Brief Reviews

Control of Cerebral Circulation in Health and Disease

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Knowledge of the physiology and pathophysiology of cerebral blood flow (CBF) is essential to the proper treatment of patients with major intracranial disease. Yet much of the existing information is fragmented and incoherent (1-4); certainly many problems remain unsolved.

This review has attempted to organize the existing knowledge about CBF into a reasonably consistent framework of facts and concepts. The available, accurate, relatively simple methods of measuring CBF are discussed first and then the nature and control of CBF in health and disease are considered. Hopefully, this integrated presentation will facilitate the evaluation of new information.

MEASUREMENT OF CEREBRAL BLOOD FLOW

Pial Artery Diameter.—Measuring pial artery diameter is a classical method of assessing variations in CBF, but acid-base changes, trauma, and hypothermia or hypoxia of the exposed cortical surface must be avoided because such conditions tend to abolish the normal vasomotor reactions. By using the split-image television technique, variations of a few percent in internal diameter can be recorded (5). In combination with micropipette application of test fluid in minute amounts on the arterial wall, this technique affords a direct way of studying the pharmacology of the brain arteries in vivo (6) without the complications resulting from systemic drug effects. Drug effects secondary to alterations in brain tissue function can also be avoided, since it is possible to study arteries that do not touch brain tissue so that the test fluid reaches the artery only. This technique also circumvents the blood-brain barrier (the endothelium of the brain vessels) and allows the effects of very high local drug concentrations to be studied. For both reasons, caution must be used when the results are interpreted in terms of effects of the same drugs given systemically.

Microsphere Method.—Injection of labeled microspheres into the left ventricle of the heart allows accurate calculation of CBF by the bolus-fractionation principle (7-9). Experience with the distribution of such particles inside organs, however, throws some doubt on the validity of this method for assessing local CBF in small brain areas. The microsphere method does eliminate two of the most serious sources of error in quantitative measurements of CBF in animals: extracerebral tissue indicator uptake and trauma to the brain tissue.

Autoradiographic Method for Measurement of Local CBF.—This method is based on the measurement of the brain tissue concentration of a freely diffusible indicator by an autoradiographic procedure (10), but analysis of tissue samples can also be employed. The most widely used indicator is \(^{14}\text{C}\)-labeled antipyrine. The blood-brain barrier does not allow totally free diffusion of antipyrine; consequently, CBF is underestimated particularly at high flow rates. A fairly short indicator infusion period of 30 seconds minimizes this error, but other errors due to difficulties in timing can arise (11). It is preferable to use indicators which cross the brain vessel walls more readily, e.g., \(^{14}\text{C}\)-labeled alcohol.

Inert Gas Inhalation Method.—The Kety-Schmidt inert gas method is based on measurement of the mean transit time, \(\bar{t}\), for the tracer molecules traversing the brain. The technique involves 10-15 minutes of inhalation of a suitable inert gas, e.g., \(\text{N}_2\text{O}, \text{Ar}, ^{85}\text{Kr}\) or \(^{133}\text{Xe}\), at a constant concentration and collection of samples of arterial and cerebral venous blood (12-15). The method yields a value for the average CBF (ml/100 g tissue min\(^{-1}\)) without measurement of total brain flow and total brain weight.

In man, the method is practically atraumatic: the internal jugular vein can be either punctured...
directly or catheterized from the cubital or femoral vein. In animals, cerebral venous blood is suitably obtained from a small craniotomy over the superior sagittal sinus. With \(^{133}\)Xe as the inert gas and taking 50-μl blood samples, Eklof et al. (16) have recently used this approach to measure CBF in rats. In contrast to the autoradiographic method, the inert gas inhalation method allows measurement of the very high flow rates which occur during marked hypercapnia. The Kety-Schmidt method is particularly valuable because it allows measurement of the rate of cerebral metabolism of oxygen or other metabolites. This rate is expressed as the product of CBF and the corresponding arteriovenous oxygen difference \((A - V)O_2\).

**Intra-Arterial \(^{133}\)Xe Injection Method.**—This method is based on measurement of the regional mean transit time, \(t\), of the tracer gas with externally placed scintillation detectors (17-19). The radioactive inert gas is dissolved in isotonic saline and injected as a bolus into the internal carotid artery or the vertebral artery. The washout is followed over 10-15 minutes. Despite the technical differences, the method should be considered a modification of the Kety-Schmidt technique: both measure \(t\) and use this value to calculate CBF in ml/100 g min\(^{-1}\). The two methods also yield the same normal values.

