangible change in resistance when luminal changes occur even though they may be insignificant.10 In smaller pial arteries (under 100 \( \mu m \) in rabbits) the actual relation of angles and diameters of ramifications causes considerable resistance under normal conditions, but vasodilatation occurring after a deficiency of blood supply to the cerebral cortex results in the changes mentioned, a relationship that provides a minimum resistance for blood transport through the blood vessels.102

The third criterion for efficiency of the regulatory system is the optimal selection of the possible effectors of regulation. An increase or decrease of CBF may be achieved in different ways, i.e. by a change in the perfusion pressure or in the resistance in some parts of the cerebral arterial system: in the major, pial, or intracerebral arteries. Regulation of CBF is achieved usually in the most rational way. For instance, during an increase in the metabolic demand of cerebral tissue, an increase of its blood supply does not result from a rise of the systemic arterial pressure, as this would entail an increase of the perfusion pressure for the whole brain and for all other organs of the body as well. Nor does it occur by a decrease in resistance in the major arteries of the brain as blood flow would become inadequate for the whole brain. Further, blood supply does not result from dilatation of the cortical arterioles as this would entail compression of the surrounding tissue elements. What does occur is dilatation of the respective small pial arteries which allows an increase of blood flow only in those regions where the metabolic demands are increased.

Maintenance of a constant CBF during changes in systemic arterial pressure is achieved by changes in resistance in the major arteries (internal carotid, vertebral and larger pial arteries). Use of the small pial arteries as effectors of regulation would interfere with the simultaneous regulation of adequate blood supply to the microvascular system.

Interaction of Different Types of CBF Regulation

Synergism and Antagonism

Different types of CBF regulation operate not in isolation but in various combinations, and there is
evidence not only for synergism, but for antagonism which may decrease the efficiency of the regulation of cerebral blood supply.

An example of synergism between 2 types of regulation is the maintenance of a constant CBF during changes in systemic arterial pressure and the regulation of an adequate blood supply to cerebral tissue. If the changes in the perfusion become too great the regulation accomplished by the major and large pial arteries may become insufficient to maintain a constant CBF which would inevitably cause a disturbance in adequate blood supply to the brain. In this situation, the small pial arteries start to operate and accomplish the second stage of CBF regulation, tending to keep an adequate blood supply to cerebral tissue.

An antagonistic relationship of CBF regulation may occur following cerebral ischemia, asphyxia or a considerable increase in neural activity throughout the cerebral hemispheres. In this situation 2 types of regulatory mechanisms having opposite tendencies start to operate simultaneously. The rise in the metabolic demand causes dilatation of the small pial arteries which increases the blood supply to the brain and the brain blood volume. The increased cerebral blood volume must be controlled or reduced by another regulatory mechanism, i.e., by constriction of the major arteries of the brain. These oppositely directed vascular reactions, i.e., constriction of the major and dilatation of the small pial arteries, seem to be contradictory inherent functions of these vascular mechanisms. Under these conditions the overall cerebrovascular resistance and, hence, the CBF, would be determined by the algebraic sum of these segmental resistances. The resistance may either increase, resulting in a decreasing CBF, or decrease, causing an increase of CBF. Under natural conditions an optimal relation of these opposite tendencies for change of CBF is determined by the operation of the respective regulatory mechanisms.

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