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Regulation of cerebral blood flow

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REGULATION OF CEREBRAL BLOOD FLOW

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INTRODUCTION

Continuous function of the central nervous system is vitally important to the organism as a whole and such function is very strongly dependent upon a continuous and adequate blood supply. Interruption of cerebral blood flow for a few seconds leads to unconsciousness and for a few minutes may lead to irreversible changes in the brain. Thus, the physiologic and pharmacologic regulation of cerebral blood flow (or CBF as it is frequently referred to) becomes especially important. A discussion of the methods of study is helpful in understanding current concepts of this regulation.
METHODS OF STUDY

Anatomical problems include the great complexity of the anatomy of cerebral circulation and the extensive communications between cerebral and extracerebral circulation. This is especially a problem in the usual laboratory animals.

Measurement of flow to any one of the major cerebral vessels is subject to such limitations as being representative of an indeterminant portion of the brain or being contaminated by extracerebral flow. In all animals the anastamoses with the vertebral plexus of veins and other veins make measurement of CBF on the venous side almost impossible. However, this has been done on the isolated head (1), but this could hardly be considered physiologic.

In man the blood of the superior bulb of the internal jugular vein makes a relatively uncontaminated and representative specimen of cerebral venous blood (2) (3). This has allowed many of these anatomical problems to become minimized in the development of quantitative methods for measuring CBF (4) (5) (6).

The various techniques of study must be evaluated in the light of these anatomical problems and in their inherent sources of error.
A. Direct observation of intracranial or related vessels may utilize gross, microscopic or photographic methods. By inserting a cranial window (7)(8), observations can be made under more physiologic conditions. A comparable technique more applicable to man is funduscopic examination of the retinal vessels which are anatomical extensions of the cerebral vessels and react similar to them in many instances (9)(10)(11). It must be remembered that this provides only qualitative information on the behavior of the cerebral blood vessels and not the CBF which is also dependent upon other factors. Observation of the superficial vessels of the brain or retina is limited to the relatively large vessels whose responses may differ qualitatively and quantitatively from those of the small intracerebral arterioles which are most important in determining CBF.

B. Thermoelectric devices may be used to detect changes in CBF (12)(13)(14). The various types of thermostromuhrs which permit measurement in intact vessels are not very reliable. However, thermocouples inserted into the bloodstream of the otherwise intact vessel are more satisfactory. Both the heated and the cooled types are used. In the former the thermocouple is cooled and in the latter it is warmed by the flow of blood, the
change in temperature resulting in a change in electrical current varying proportionately to the rate of blood flow.

A Gibbs thermoelectric flow recorder (15), i.e. in the form of a needle, has been used for studies in the internal jugular vein in man. This needle and its modifications have been inserted directly into brain tissue and have been found capable of indicating directional changes in blood flow. Its advantages include its simplicity, convenience, and ability to follow continuously the change in blood flow. Disadvantages include: does not provide reliable quantitative data when used in vessels subject to the previously mentioned anatomical limitations, temperature changes in the blood or immediate environment, clot formation around the needle, change in vessel diameter, change in relation of the stream of blood to the position of the needle and inflammatory changes of the tissues.

C. Various flow meter techniques: There are a number of instruments, which when inserted in series with a vascular channel, can measure with reasonable accuracy the rate of blood flow through that vessel (12). This is essentially a glass tube of known cross-sectional area, which when inserted between the severed ends of a
blood vessel, permitted the measurement of the blood flow velocity by quantitating the movement of an air bubble trapped within it. From the velocity, the volume of blood flow could be calculated. By placing the instrument in a single, isolated, common arterial pathway to the brain after surgical occlusion of all other possible arterial channels and anastomoses with the extracerebral circulation, it was possible to exclude many of the anatomical problems mentioned above. In most laboratory animals this involves very extensive surgery and alteration of the normal physiology, but in monkeys this method is more applicable.

D. Artificial perfusion of the brain has been used to study alterations in CBF (16)(17)(18). A major advantage of this method is in being able to control certain factors involved in blood flow, for example blood pressure, the fluctuation of which is a frequently encountered variable. By perfusing at a constant arterial blood pressure this variable can be excluded. However, again the disadvantages of major surgery and anesthesia required to isolate the cerebral circulation are encountered.

E. The difference in oxygen contents or saturations between arterial and cerebral venous blood is directly proportional to the oxygen consumption and inversely
proportional to the CBF. Thus, an important requirement is that the venous blood be representative of the brain as a whole and especially uncontaminated by blood from extracerebral sources. Such blood is easily obtained from man from the superior bulb of the internal jugular vein (19)(2)(3). When cerebral metabolic rate remains constant, a change in the arteriovenous oxygen difference reliably indicates the direction and degree of change in CBF. When this latter condition is fulfilled, this method, because of its simplicity, is especially useful in man.

F. Because the normal adult craniovertebral cavity is essentially a rigid, indistensible container completely filled with incompressible material, any increase in volume of one of its contents must be at the expense of another. On this basis, Ferris has applied the principles of venous occlusion plethysmography to the measurement of intracranial blood flow in man. Unfortunately he assumed that the inflation of a cuff around the neck to a pressure of 60 to 80 mm Hg would occlude the venous outflow from the cranium and thus the rate of displacement of spinal fluid through a needle in the lumbar subarachnoid space would equal the rate of continued arterial blood flow into the
cranium. Such an assumption cannot be made, however, This method completely ignores the numerous pathways other than the internal jugular veins through which venous blood may leave the cranial cavity. Consequently, this method is of very little value in determining CBF.