In man, the intra-arterial \(^{133}\)Xe method is usually combined with arteriography. The injection, therefore, involves no separate risk; indeed serious complications have been very rare in 4,000 studies performed in 18 clinical centers (20). This procedure is now the standard method for measuring regional CBF in man. The number of detectors employed in the procedure have gradually been increased; in the instrument most recently developed, 256 individual detectors are used. The larger number of detectors yields a better count rate per detector field than that obtained with the conventional single crystal Anger gamma camera (21, 22). The large number of anastomoses between the extra- and the intracerebral circulation in most species other than man makes a selective labeling of brain tissue difficult. This problem arises even in the baboon and necessitates surgical removal of the soft tissues as well as careful collimation (23). In dogs, it has proved advantageous to inject the isotope via the vertebral artery (24). The risk of traumatically induced spasms of the arteries to the brain following surgery is an important source of error in such animal experiments (25).

**Arteriovenous Oxygen Difference Method.**—This method was proposed by Lennox and Gibbs in 1932 (26). They assumed constancy of the cerebral oxygen uptake so that \(O_2\) uptake \(=\) CBF \(\times\) \((A - V)O_2\). By employing the Kety-Schmidt method, this assumption has been verified for a number of experimental situations. Specifically it holds during induced variations in arterial blood pressure and arterial \(P_{CO_2}\) and \(P_{O_2}\) over the wide range tolerated without signs of brain dysfunction. The constancy of cerebral oxygen uptake means that the percent variations in CBF can be assessed by measuring the percent variations in \(1/(A - V)O_2\). The main technical problem involves the accurate determination of the arteriovenous \(O_2\) difference. Usually a spectrophotometric method is employed for assessing \(O_2\) saturation without correction for physically dissolved \(O_2\) or for possible variations in hemoglobin concentration. The method is applicable to animal studies as well as human studies (16, 27), and it has the advantage of simplicity. Many CBF measurements can be made in the same examination; my research group generally makes 12-15 measurements over approximately 2 hours to obtain detailed information about the control of CBF in the individual subject (28).

**Other Methods.**—Several attempts have been made to develop completely atraumatic methods for serial studies of CBF in normal man. One such procedure is the \(^{133}\)Xe inhalation–external counting method (29). The labeling of extracerebral tissues constitutes a serious source of error which invalidates the procedure in many situations, particularly those involving drug studies (30-32). However, Townsend and co-workers (33) applied the method during normal sleep and reported that the contamination did not appear to seriously distort the signals from the brain.

There are many more methods of measuring CBF and some are of considerable value in specific contexts. Determinations of heat clearance from the cortex or the internal jugular venous blood and measurements with electromagnetic flowmeters applied to the venous outflow both have the advantage of a very short time constant. Both procedures also allow continuous recording over prolonged periods (34, 35). \(H_2\) clearance measured by platinum electrodes (36) is also useful at times.

**CEREBRAL BLOOD FLOW IN HEALTH**

**Metabolic Control of CBF.**—In normal man, the average blood flow of the whole brain is almost
CONTROL OF CEREBRAL CIRCULATION

constant at about 50 ml/100 g min⁻¹ provided that arterial Pco₂ does not vary. This average value is practically unaffected by the normal physiological changes in brain function associated with sleep, intellectual work, muscle movements, or sensory perception (37). Results obtained with the intraarterial ¹³³Xe method have recently led to revision of this picture: clear-cut evidence now indicates that blood flow increases in regions with increased function. A conspicuous example of a regional increase in CBF associated with a local increase in the level of functional activity is the marked increase in regional CBF in the contralateral sensory-motor area which results from vigorous hand exercise (38). Mental effort associated with the performance of simple psychometric tests elicits more moderate changes in CBF in wider areas (39).

These functionally induced regional variations in CBF might indicate metabolic control of cerebral blood flow: an increase in metabolism is in some way matched by an increase in flow. It is likely that pH effects are involved in the metabolic control. In patients with a brain infarct, function, metabolism, and flow are typically decreased even in the opposite hemisphere (as well as in noninfarcted parts of the involved hemisphere) (40). This so-called transhemispheric depression is presumably caused by the decrease in the general level of neuronal activity, and the flow reduction can be taken as an expression of metabolic control of CBF. Epileptic seizures and coma, as diagrammatically illustrated in Figure 1, constitute other examples of this type of control.