G. Since its introduction by Kety and Schmidt approximately fifteen years ago (20)(6), the nitrous oxide technique has become the standard method for studying the cerebral blood flow. This method is based on the Fick Principle (21). This principle represents a practical application of the law of conservation of matter to the problem of blood flow measurements. This might be explained as: blood flow to any organ or to the body as a whole may be obtained as the ratio between the uptake of inert gas per unit time and the arterio-venous inert gas difference across the organ in question. Kety and Schmidt applied this method to the cerebral circulation in man. Since then it has been applied to various other organs and animals with similarly satisfactory results.

The procedure may be described briefly as follows: During a suitable period of inhalation of a constant concentration of gas (in this example nitrous oxide), blood samples are taken from a peripheral artery--
assumed to be representative of the cerebral arteries--
and from the main venous drainage from the brain, the
internal jugular vein. After a suitable experimental
period, which allows approximately complete saturation
of all cerebral tissues, (frequently ten minutes), it
is possible to estimate indirectly the gas uptake per
unit weight of brain from the venous concentration.
Since the nitrous oxide content of the brain cannot be
determined directly, the brain nitrous oxide concen­
tration at ten minutes is estimated from the tenth minute
value of the cerebral venous nitrous oxide concentra­
tion to which it is assumed to be equal. This assumption is
based on evidence that by the tenth minute brain and
mixed cerebral venous blood have achieved approximate
equilibrium and the brain;blood partition coefficient
is normally 1.0 (22).

Since the concentration rather than the total con­
tent of nitrous oxide is employed in the calculation,
the derived values of blood flow represent the average
blood flow rate per unit mass of brain taken as a whole
and not that of the total brain. The unit mass of brain
used is usually 100 gram.

Because some of the basic assumptions are only
approximately correct, it becomes very important that
the validity of the method has been clearly demonstrated by Kety and Schmidt (23)(24). These authors found close agreement between this method and the direct blood flow method in experiments covering a large span of perfusion values, i.e., 17 to 76 cc/100gm/min.

Since its accuracy has been accepted as being reasonably reliable, several variations of the original method have appeared. For example, Scheinberg and Stead (25) have simplified the method and reduced the amount of blood sampling necessary, but only at the expense of decreased accuracy. Kennedy and his co-workers (26) have adapted it to children by decreasing the volume of the blood samples. Precision has been increased by increasing the number of blood samples, the use of Kr$^{85}$ (a Beta-emitting isotope of krypton) and by sampling from both internal jugular veins (26)(27). Lewis and associates, using the V-emitting Kr$^{79}$ as the inert gas, made a more fundamental modification. By direct and continuous external measurement of the amount of inert gas in the whole brain and simultaneous blood sampling, they made it possible to calculate the total cerebral blood flow and to follow any fairly rapid changes in this flow (28)(29).

H. A non-diffusible tracer substance which remains in the circulatory system when injected into a cerebral
artery, is diluted by the DBF in passing through the cerebral vascular bed. The degree of dilution, as determined from the quantity or rate of injection of the tracer material and again the difference in arterial and representative cerebral venous blood was interpreted by Gibbs et. al (14) to be a measure of CBF. However, as demonstrated by Shenkin et. al (3), dye when injected into a single cerebral artery is not uniformly mixed and thus the blood drained in one internal jugular vein is then not representative of that of the brain as a whole. This might be overcome by bilateral intracarotid injection or bilateral internal jugular vein sampling, or perhaps both are required. The end result of this complexity is that the method is not often used.

I. Radioactive inert gas technique for the quantitative determination of regional cerebral blood flow:

As previously mentioned, the rate of blood flow to any given area of the brain may vary independent of that to another area of the brain (30)(31)(32). Only one of the above mentioned methods provides data on the blood flow of individual regions of the brain. Thermocouples inserted in the various area of the brain may indicate local changes in blood flow, but they are subject to numerous limitations and yeild only qualitative infor-
A method has been described by Kety and his associates which measures simultaneously and quantitatively the blood flow in as many as twenty-eight structures of the brain (33)(30)(31). The method is based on the principle that the uptake of an inert radioactive gas by a tissue is a function of the preceding history of the arterial concentration of the gas, the partition coefficient of the gas between the tissue and blood, the time, and the blood flow of that tissue. During intravenous infusion of a solution of the radioactive gas, arterial concentration is continuously monitored by a scintillation counter. Then, at a specific recorded time the head is removed, frozen and the concentrations of the gas in the various cerebral structures are determined by a radioautographic technique. Thus with these data, using the measured solubilities of the gas in blood and brain tissue, the blood flow in the various areas can be calculated. This method gives reliable results but obviously is useful only on laboratory animals (30) (31)(32).
There are numerous reviews of the physiology of the cerebral circulation (34)(35)(36)(37)(38)(13)(39). Drugs usually alter the cerebral circulation by influencing the physiological mechanisms normally regulating it. It should be remembered that the brain is the organ which receives highest priority in the body's effort to preserve its most vital organs from circulatory insufficiency. In order to accomplish this, the regulation of the CBF must be unique.

As in all vascular beds, the blood flow is ultimately determined by two major hemodynamic factors: (1) the net pressure gradient across the vascular bed, (2) the total resistance to blood flow in the vascular channels. These two factors, in turn, are determined by the numerous forces that alter, regulate or contribute to them. It is by altering one or both of these major factors that physiologic and/or pharmacologic changes in the CBF are accomplished.

A. Cerebral blood pressure gradient:

Cerebral venous pressure is very low in relation to usual cerebral arterial pressure and is therefore generally of very little importance in determining CBF. However, in instances where it is greatly
altered, it may assume a more significant role. For example, a marked fall in cerebral venous pressure may be an important mechanism in maintenance of CBF under gravitational stress (40). Likewise, a marked elevation of cerebral venous pressure might also be expected to influence CBF. However, this has not been clearly demonstrated (41).