**Autoregulation of CBF.**—In the normal brain, CBF is maintained constant despite rather wide variations in cerebral perfusion pressure—the pressure difference between brain arteries and brain veins (the intracranial pressure can in most instances be assumed to represent that of the cerebral veins). Autoregulation occurs in many other tissues. This fact argues for a common mechanism. In both the brain and other tissues, good evidence indicates that the autonomic nervous system (periarterial nerves) is not involved (41-43). It is probable that the autoregulation results from myogenic responses of the smooth muscle cells of the arteriolar wall to stretch induced by variations in transmural pressure. The autoregulation is easily abolished in acute brain damage with associated brain tissue lactic acidosis. The chemically (acid pH) induced vasodilatation appears to override the myogenic mechanism.

A test for autoregulation of CBF can be made by using drugs such as trimetaphan and angiotensin II to influence systemic blood pressure. There is evidence that these drugs have no direct effect on the cerebral vessels (44, 45), presumably because they do not readily penetrate the vascular endothelium of the brain vessels. Thus, the drugs only indirectly influence the tone of the cerebral resistance vessels via their effects on systemic blood pressure.

The autoregulation has a lower limit as well as an upper limit (Fig. 1). This point will be considered further when arterial hypertension and CBF are discussed. These limits are not fixed; rather, they vary with arterial Pco₂ (46).

Autoregulation of CBF can also be tested by inducing changes in intracranial pressure. In two studies, such changes produced precisely the same pressure-flow relationship as did primary variations in arterial blood pressure (47, 48). In a third study, a rise in CBF at a severely increased intracranial pressure was demonstrated (49). Most likely, this rise represents a reactive hyperemia, perhaps caused by a transitory excessive rise in pressure; it was not observed in the two former studies (47, 48).

When cerebral perfusion pressure is reduced below about 40 mm Hg—the point at which tissue perfusion fails—a powerful sympathetically mediated increase in systemic blood pressure sets in, presumably caused mainly by ischemia in the brainstem (Cushing response). Sagawa et al. (50) have demonstrated that the gain of this pressure reflex is about ten times that of the peripheral baroreceptor reflex.

**Chemical Control of CBF (CO₂ and O₂).**—Variations in arterial Pco₂ exert a profound influence on CBF (Fig. 1). Hypercapnia causes intense cerebral vasodilatation, and hypocapnia causes a con-

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**FIGURE 1**

*Schematic representation of the control of cerebral blood flow (CBF). ECF = extraceerebral fluid.*

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striction so marked that the limit of brain hypoxia is reached. Around the normal level of arterial PCO₂ CBF changes 4%/mm Hg change in arterial PCO₂. Since the accuracy of the intra-arterial 133 Xe method is on the same order of magnitude, the effects of 1-mm Hg variations in arterial PCO₂ are measurable. Very accurate arterial PCO₂ determinations are consequently indispensable for evaluating CBF data.

The CO₂ reactivity is mediated by pH variations in cerebrospinal fluid (CSF) around the arterioles (6, 51-55). The pH at this site also depends on the local CSF bicarbonate concentration. This dual nature of the chemical control of CBF (Fig. 2), by arterial PCO₂ and by CSF bicarbonate, is of importance for understanding the vasoparalysis seen in brain tissue lactacidosis, as will be discussed later. It is unclear how the pH variations influence the tone of the smooth muscle cells. It is likely that the pH inside these cells is the important factor (5) and that the effect involves changes in the concentration of ionized calcium.

The arterial PCO₂-induced flow changes appear to subserve the homeostasis of pH in the brain. With a rise in arterial PCO₂, flow increases and allows a more efficient washout of metabolically produced CO₂, with the result that the change in tissue PCO₂ (and consequently in tissue pH) is dampened. The converse holds for a decrease in arterial PCO₂. Of even greater importance to the homeostasis of tissue PCO₂ and pH are the changes in pulmonary ventilation that are caused by CO₂-induced pH changes in CSF at the level of the brainstem. Thus, CBF and ventilation, both of which monitor brain extracellular pH, combine to keep this value rather constant: this system can dampen approximately 95% of a step change in arterial PCO₂. Adding the buffering capacity and the metabolically induced HCO₃⁻ changes, it must be concluded that brain tissue pH is safeguarded in a truly remarkable way against acute respiratory acidosis and even more against acute respiratory alkalosis.