Much more important in determining CBF is the mean arterial blood pressure. Earlier it was assumed that the CBF passively followed the mean arterial pressure (42)(13)(39). Later studies carried out in man showed that intrinsic regulation of the cerebral vascular resistance also occurs. This tends to keep the CBF within certain normal limits despite changes in blood pressure and may alter it independent of blood pressure. Fog (43) had earlier reported that pial vessels of animals under direct observation constricted in response to an increase in arterial blood pressure and dilated in response to a fall in arterial blood pressure. Likewise, in man the CBF does not increase in essential or drug-induced hypertension (44)(45)(46)(47) because of this increase in cerebral vascular resistance in these instances. Also consistent with Fog's
observation is the finding that cerebral vascular resistance also buffered the effects of arterial hypotension (48)(49)(50).

In normotensive subjects it was also found that reducing the mean arterial blood pressure to approximately 30 mm Hg., or one-third the normal level resulted in clinical signs and symptoms of cerebral ischemia (51). This was accomplished by use of hexamethonium and/or tilting the subjects. It was also noted that subjects with malignant hypertension or postural hypotension did not reduce their cerebral vascular resistance as effectively and thus developed signs and symptoms of cerebral ischemia with a smaller decrease in mean arterial blood pressure. In all cases the evidence of cerebral ischemia appeared when the CBF fell to a mean of 31.5 ml per 100 grams per minute. This is approximately sixty percent of the control level. It is also postulated (52) that in secondary shock and other hypotensive states resulting in unconsciousness that the mean arterial blood pressure falls below the limits of compensation by changes in cerebral vascular resistance.
B. Cerebral vascular resistance:

Under physiological conditions CBF is regulated chiefly by changes in the cerebral vascular resistance. For quantitative determinations this is defined as the ratio of cerebral blood pressure gradient to blood flow.(6). Actually it is made up of a number of factors which tend to impede the flow of blood through the cerebral vessels. These factors will be discussed individually below:

1. Blood viscosity:

Blood viscosity varies mainly with red blood cell concentration but also with marked changes in the plasma proteins or other cell concentrations. An increase in RBC concentration leads to an increase in resistance and a decreased concentration to a decreased resistance to flow. The increase in resistance becomes more marked as the upper limits of normal red cell concentration are exceeded (53). Thus in polycythemia vera we see an extremely low cerebral blood flow and a high cerebrovascular resistance (35). Likewise there is an increased CBF seen with anemia (54)(55).

2. Intracranial pressure:

The cerebral vessels are partially exposed to the direct pressure of the cerebrospinal fluid.
As the cerebrospinal pressure increases, one would expect the size of the vessel lumen to decrease and thus the resistance to blood flow to increase. Likewise, as the cerebrospinal fluid pressure decreases, one might expect to see a certain amount of expansion of the blood vessel wall and an increase in blood flow. Observations made to date do not seem to be so clear-cut (56)(57)(58)(59). However, observations made on normal subjects would seem to indicate that a reduction in intracranial pressure, as occurs on assumption of the erect position (25) or under the influence of positive radial acceleration (60), tends to increase the CBF by lowering the cerebrovascular resistance. Because most of the inconsistent observations and reports were not made on normal subjects, this author tends to give them less emphasis.

3. Size and tone of cerebral vessels:

It is largely through the adjustment of the diameter or tone of the cerebral vessels and the consequent alteration of cerebrovascular resistance that the normal regulation and remarkable hemeostasis of the cerebral circulation
is accomplished. It is also through their effect on the cerebrovascular tone that most drugs and diseases cause their alteration in the CBF.

Anatomical narrowing of the vessel lumen and therefore increased resistance are seen in the two most common vascular diseases: arteriosclerosis and hypertension (61)(11)(62)(63)(64).

Alterations in CBF may be brought about by (1) direct changes in the vessels themselves as above or (2) by alterations of some of the following control mechanisms of the cerebrovascular tone:

a. Neurogenic control:

Because of the minute size and great number of vessels and nerve pathways and many other technical difficulties involved, this area of study is very difficult. It would seem to this author that the following conclusions may be valid: (1) Neural vasomotor mechanisms in the cerebral vasculature do exist but their role in the regulation of cerebrovascular tone is not obvious at this time. (2) Evidence seems to suggest that there is no resting neurogenic vasoconstriction.
tone mediated through the cervical sympathetics. (3) It also seems unlikely that there is any resting neural vasodilator tone. (4) The cerebral vasomotor reflexes are not integrated into the general circulatory reflexes such as those from the carotid and aortic pressoreceptors. (5) When neurogenic vasomotor effects are demonstrated, they are of small magnitude. These conclusions were suggested by the following works, (65)(66)(67)(68)(69)(70)(14)(71) (72)(39)(73)(74)(75)(76)(77), and do not seem to be of major importance.

b. Chemical control:

The only major changes in CBF that have been experimentally induced are those caused by chemicals. The endogenous chemicals that are most prominently involved in the normal regulation of cerebrovascular tone will be considered at this time.

The respiratory gasses, i.e. oxygen and carbon dioxide, are the most potent agents of this type. An increase in the blood carbon dioxide causes a marked vasodilatation and increase in the CBF, as if to get rid of the
excess waste product. A decreased blood carbon dioxide level, as in hyperventilation, causes a vasoconstriction and a decrease in CBF (35)(13)(39).

An increase in blood oxygen concentration causes a vasoconstriction and a decrease in CBF. A decrease in blood oxygen concentration causes a vasodilatation and thus an increased CBF tending to compensate for the oxygen lack. (78)(79)(80).

Thus in general we have carbon dioxide acting as a vasodilator and oxygen acting as a vasoconstrictor. When the forces of the two are opposing one another at usual physiologic concentrations, carbon dioxide seems to be the stronger of the two (35)(13)(39). However, if the hypoxemia is great enough, it will overcome the vasoconstrictor effect of low carbon dioxide (81)(78)(82).