Chronic changes in arterial PCO₂ tend to be so well compensated for that CSF pH is almost normal due to HCO₃⁻ changes. In this case, CBF is normal, since the adaptation in CSF pH parallels (and causes) CBF adaptation (7, 53, 56). A clinical implication of the slowness of these adaptive processes (they take about 24–36 hours) is that a chronically elevated PCO₂ should usually not be acutely normalized (57). If it is, the patient will temporarily suffer signs of hypocapnia, including dizziness and somnolence with low CBF. This situation can be avoided by normalizing PCO₂ gradually over 1 or 2 days.

Moderate changes in the O₂ tension in arterial blood do not influence CBF measurably. Thus, in moderate arterial hypoxia or arterial hyperoxia, the unchanged CBF and the unchanged O₂ uptake mean that tissue Po₂ is not a controlled factor. With a more marked arterial hypoxia, flow increases. This increase appears to be a threshold phenomenon, since a measurable flow increase is not seen until the arterial Po₂ gets below about 50 mm Hg (58, 59)—the same Po₂ level below which progressive brain tissue lactacidosis sets in (60). This finding suggests that in hypoxia CBF is regulated by the periarteriolar pH. If this is correct, then chemical control by CO₂ and O₂ are basically the same.

Variations in the O₂-carrying capacity of the blood as seen in anemia and polycythemia cause compensatory flow changes which keep cerebral venous gas tensions quite normal. Therefore, no stimulus for chemical control is detectable. The percent changes in blood viscosity assessed in vivo are approximately equal to those in CBF (61–63). Therefore, changes in diameter of the arterioles might not actually take place. If this is so, then clearly purposeful flow changes are not caused by any of the cerebrovascular control mechanisms but merely by the viscosity changes. This fact should not be taken to mean that viscosity is a limiting factor; even in polycythemia CO₂ inhalation produces a sharp increase of CBF and in anemia hyperventilation decreases CBF.

**FIGURE 2**

Cerebrospinal fluid pH is the main factor controlling cerebral blood flow: it is apparently responsible for the chemical control of cerebral blood flow (CBF) (CO₂ and O₂), the adaptation of CBF, and probably also the metabolic control of CBF.
same nerve strands of the autonomic plexus (64), an arrangement suggesting a functional interaction, the nature of which, however, is as yet quite obscure. It is currently being debated whether the small arteries inside the brain tissue (intraparenchymal) are innervated too. The electron-microscopic data of Dahl (65) show no such nerves, although Cervos-Navarro (66) has found evidence for such innervation. In a recent study, Angelakos et al. (67) have found adventitial noradrenergic nerve terminals on large intraparenchymal arteries but not on small ones.

The trophic center for the sympathetic nerves is the superior cervical ganglion. The parasympathetic fibers can be traced to the facial nerve (VII) as demonstrated many years ago by Cobb and Fine-singer (68) and by Chorobski and Penfield (69).

The pial artery smooth muscle cells respond to norepinephrine and acetylcholine, as evidenced by a narrowing and a widening, respectively, in arterial diameter in response to topical application (70, 71). The responses are very weak compared with those in other arteries. They are blocked by the corresponding specific antagonists, but the blockers themselves do not influence the vessel diameter when they are applied in the low concentrations that counteract the agonists. Thus, under the conditions studied, no evidence of tonic autonomic control over pial arterial tone has been adduced.

Numerous studies have been devoted to elucidating the functional role of the autonomic innervation of the brain arteries. In his recent monograph, Purves (72) emphasizes the evidence pointing to a fairly strong neurogenic control of CBF. His own experimental studies with the intraarterial $^{133}$Xe method in the baboon must, however, be criticized. A ligature on the neck around the arteries normally supplying the extracerebral tissues tends to divert blood from the circle of Willis to these tissues. The influence of this extracerebral contamination is counteracted by removing the soft tissues over the brain and by using proper collimation as done by Harper and Jennett (23) but not by Purves (72). Harper et al. (25) have pointed out another, perhaps an even more critical point, namely the interference with the arterial inflow to the brain. They have showed in the baboon that even gentle mechanical handling of the carotid artery causes a state of contraction (spasm) which reduces the maximal inflow to the brain. In fact, Harper et al. (25) have found that this contraction, which hardly can be avoided when approaching the perivascular nerves, yields the same marked changes in CBF responsiveness as those described by Purves (72), but without interfering with the nerves (25).