Acids and bases have been reported to cause cerebral vasodilatation and vasoconstriction, respectively (17)(13)(39)(8). Despite the markedly lowered blood carbon dioxide which occurs in diabetic coma, there is a reduced
cerebrovascular resistance and increased CBF. This would suggest that the severe acidosis existing in this condition might have more influence on the cerebral vessels than the reduced carbon dioxide. Thus while in usual physiologic ranges we find carbon dioxide a more potent agent than changes in pH or oxygen concentration, when the latter two are far enough from the normal range, especially when they are attempting to dilate vessels, they become more potent.

These observations can be integrated if one notes that the normal chemical products or consequences of increased tissue metabolism, for example, increased carbon dioxide, reduced oxygen, and also, perhaps, lowered pH, tend to produce cerebral vasodilatation; and since changes in the opposite direction which would accompany decreased cerebral metabolic activity cause vasoconstriction, it has been suggested that CBF may be adjusted via such chemical means to local metabolic activity.

This mechanism would tend to maintain chemical hemostasis which is what is required and
observed in most physiologic regulatory systems (83)(81)(84)(13)(14). That such a homeostasis mechanism exists is supported by the good correlations between the levels of CBF and oxygen consumption in man (35) and in the monkey (85), and by the parallel increase in both during metrazol convulsions in the monkey (85). Other findings supporting this theory are close correlations between CBF and cerebral activity seen in the rabbit (86) and cat (87)(88).

In man, low metabolic rates and low CBF have been observed in various pathological states of depressed mental function (35), but normal variations of mental activity, for example, normal sleep (89) or performance of mental arithmetic (90) seem to produce no detectable change in CBF. It should be emphasized that this does not mean that such changes do not take place. One explanation might be that these changes are too subtle to be detected with present methods and equipment. Another explanation might be that such changes take place only locally in the specific area of
of the brain that is involved in the greater activity while the rest of the brain has a decreased rate of metabolism and oxygen consumption, thus giving no net change in oxygen consumption and CBF as measured for the whole brain by most methods.

Then to the first theory of CBF regulation locally by metabolic chemicals, we add secondly that the mean arterial blood pressure tends to be maintained constant at the brain because of nervous vasomotor reflexes of the baroreceptor type. The cerebral vessels seem to be independent of these neural vasomotor mechanisms. It is this independence which allows the blood flow to the brain to be maintained in certain circumstances at the expense of other tissues.
THE EFFECTS OF DRUGS ON THE CEREBRAL CIRCULATION

In spite of the remarkable ability of the CBF to maintain hemostasis, its limits of compensation naturally can be exceeded. In such instances it may be desirable to administer drugs in an effort to restore the abnormal CBF to within normal limits. A brief discussion of the many drugs used for this purpose follows. In this discussion these drugs will be grouped as they usually are in pharmacology rather than by any system regarding only their use for the effect on the CBF.

In deciding how much time to devote to each drug the factors considered were: its importance in the general practice of medicine today, its usefulness in altering CBF, and finally how much research has been done on the effects of this drug on the CBF.

A. The respiratory gases are given further consideration:

1. Carbon dioxide:

   The effects of hyperventilation betray the fact that the carbon dioxide normally present in blood exerts a continuously tonic vasodilator action on the cerebral vessels (91)(92)(4) (93)(94)(78)(95).

   The mechanism or method by which carbon dioxide alters the tone of the cerebral vessels
is not known for certain but two suggestions are offered. One is that it is a local axon reflex which has not been demonstrated thus far. A more likely explanation is that it is the direct action of carbon dioxide upon the smooth muscle of the vessel wall as it diffuses through this wall from the surrounding tissues. One might consider the finding that oxygen diffuses through the walls of relatively large pial veins to be in support of this theory (39)(96).

Some of the quantitative studies of the effects of carbon dioxide are as follows: Kety and Schmidt originally noted that the CBF of young and old subjects alike increased approximately seventy-five percent during the inhalation of five to seven percent carbon dioxide (78)(62)(91). What may be more exact observations report that inhalation of five percent carbon dioxide increases CBF approximately fifty percent (78)(97)(64), whereas inhalation of seven percent carbon dioxide, the concentration with approximately maximal effects on pulmonary ventilation and blood pressure (98), more than doubles the blood flow (78)(99)(95)(97)(64). One cannot say whether seven percent
also produces maximal cerebral circulatory changes because reliable comparable data from man with higher concentrations is not available.

Regarding lower concentrations, it was found that inhalation of two and one-half percent carbon dioxide does not alter the CBF. However, 3.5% CO₂ produced a slight but significant increase in CBF of ten percent (97).

Quantitative studies of hypocapnea in man (91)(92)(4)(94)(78)(99)(95) show a greater degree of cerebral vasoconstriction than has been obtained by any other method, i.e. 60% of the control flow achieved by lowering blood carbon dioxide from 45 to 26 mm mercury by active or passive hyperventilation. This low level of CBF approaches that at which syncope occurs (51) as expected evidence of cerebral ischemia was present. The response of the CBF to alterations of arterial carbon dioxide were prompt, almost immediate, the latency obtained is largely attributable to the inaccuracies of the technique (99)(95).

The threshold of the cerebral circulatory response to increased carbon dioxide concentrations in the inspired air is reduced when combined with
low blood oxygen concentration (100)(97), i.e., the CBF which is already increased by hypoxemia is percentage-wise less increased by an increase in inspired carbon dioxide than it normally is by carbon dioxide alone. Apparently the cerebral vasodilatation already produced by hypoxemia (74)(61)(10)(78)(102)(13)(39)(8) represents a contributary part of that which would result from a raised carbon dioxide tension alone and tends to combat the vasoconstriction effect of a reduced carbon dioxide tension. One might even carry this further and expect to find the exact point of lowered oxygen tension at which the effects of carbon dioxide are negligible. This point, of course, must be exceeded if we are to reach the point where the oxygen concentration becomes far enough from the physiologic range that the vasodilatation power of hypoxemia exceeds the constrictive power of hypocapnea. Quantitative studies in the dog by Noell and Schneider (82) indeed show that this point is at a cerebral venous oxygen tension of approximately nineteen mm. mercury. Observation of similar phenomenon in man is also reported (81).
In the clinical conditions of respiratory arrest (103) or rebreathing (101) in which again combined hypoxemia and hypercapnea are encountered, this action allows at least a temporary protective mechanism for the central nervous system. In these instances the administration of additional carbon dioxide with the intention of improving cerebral circulation would probably be of very little help and indeed raises the immediate danger of increasing the carbon dioxide level to a depressant level. It has been definitely shown that carbon dioxide becomes less effective as its blood tension deviates further from the normal physiologic range (82). However, in conditions of hypoxemia not complicated by carbon dioxide retention, but rather by hypocapnea secondary to hyperventilation, the administration of carbon dioxide provides effective aid against the cerebral effects of oxygen lack (101).

The action of carbon dioxide on the cerebral circulation is altered very little, if at all, by elevated blood oxygen tensions (104). This illustrates what a relatively weak cerebral vasoconstrictor hyperoxemia is (54)(105)(78)(79)(102)
Thus the combination of high oxygen and high carbon dioxide concentrations in inspired air which is so frequently employed clinically is a very helpful combination, i.e., the patient receives almost the same degree of augmentation of the CBF as with pure carbon dioxide---plus the higher oxygen concentration.

As mentioned previously, acidosis causes cerebral vasodilatation (17)(107)(13)(39)(8), and when severe enough, this acidosis may override the effect of a reduced blood carbon dioxide in diabetic coma (108). On the other hand, in metabolic alkalosis the cerebral vascular responses to carbon dioxide are not decreased (109).

There is much speculation concerning the loss of vascular wall elasticity associated with advancing age (61)(91)(110)(63)(64) and/or cerebral vascular disease (61)(91)(110)(62)(64). Schieve and Wilson (64) came to the conclusions that cerebral vascular reactivity to the inhalation of five and seven percent carbon dioxide decreases gradually with age, falls markedly with cerebral vascular disease and that it could be used clinically to distinguish between senile dementia.
arising from primary brain degeneration and that secondary to cerebral vascular disease. However, further investigation has tended to indicate that although the degree of reactivity is somewhat reduced, especially when the disease is organic and associated with old age, this change in reactivity does not appear to be sufficiently pronounced or uniform enough to be used as a reliable test for organic cerebrovascular disease. (91)(78)(63)

Study has also been made on the effect of carbon dioxide on local cerebral circulation (72) (111)(70)(14)(71). Kety and associates (33) (30)(31) show that blood flow to all parts of the brain is increased by carbon dioxide, but the increases were not uniform (112). The changes were absolutely and relatively greater in gray matter than in white.

As for the mechanism of action of carbon dioxide on the CBF, it seems to be almost entirely through its effect on cerebrovascular resistance (61)(91)(78)(62)(97). Of the various previously mentioned factors which determine resistance, only two are greatly altered. First, the cerebrovascular tone is markedly decreased by
carbon dioxide. Active dilatation of the pial vessels has been directly visualized without any associated drop in arterial blood pressure (113)(8), thus the resultant increase in CBF. The second factor which is altered, namely the intracranial pressure, is increase by the vasodilatation and resultant increased blood volume, content and flow to the brain (114)(115)(116)(9)(117). This increase in intracranial pressure would tend to increase rather than lower cerebrovascular resistance, but its effect is a minor one. The mechanism of this dilatation is probably by direct action of carbon dioxide on the smooth muscle of vessel walls (39)(96) as mentioned earlier.

The increase in CBF caused by increased carbon dioxide is associated with an increase in the mean arterial blood pressure of man and laboratory animals (61)(78)(62)(98)(118)(74)(111). This would also contribute to the rise in CBF but this does not seem to be responsible for most of this increase (91)(78)(39). This increase arterial blood pressure is due to a stimulation of the vasomotor center by carbon dioxide and a resultant vasoconstriction in the extracranial circulation.

Useful applications of the effects of carbon dioxide might include:

(a) It is useful to aid recovery from general anesthesia because it stimulates pulmonary ventilation, thus increasing the rate of elimination of volatile anesthetics, and because of the greater CBF there is a faster removal of the anesthetic agent from the central nervous system.

(b) In circulatory collapse or secondary shock carbon dioxide may be useful. By dilating cerebral vessels and constricting the extracranial vascular bed, except for the coronary vessels, (125), the cardiac output is redistributed to favor the brain at the expense of less vital tissues (119)(103)(120)(102)(121)(123)(14)(124). It might also counteract the hypocapnea secondary to the hyperventilation frequently associated with these conditions and thus prevent the expected cerebrovascular constriction.
(c) It is probably because of the above mentioned redistribution of cardiac output that it gives a greater tolerance to positive radial acceleration and thus delays the loss of consciousness (126) (127) (128).