A long list of other flow studies demonstrating important extracerebral influences will not be included in this review, because the contradictory nature of the results suggests serious technical problems. Another reason is that consistent results with the autoradiographic and microsphere methods, both avoiding such influences, have recently become available. They show that maximal electrical stimulation of the sympathetic nerves results in a reduction in CBF on the order of 5–10%. This result is apparent only when a comparison of the data is carried out, since the changes fail to reach statistical significance in some of the studies (8, 73, 74). A similarly moderate vasodilator response to parasympathetic stimulation has also been shown (75). That the cerebral circulation in fact responds to autonomic nerve stimulation is supported by pial artery diameter measurements (Purves [72]).

The aforementioned studies show that the blood flow changes in response to maximal electrical stimulation are quite small. They correspond to the effect of changes in arterial Pco$_2$ of 1–2 mm Hg and can be of no significance for tissue blood supply, which normally, as discussed under chemical control, is not by any means critically low (in fact, during hypotension, CBF can be reduced by almost 50% before any signs of cerebral hypoxia develop). The possibility of a decisive role for neurogenic control of CBF in local brain areas finds no support in these aforementioned autoradiographical and microsphere studies.

With the reservation that the number of experimental situations studied is somewhat limited, these results indicate that CBF as such is not under significant neurogenic control. Indeed, it is quite doubtful whether autonomic impulses of the intensity produced by direct stimulation even occur physiologically. Yet, taken as a whole, the findings suggest an autonomic influence of unknown functional importance on brain artery vascular tone. It would be of interest to study the influence of unilateral chronic autonomic denervation on variations in pial artery diameter, CBF, and the histology of the brain arteries and to do it in the control state as well as under various experimental conditions such as chronic arterial hypertension.

Before ending this survey of neurogenic control of CBF it is appropriate to mention the theory of Deshmukh et al. (76). They have proposed that the neurogenic influence on the larger arteries is
counteracted by the autoregulatory responses of the smaller arteries, the two mechanisms tending in combination to maintain CBF rather unchanged. This theory implies that, if the vascular tone of the small (intraparenchymal) arteries could be abolished, the neurogenic effects on the larger arteries could more readily be revealed. Deshmukh et al. (76) have found evidence that sympathetic stimulation reduces CBF more conspicuously in hypercapnia than it does in normocapnia. However, this observation was not confirmed in the microsphere study of Alm and Bill (8). Even lack of enhancement of the sympathetic vasoconstriction by hypercapnia does not contradict this theory, since acidosis could well reduce (or abolish) the noradrenergic influence on the larger arteries. In conclusion, the theory emphasizing neurogenic influences on the pial arteries—influences that are counteracted by small artery responses—is a reasonable, but unproved theory. However, it does not provide any understanding of the importance of these nerves. Despite almost staggering experimental assaults, they remain enigmatic. Perhaps the answer is that the nervous control is related to cerebral vascular volume regulation, which again is important for intracranial pressure regulation, as suggested independently by Edvinsson et al. (77) and by Deshmukh et al. (76).

A brainstem center for neurogenic control of CBF has been suggested on the basis of flow changes in the brain hemispheres following blocking or stimulating at various sites in the brainstem (78, 79). The effects might, however, be secondary to alterations at the level of cortical function and should in that case be considered as an example of metabolic control of CBF. In this context, it should be noted that brainstem mechanisms apparently are not involved in the autoregulation and the chemical control of CBF. Kindt (80) and Kindt et al. (81) have found that both reactions are preserved in the isolated spinal cord. Skinhøj and Paulson (82) have demonstrated that changes in arterial Pco2 in the area of supply of one carotid artery will result in changes in CBF in that region, although changes in arterial Pco2 in the blood perfusing the brainstem (vertebral artery) do not influence blood flow in the hemispheres.

**Cerebral Blood Flow in Disease**

**Brain Tissue Acidosis (Lactacidosis).**—Even a very brief period of inadequate perfusion of brain tissue leads to an intense production of lactic acid. Brain lactacidosis is actually a more common and more dangerous disorder than the well-known systemic acidoses such as uremic acidosis, diabetic ketoacidosis, and systemic lactacidosis.

Brain lactacidosis is marked in patients resuscitated after cardiac arrest. It is present in areas of focal ischemia due to cerebrovascular disease and often develops in severe traumatic brain injury or in cases of brain tumor (83). In the latter two situations, the ischemia is presumably due to severe, often transitory, increases in intracranial pressure. Perhaps even the concept of a local increase in brain tissue pressure can be invoked. Thus, it would be reasonable to believe that the brain tissue around an acute hematoma is locally under an increased pressure which limits circulation.

With this many examples—brain hypoxia, ischemic infarction, trauma, tumor, hematoma (which could be called an "acute tumor")—the list is still not complete. Brain lactacidosis is probably also present in severe cases of meningitis and subarachnoidal bleeding, and it reaches extreme degrees in so-called brain death. It is on this basis that brain tissue lactacidosis claims far more clinical importance than do classical systemic acidoses. Brain tissue acidosis is characterized by a state of cerebral vasomotor paralysis, particularly abolition of CBF autoregulation. This so-called luxury perfusion syndrome (84) is a pathophysiological consequence of chemical control: the local acidosis causes a dilatation of the brain arteries. The blood flow sometimes exceeds the normal flow level but more often the hyperemia is only relative, i.e., in excess of local metabolic demands. A frequent phenomenon is the paradoxical flow responses that occur when strong vasodilator stimuli such as CO2 or papaverine lead to a flow decrease (intracranial steal). Conversely, vasoconstrictor stimuli such as hypocapnia or theophylline can increase flow in some acidic brain tissue (inverse intracranial steal). Variations in intracranial pressure appear to underlie many of these paradoxical reactions.

Brain edema is often associated with lactacidosis. The edema is, in part at least, related to the vasomotor paralysis that tends to increase the capillary hydrostatic pressure. Blood-brain barrier damage is also commonly involved as evidenced by the radioisotope scanning technique used clinically. The edema causes distortion of brain tissue and a rise in intracranial pressure; both these factors tend to induce further tissue hypoxia and hence further tissue lactacidosis. A most dangerous vicious circle is thus operating.

It is therefore important to combat the acidosis by securing adequate oxygenation of the arterial blood and by reducing the arterial Pco2. Con-
trolled, moderate hyperventilation by intubation and respirator assistance is now widely used in the intensive therapy of brain-injured patients, in particular patients with traumatic brain injury. Another therapeutic aim is to avoid cerebral vasodilator drugs. To give a specific example, drugs that depress respiration (morphine, demerol, etc.) are most emphatically contraindicated in a brain-injured patient with spontaneous respiration. This contraindication also holds for volatile anesthetic gases such as halothane, which can induce a most dangerous triad of hypotension, hypercapnia, and cerebral vasodilatation beyond that caused by CO₂. Administration of such drugs is safe only when it is combined with control of ventilation and blood pressure.

Recognition of these facts is not based on CBF measurements alone. Indeed, intracranial pressure measurements have been more important. Yet, it is the combined pressure and flow data that constitute the conceptual basis for the intensive care (including neuroanesthesia) of the acutely brain-injured patient.

CBF in Cerebrovascular Diseases.—In apoplexy (stroke), the patient acutely develops focal neurological symptoms. An arterial disease, thromboembolic or hemorrhagic in nature, is usually suspected. But, surprisingly often—in about 50% of the cases in many investigations—the arteriographic study obtained by intra-arterial injection of X-ray contrast material is negative in that no relevant lesions can be seen.

CBF studies have contributed to what appears to be the solution of this riddle by demonstrating that even angiographically negative stroke cases have widespread changes in flow: regions with low or high CBF occur and vasomotor responses are abolished (85). This finding supports the theory that lysis of a thromboembolic occlusion often takes place.

Two studies of experimental apoplexy produced by clipping the middle cerebral artery are of particular interest, because the size of the infarct diminished markedly when the animals were hyperventilated (86) but increased when diamox was given (87). In the normal brain, hypocapnia due to hyperventilation reduces CBF, and carbonic anhydrase inhibition due to diamox increases CBF. In the vasoparalytic focal area, the flow changes go in the opposite direction (paradoxical reactions). Christensen et al. (88) have recently tried to employ hyperventilation as a treatment in a series of patients with apoplexy. No convincing clinical improvement was seen, however. A likely explanation is that the treatment was not started until several hours after the onset of symptoms.