(d) Carbon dioxide has been reported to inhibit petit mal seizures (129), but it should be noted that the etiology of these seizures does not involve the cerebral circulation (130) (93). The mechanism of action in this example is probably related to the effects of carbon dioxide on the electrical activity of the brain which will be discussed below. (81) (121)

(e) The therapeutic use of carbon dioxide in chronic cerebral vascular insufficiency is questionable. Three percent carbon dioxide is useful in counteractin the mental effects of anoxemia (131) and the increased cerebral venous oxygen saturation is secondary to the augmentation of the CBF by carbon dioxide. However, the improvement in the mental and electrical activities cannot entirely be attributed to better oxygenation of the brain. Gibbs reported mental and electroencephalographic abnormalities in subjects
inspiring gas mixtures free of carbon dioxide and low in oxygen concentration when the cerebral venous oxygen concentration was at a level during which these functions had been normal when the subjects were breathing carbon dioxide-enriched low oxygen mixtures (101). It is felt that the anoxemia and its secondary hyperventilation lowered the carbon dioxide concentration of the blood and brain below the optimum concentration of carbon dioxide which is necessary to maintain normal cortical electrical activity and mental function (81)(121).

2. Oxygen:

Quantitative studies demonstrate that the vasoconstrictive effects of higher cerebral arterial oxygen concentration are less potent than the vasodilatation caused by hypoxemia. The breathing of eighty-five to one hundred percent oxygen concentration causes only a mild decrease in CBF of approximately twelve to fifteen percent (54)(78)(79). At one atmosphere breathing, fifty or eighty percent oxygen concentration has a negligible effect on CBF. In contrast, reducing the arterial oxygen concentration by breathing ten percent
oxygen causes an increase in the CBF of almost fifty percent and a marked decrease in cerebrovascular resistance (78). This homeostatic type of response by the cerebral vasculature to hypoxemia allows a greater decrease in the arterial oxygen concentration before the critical concentration is reached in the tissue and venous blood. This is illustrated by the fact that the oxygen concentration of internal jugular venous blood, which reflects the concentration of cerebral tissue, falls more slowly than arterial oxygen concentration upon the inhalation of low oxygen mixtures (121).

The approximate critical range of cerebral venous oxygen concentration below which consciousness is lost is between twenty-four and thirty percent (132). This corresponds to an oxygen tension of approximately fifteen to twenty mm Hg. There is no detectable change in cerebral oxygen consumption as the subject becomes unconscious (78). This holds true for oxygen concentrations as low as eight and ten percent (80). This does not necessarily mean that they do not exist, as these changes may be too subtle for present methods to detect.
The changes in cerebral circulation caused by hypoxemia are not uniform for all areas of the brain (1120(133)). The circulation to the gray matter, which is generally greater than that of white matter, has a greater absolute and relative increase. The alterations are not even uniform for all areas of gray matter.

It has been suggested that the mental changes of hypoxemia may be due to the reflex hyperpnea and hypocapnea, i.e. the same mechanism responsible for the mental symptoms seen without lowered cerebral oxygen utilization during hypocapnea produced by hyperventilation (78). It is interesting that at approximately the same critically low level of cerebral venous oxygen both consciousness and the normal electroencephalographic pattern are lost (132)(121).

The mechanism by which oxygen concentration causes its effect on cerebral vessels is not very well understood at this time.

Generalized convulsions are frequently seen during prolonged inhalation of oxygen at pressures greater than one atmosphere (134)(135). Because changes in CBF and carbon dioxide retention.
secondary to oxygen saturation of venous blood have been excluded as etiological factors, it is suggested that there may be a direct toxic effect of high oxygen tensions on the enzyme systems of the central nervous system (134)(135)(79).

When premature infants are subjected to prolonged periods of high oxygen concentration inhalation, a phenomenon called retrolental fibroplasia takes place (136)(137). The high oxygen tension apparently allows obliteration of part of the vascular bed which is needed when the oxygen concentration of the blood is allowed to return to normal.

The administration of oxygen to patients with chronic pulmonary disease is well known as a source of problems (106)(138)(139)(140)(141). The paradoxical response frequently seen here is the apnea caused as oxygen administration removes the hypoxic stimulation of a respiratory center no longer sensitive to change in the markedly abnormal carbon dioxide concentration.

3. Miscellaneous agents which alter respiratory gas transport or function:
   a. Acetazoleamide (Diamox) if given in large enough doses to inhibit nearly all carbonic anhydrase
activity (i.e., 10-50 mg/Kg.) results in an increase in CBF which persists over an hour after injection (142). Although the arterial carbon dioxide content is decreased by the hyperventilation, there is an increase in the venous and tissue carbon dioxide concentrations because of the carbonic anhydrase inhibition.

b. Carbon monoxide interferes with blood transfer of oxygen and thus produces vascular changes similar to hypoxemia. Breathing concentrations as low as 0.2 to 0.3% cause up to forty to eighty percent dilatation of pial arteries (143).

c. The increased volume of the brain subsequent to cyanide administration suggests cerebral vasodilatation. Its cytotoxic anoxic mechanism causes changes similar to those of hypoxemic anoxia (144).

B. Acids, Alkalis, Electrolytes, Inorganic Ions and Fluids:

Acids and alkalis have been discussed previously and their effect is not especially impressive. However, certain electrolytes, inorganic ions and fluid agents cause their effect because they are acids or alkalis. It has been suggested that the potassium ion may be a cerebral vasodilator (13)(85). Calcium ion is
reported to have no effect (121). Barium ion, as five percent barium chloride, is a potent vasoconstrictor of all vessels. However, lower concentrations have very little effect (145).

In general, it does not appear that these agents cause much effect on CBF. The major exception being the decrease in cerebrospinal fluid seen after administration of hypertonic solutions, urea, or after diuresis. The major mechanism operating is the decrease in cerebrospinal fluid pressure and the secondary decrease in cerebrovascular resistance. There is also some alteration in the cerebral hemodynamics due to the change in blood viscosity.

C. Drugs acting on the central nervous system:

1. Central nervous system depressants:
   a. General anesthetics: When administered to the point of respiratory depression, all anesthetic agents cause cerebral vasodilatation and increased blood flow secondary to hypoxia and carbon dioxide retention.

   The nitrous oxide method can only be used in the presence of volatile agents if the radioactive krypton modification (146)(99)(95)(147) is employed because of the interference in blood nitrous oxide determinations.

   -38-
Diethyl ether has repeatedly been demonstrated to have a specific cerebrovascular dilating effect, (148)(149)(150)(39)(115)(114) (14)(72)(71), and an extracranial vasoconstriction similar to carbon dioxide. Then when the medullary centers become depressed, the extracranial vasoconstriction relaxes. The CBF, however, continues to be augmented.

Most experimental evidence seems to suggest that in general volatile anesthetics tend to dilate cerebral blood vessels. (13)(14)(39) (149)(152)(151)(113)(153)(43) It must be remembered that much of the information available, especially that obtained from animals, was obtained while the subject was under some type of anesthesia.

Many reports of the effects of barbiturates on CBF are available and they can be taken to be somewhat representative of the general anesthetics. The one exception is ether. Any major effect that these agents do have is probable secondary to their effects on blood pressure, cerebral metabolic rate, and the respiratory gas tensions of the blood.
The one effect demonstrated to be due to the barbituate is decreased metabolism rate and thus decreased oxygen requirement (154)(155)(156)(157)(64)(158)(159)(115). Because of the chemical regulatory mechanisms described earlier, there is then a decreased cerebral blood flow. The greatest reduction of blood flow takes place in the primary sensory areas of the cerebral cortex. Thus the net result is that the differences in blood flow among the various cortical areas, so prominent during consciousness, are eliminated (30)(31).

b. Local anesthetics: No effect could be demonstrated by systemic administration of 750 mgm porcaine or novocaine to normal subjects (160). However, there have been reports of rapid clearing of neurological abnormalities secondary to cerebral gas embolism after the intravenous administration of procaine(161).

c. Narcotics: These drugs cause no significant direct effect on CBF. Their effects when they do occur are due to influence on respiratory rate and the secondary carbon dioxide retention. The resultant cerebrovascular dilatation is probably responsible for the increase in cerebrospinal
d. Ethyl alcohol: Venous concentrations of 200 mgm% have no effect on cerebral metabolic rate, vascular resistance or blood flow (162) (163)(164)(165). With higher concentrations, an increase in CBF has been demonstrated, but whether alcohol is directly responsible is yet to be proven (162)(163).

Methyl alcohol, however, causes a decrease in both cerebral blood flow and metabolic rate (163)(166).

e. Hypnotics, sedatives, analgesics and anti-convulsants: With one exception, there has been no significant effect demonstrated by these agents. Unlike adults, it has been reported that cerebral blood flow was significantly reduced in epileptic children. Effective therapy with diphenylhydantoin restored these values to normal. The mechanism is not understood (167) (92)(93).

2. Central nervous system excitants:

a. Convulsant drugs: Only with large enough doses of these drugs to cause convulsions is the CBF and oxygen consumption increased. Following the seizure the CBF, metabolic rate, and functional
activity were markedly reduced. When no convulsion occurred, the same or even larger dosage failed to produce an increase in the CBF (74)(85). Thus the alteration in CBF is due to the same chemical phenomenon that normally accompanies changes in metabolic rate (168)(88). However, the compensation that occurs is inadequate and cerebral oxygen concentration may fall to remarkably low levels during convulsions (35)(168). Thus the therapeutic use of analeptic drugs to stimulate a depressed nervous system can be hazardous.

b. Xanthines: Intravenous administration of therapeutic doses of caffeine sodium benzoate, theophylline and aminophylline has been shown to cause a decrease in CBF of up to twenty-five percent (169)(170). This effect has been employed successfully to treat hypertensive headaches (171). The conclusion was made that this was due to relief of vascular distention.

Moyer and co-workers (172) have come to the conclusion that these drugs arrest Cheyne-Stokes respiration by direct stimulation of the respiratory center. However, alternatives include such suggestions as relative ischemia,
anoxia and/or carbon dioxide accumulation in the respiratory center.

3. Psychotropic drugs: (There are so many new drugs of this type that only a representative few will be mentioned)

   a. Psychotomimetic drugs:

       Mescaline, a drug which produces psychic aberrations and visual hallucinations was shown to increase CBF and metabolic rate (173)(174) (45)(175).

       D-lysergic acid (LSD-25), a partially synthesized derivative of ergot, produces similar effects in extremely minute doses (176) (177)(178). Studies on man failed to reveal detectable changes in CBF or metabolism. However, doses twenty times those used in man caused an increase in CBF in the isolated cat head (179).

   b. Psychotherapeutic drugs:

       In this group of drugs there has been no demonstration of change in metabolic rate or CBF.

       Summarizing the psychotropic drugs as a group, it would seem that their psychological and mental changes are to some extent similar to those of the barbituates or of schizophrenia,
i.e., without any change in cerebral metabolic rate or blood flow that can be detected by present methods.

D. Autonomic Drugs:

1. Sympathomimetic Drugs:
   a. Epinephrine: Less than pressor doses of epinephrine have little or no effect on cerebral circulation and metabolism (46). However, when pressor doses are used, the CBF increases in proportion to the rise in blood pressure because the cerebrovascular resistance remains unchanged (169)(45). The expected vasoconstriction response to the blood pressure increase is probably neutralized by the increased metabolic rate and its associated vasodilatory influence (43)(45).
   
   b. L-Norepinephrine (Levophed): In the normal state the vasoconstriction influence of this drug is neutralized to some extent by the pressoreceptor reflexes (180)(45)(46). Because the cerebral vessels are not under the influence of these reflexes, they are constricted more than the rest of the vascular bed (13)(39). The result is a decrease in CBF while the metabolic rate remains unchanged.
In hypotension due to secondary shock
the mechanism is less understood but it causes
an increase in blood flow and oxygen tension
in the brain (18). Some of this effect is due
to the rise in cardiac output produced by this
drug in certain stages of hemorrhagic shock (182)
(181)(183).
d. Wyamine: Actions resemble Epinephrine (185).
e. Amphetamine: This drug causes an increase in
blood pressure but does not alter CBF or cere­
bral metabolic rate.