Many people, lay as well as medical, think that common senile or presenile atrophic brain disease (senile dementia or just senility) is caused by a cerebrovascular disease in the form of a chronic, relentlessly stenosing arteriosclerotic process. Dementia in the old is often simply called cerebral arteriosclerosis, a term expressing this thought. However, this thought is erroneous: there is no relationship between the location of the pathological changes in the brain and the vascular anatomy. Patients with senile dementia have a reduced CBF, but it is only reduced in proportion to the lowering in cerebral O₂ uptake, i.e., the blood supply relative to demand is normal (89). The control of cerebral circulation including its autoregulation is normal in sharp contrast to what would be predicted by the chronic, progressive-stenosis concept (90).

CBF in Arterial Hypertension.—Many years ago it was established that subjects with arterial hypertension but without brain symptoms have a perfectly normal CBF (37). In other words, the cerebrovascular resistance is increased in proportion to the increase in pressure.

Detailed studies have recently been published on the effect of variations in arterial blood pressure on CBF in chronic arterial hypertension (27). Autoregulation is preserved, but it is reset at a higher pressure level. Thus, the lower limit of autoregulation, i.e., the lower limit of maintenance of unchanged flow, which in normotensive individuals lies at a mean arterial blood pressure of about 60–70 mm Hg, can be as high as 110 or even 130 mm Hg in hypertensive individuals. This phenomenon agrees with the clinically well-known fact that symptoms of cerebral ischemia occur at pressure levels (ischemia threshold) which are considerably higher in hypertensive individuals than they are in normotensive individuals.

Perhaps the observations made during angiotensin-induced hypertension are of even greater interest. In normotensive and hypertensive individuals, an upper limit of autoregulation of CBF has been found beyond which CBF suddenly increases (27, 91). This upper limit likewise shifts towards higher pressure values in hypertensive individuals. Angiotensin does not cause a decrease in flow in any single patient. These findings suggest that the cerebral symptoms characteristic of malignant hypertension (hypertensive encephalopathy) are related to this so-called breakthrough of autoregulation, i.e., the symptoms are due to overdis-
tention of vessel walls and outfiltration of edema fluids, not to vascular spasms as often previously assumed (92).

**CBF in Epileptic Seizures.**—The marked flow increase in the brain during seizure activity has long been recognized. In spontaneously breathing animals and man, a temporary asphyxia supervenes. But CBF increases by about 100% even if normoxia and normocapnia are maintained throughout by artificial ventilation combined with curarization (93, 94).

The mechanism of the flow increase has recently been debated. In spontaneously breathing animals, a pronounced brain tissue lactacidosis develops during the seizures (95–97). In animals kept normoxic and normocapnic, it is more difficult to demonstrate the acidosis (93, 98, 99). Now this problem has been solved; animal experiments involving very rapid freezing of the brain tissue show about a sixfold increase in tissue lactate (from 1.1 to 6.7 mEq/liter) after only 5 seconds of seizure activity (100). Supportive evidence is available from the observation of a temporary rise in the respiratory quotient of the brain (from just below 1.0 to about 1.3) during induced seizures (93, 94). The simultaneous rise in cerebral venous PO₂ indicates that tissue hypoxia probably is not involved in producing the lactic acidosis. Perhaps the accelerated utilization and production of adenosine triphosphate (ATP) change the balance between the initial (glycolytic) and the final (oxidative) breakdown of glucose without oxygen lack being involved.

Secondary factors might, however, also play a role. The autoregulation of CBF is not upheld during seizures (93, 101) presumably because of the acidosis. The increase in blood pressure during seizure will therefore contribute to the increase in CBF. Other flow-increasing factors such as a rise in brain extracellular fluid potassium concentration or osmolality could also be involved.

The mechanism of seizure hyperemia is of particular interest because it could well be the same as that involved in adjusting CBF to local increases in neuronal activity associated with normal functional activation. Voluntary muscular effort in man, e.g., opening and closing the fist at a fairly rapid pace (1/sec), produces a double in CBF in the contralateral sensory motor cortex (38). The magnitude of the local flow response is thus comparable to that seen globally during seizures. The functional activation tends to increase tissue PO₂ and tissue Pco₂ as would be expected when fixed acid is produced locally (102–104).

On this basis it appears quite possible, as alluded to under the section on metabolic control of CBF, that brain tissue acidosis is the primary cause of functional hyperemia both of a normal physiopsychological nature and of a pathological nature such as that which occurs in epileptic seizure. This concept was enunciated as early as 1890 in the classical paper by Roy and Sherrington (105).