2. Parasympathomimetic Drugs:
Although the cerebral circulation is without
any significant parasympathetic nervous control,
the choline esters are capable of dilating cere­
bral vessels as they do other vascular beds, but
their effect apparently is only transiet in nature
and of minimal importance (74)(111)(14)(13)(85).
Because this vasodilatation results from their
direct action and is not a simple response to the
associated hypotension they cause, there is an
actual increase in CBF. Pilocarpine and the cholin­
esterase inhibitors do not seem to cause any
important change either (13)(14)(85). Their greatest influence on the CBF is secondary to their systemic effects, especially those on the mean arterial blood pressure.

3. Autonomic Blocking Agents:

a. Adrenergic blocking agents: The natural ergot alkaloids exert no consistent action on the cerebral vessels. They may dilate in small doses and constrict in large doses, but CBF usually follows the change in systemic blood pressure and cerebral metabolic rate is unchanged (85)(74). The findings of Wolff and his associates suggest that migraine headache results from the distention of the branches of the external carotid artery which are all extracerebral in man. They feel that ergotamine relieves the headache by constricting them and reducing the pulsations within them (186).

The dihydrogenated ergot alkaloids cause a cerebrovascular relaxation but this is probably a non-specific response to the hypotension they produce and is probably mediated by the chemical mechanisms of cerebral hemostasis (187)(188)(189)(190)(191)(28)(49)(50).
It is unlikely that the imidazoline derivatives have any significant effect on the cerebral circulation (192)(193)(194).

Dibenzyline produces its effect only by its influence on the arterial blood pressure (195)(196).

b. Drugs which block post-ganglionic cholinergic nervous function show no reliable evidence that they have a significant influence on CBF.

c. Ganglionic blocking agents exert their effect only by the hypotension they produce (196).

d. Nicotine and related drugs cause an increase in cerebral metabolic rate and CBF up to 30% when large enough doses were used (197). This may be due to stimulation of the carotid and aortic chemoreceptors (198), the release of epinephrine (198), or to direct stimulation of the central nervous system.

E. Miscellaneous Vasodilatory Drugs:

This group has in common the ability to produce arteriolar and/or capillary dilatation of the cerebral and extracerebral circulation by direct action on the vessel walls.

1. Histamine causes cerebral vasodilatation in men and animals but because of its secondary hypotension...
caused by a similar systemic effect, it does not always increase CBF (14)(199)(169). Because its action is of transient nature, it is of little value in therapy of cerebrovascular insufficiency.

2. Nitrites cause a marked but transient cerebral vasodilatation and increased CBF (74)(169)(111). With prolonged administration the hypotension finally overcomes the cerebral vasodilatation and CBF is decreased (111).

3. Papaverine does not cause much change in the CBF because again there is an associated hypotension (200)(201)(202).

4. Nicotinic acid has no significant effect on CBF, vascular resistance or oxygen consumption (203)(204).

F. Miscellaneous Antihypertensive Drugs:

Included in this group are (1) the rauwolfia alkaloids, (2) veratrum alkaloids, and (3) hydralazine. These drugs fail to produce any direct effect on the CBF and their only influence is by decreasing the systemic blood pressure (205)(206)(207)(208)(209).

G. Hormones and Related Drugs:

1. Thyroid Hormone: The cerebral circulatory changes associated with altered thyroid function parallel those occurring in cardiac output (210)(211) and
in blood flow to most other organs and tissues. However, the metabolic rate of the brain is unchanged so this cannot be used to explain these changes. There is no evidence of a direct action on CBF by thyroid hormone but there is also no other explanation (212)(210)(213)(214)(215)(216).

2. Insulin: Insulin administration even in dosage adequate to produce coma and depress the cerebral metabolic rate have no effect on the CBF (217). Insulin deficiency, however, may produce changes but these are dependent on the disturbances in acid-base balance or carbon dioxide tension.

3. The adrenal medullary hormones have been discussed previously.

4. ACTH and the adrenocortical steroids: Prolonged daily administration of these drugs increases mean arterial blood pressure and cerebrovascular resistance proportionately, and no change in CBF or cerebral metabolic rate was detected. When the drugs were discontinued the functions returned to normal (218)(219).

5. Gonadal steroids and related compounds have no clearly understood role in regulation of CBF.

6. The anterior pituitary hormones likewise have no clearly demonstrated effect on CBF.
7. The posterior pituitary hormones have minimal influence on the CBF and this is mostly dependent on their alteration of systemic blood pressure (47).
SUMMARY AND CONCLUSION

Because of importance of cerebral blood flow to the living organism, it also becomes important to understand how this flow is maintained and altered by physiology and pharmacology. A discussion of the methods of studying this cerebral blood flow regulation is presented initially in order that current concepts might be better understood. As these concepts are reviewed, the most remarkable observation is the great resistance of the cerebral blood flow to change. There are two major factors operating in this resistance. First, pressoreceptor reflexes, including those with receptors in the internal carotid artery, a major source of supply to the brain, operate to maintain a more or less constant blood pressure head for the cerebral circulation without involving the cerebral vessels in the adjustments necessary to accomplish this. Secondly, cerebrovascular resistance is altered by chemical products of metabolism in a manner serving to maintain homeostasis. The end result is a remarkable stable blood supply to the brain which is equally resistant to therapeutic efforts to change.
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