**CBF in Migraine.**—The severe headache attacks that characterize this disease have long been suspected to be related to alterations in the circulation in the brain, extracerebral tissues or both. CBF measurements in a small group of migraine patients have recently been reported (106–108). Decreased CBF was found early in the attack (pro- dromal phase), and increased flow was found late in the attack (headache phase). This sequence of changes, with the increased flow probably representing a state of reactive hyperemia following the ischemia, finds support in a number of other, less direct, observations.

The mechanism of the ischemia is quite mysterious. It is apparently due to a vasoconstriction (spasm) so intense that the hypercapnic vasodilator stimulus is paralyzed. Thus, an understanding of the pathogenesis of the cerebral circulatory changes in migraine could be an aid in finding a more efficacious therapy and presumably also be important to an understanding of CBF regulation in normal man.

**Comment on Critical Level of CBF.**—The effect on CBF of temporary carotid artery occlusion during endarterectomy for stenosing or ulcerating lesions in the carotid artery has been studied by several groups (109–111) to assess the adequacy of collateral flow to the occluded side. The CBF data obtained by the intra-arterial ¹³³Xe method allowed the lower limit of flow below which manifest hypoxia symptoms arise to be defined rather accurately. In normal brain tissue, the ischemic threshold is about 18–20 ml/100 g min⁻¹ (112). Below this value, the electroencephalogram is altered or abolished. This threshold is presumably altered by a number of factors such as anesthesia, temperature, and Pco₂. A detailed experimental study of this basic topic is surprisingly enough not at hand. This lack probably reflects the difficulty in combining precise CBF measurements in animals with survival studies. Perhaps the percutaneous internal carotid artery catheterization performed in baboons by du Boulay and co-workers (113, 114) could be used for intra-arterial ¹³³Xe studies so as to accomplish this aim. CBF data are available in many disease states other than those commented on in this review. Only...
CONTROL OF CEREBRAL CIRCULATION

NOTE ON PHARMACOLOGY OF CEREBRAL BLOOD FLOW AND CONCLUDING REMARKS

Even a brief discussion of drug effects on CBF would necessitate the presentation of a great number of papers involving many different methodological approaches. And, because most of the studies concern effects in normal animals or normal man, it would be difficult to illustrate adequately that cerebral circulatory responses to drugs are often totally different in brain diseases. This fact was stressed in the section on brain tissue acidosis where the paradoxical CBF changes—steal and countersteal—were presented. This fact is important for the clinical application of CBF data, since it is precisely in such brain diseases that flow changes really matter. With this consideration in mind, a summary of drug effects on CBF in the normal brain will be given.

Drugs with No Effect on CBF.—Many substances such as norepinephrine, angiotensin, or trimetaphan that influence vascular tone markedly in other organs are without direct influence on CBF even if they are infused directly into the internal carotid artery (44, 45). These drugs influence CBF only secondarily, i.e., as a result of their effect on systemic blood pressure. However, epinephrine appears to increase CBF (115). But, this effect is probably a flow response secondary to anxiety and arousal not a direct vasomotor response. Alpha-receptor blocking agents such as phenoxybenzamine, phentolamine or Hydergine are without influence on CBF (32, 116, 117).

Vasodilators.—The list of vasodilators comprises diamox, papaverine, volatile anesthetic gases, and drugs that cause high arterial Pco₂ or hyperosmolality (115, 118). To this list the drugs that appear to increase brain flow secondary to enhancement of neuronal function must also be added: analeptic drugs, ketamine, nicotine, and epinephrine belong to this group.

Vasoconstrictors.—A direct vasoconstrictor action is found with drugs that cause low arterial Pco₂ or hypoosmolality and with xanthine derivatives such as theophylline (a component of many pharmaceutical preparations, e.g., aminophylline, Euphyllin, Cordalin and Complamin [119]). Drugs that depress cerebral function also tend to decrease CBF (if an independent vasodilator effect is absent): the barbiturates belong to this group. Hypothermia also causes vasoconstriction.

Does the cerebral circulation autoregulate? Will papaverine increase CBF? The correct answer to both questions is it depends! It depends on the state of the brain tissue, the value of Pco₂, and the level of perfusion pressure; it might even depend on whether the brain arterioles are normal or sclerotic. This situation implies that brain circulation research should cover both health and disease; it should include measurements not only in normal man and animals but also in certain patient categories and appropriate animal models that mimic relevant clinical situations.

References


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