

THE EFFECTS OF CARBON DIOXIDE ON THE CEREBRAL CIRCULATION

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CARBON dioxide has long been suspected of a special role in the regulation of the cerebral circulation. In 1890, Roy and Sherrington⁵⁰ in a discussion of the "regulation of the blood supply of the brain" stated, ". . . the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the calibre of the cerebral vessels . . . in this re-action the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity." Almost all subsequent work has tended to confirm the remarkable insight of this hypothesis, and because of its potent tonic action on the cerebral vessels, CO₂ has come to be considered the metabolic product chiefly responsible for this regulation.^{16, 19, 29, 54, 61, 62, 70}

EFFECTS OF CARBON DIOXIDE ON CEREBRAL CIRCULATION IN NORMAL MAN

It is generally agreed that CO₂ exerts more powerful effects on the cerebral circulation than any other means of physiological or pharmacological significance.^{16, 31, 39, 52, 61, 70} The quantitative effects of CO₂ on the cerebral circulation are best described by the studies in man using the nitrous oxide technique⁵² and its modifications.^{10, 11, 54} The results of some of these studies^{15, 11, 23, 36, 47, 48} are summarized in table 1.

Effects of Increased Arterial P_{CO₂}. The original observations by Kety and Schmidt⁵⁰ of an approximately 75 per cent rise in cerebral blood flow and a comparable fall in cerebral vascular resistance during the inhalation of 5 to 7 per cent CO₂ in room air have been amply confirmed in normal human subjects both young⁴⁷ and elderly¹⁴ (table 1). Inspired air concentrations of 5 per cent CO₂ raises cerebral blood flow approximately 50 per

cent^{56, 47}; 7 per cent CO₂, the concentration with approximately maximal effects on pulmonary ventilation and arterial blood pressure,¹ more than doubles cerebral blood flow.^{36, 44, 6} Whether 7 per cent CO₂ also produces maximal cerebral circulatory changes is uncertain, for 1.0 reliable comparative quantitative studies have been carried out in man with higher concentrations. Gibbs and co-workers²¹ found that 10 per cent CO₂ also doubles cerebral blood flow; but the method employed in these studies was the dye dilution technique with unilateral internal jugular venous sampling, a method subject to serious error.²⁰

Recent studies by Patterson and his associates¹⁸ indicate that the cerebrovascular response to increased carbon dioxide is a threshold phenomenon. In normal human subjects the inhalation of 2.5 per cent CO₂ in room air fails to alter cerebral blood flow, but 3.5 per cent CO₂ produces a significant increase of about 10 per cent.¹⁸ At this concentration pressor effects of carbon dioxide are absent, and the increased blood flow results only from a dilatation of the cerebral vessels. The threshold in man for cerebral vascular dilatation lies, therefore, between these two inspired air concentrations and has been estimated¹⁸ to correspond to an approximately 4.5 mm. of mercury change in arterial P_{CO₂}. This threshold is somewhat higher than the one observed by Noell and Schneider⁴⁶ in anesthetized dogs; in this preparation a 2 mm. of mercury change in arterial P_{CO₂} was sufficient to alter the arteriovenous oxygen difference by an amount indicative of an 8 to 10 per cent change in cerebral blood flow.

Effects of Decreased Arterial P_{CO₂}. The carbon dioxide normally present in the blood exerts a tonic vasodilator action on the cerebral blood vessels, and a fall in arterial P_{CO₂} normally results in cerebral vasoconstriction and reduced cerebral blood flow (table 1). In the studies of Kety and Schmidt,⁵⁰ for example, a reduction in arterial P_{CO₂} from 45 to 26 mm. of mercury by means of active

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TABLE I
EFFECTS OF ALTERED ARTERIAL BLOOD CO₂ TENSION ON CEREBRAL CIRCULATION IN MAN

Inspired Air	Clinical State	Cerebral Blood Flow (ml./100 Gm./minute)		Cerebral Vascular Resistance (mm. Hg./ml./100 Gm./minute)		Mean Arterial Blood Pressure (mm. Hg.)		Arterial Blood CO ₂ Tension (mm. Hg.)		Arterial Blood pH		References
		C		E		C		E		C		
		C	E	C	E	C	E	C	E	C	E	
2.5% CO ₂ in room air	Normals and convalescent patients	51	52	1.7	1.8	87	90	48	43	7.41	7.36	48
3.5% CO ₂ in room air	Normals and convalescent patients	52	57*	2.0	1.8*	98	95	39	45*	7.40	7.35*	48
5.7% CO ₂ in room air	Young normals	53	93*	1.6	1.1*	82	92*	43	52*	7.38	7.33*	36
5% CO ₂ in room air	Young normals	53	71*	1.8	1.2*	91	95*	45	50*	7.36	7.30*	47
5% CO ₂ in room air	Normotensive elderly	55	56*	2.0	2.2*	93	115					14
5% CO ₂ in room air	Essential hypertension	52	86*	2.6	1.7*	136	150*	40	48*	7.41	7.35*	47
5% CO ₂ in room air	Hypertensive elderly	39	47*	3.6	3.2	133	133					11
5% CO ₂ in room air	Arteriosclerosis	47	55*	2.1	1.9	91	98	46	53*	7.31	7.30*	47
5% CO ₂ in room air	Hypertensive arteriosclerosis	46	49*	3.7	3.0*	132	139*	58	48*	7.41	7.37*	47
5% CO ₂ in room air	Cerebral vascular disease	45	51*	3.5	2.8*	112	130*					13
5% CO ₂ in 85-90% O ₂	Essential hypertension	57	66	3.0	2.7	169	161	40	45*			23
Hyperventilation in room air	Young normals	52	31*	1.7	2.9*	90	98*	45	26*	7.38	7.51*	36
	Normotensive elderly	51	39*	1.9	2.6*	100	90					14
	Hypertensive elderly	45	32*	3.1	3.8*	128	116					11

* P < 0.05.
C = Control. E = Experimental.

or passive hyperventilation was associated with a decline in cerebral blood flow to about 65 per cent of the control level and an even greater rise in cerebral vascular resistance. The cerebral blood flow at this low level of arterial P_{CO₂} was close to the critical value below which syncope occurs,¹⁵ and, indeed, mental signs and symptoms of cerebral ischemia were present. As discussed below, there is evidence to indicate that there are limits below which increasing hypoxaemia can no longer decrease the cerebral blood flow^{15, 16}; ultimately the cerebral vasodilator action of the low tissue oxygen tension caused by the cerebral ischemia becomes so great as to block the effects of any further decrease in P_{CO₂}.

Time Course of Carbon Dioxide Effects. The studies cited above on the effects of altered arterial P_{CO₂} on cerebral blood flow were all performed during the steady state following several minutes of equilibration with the experimental respiratory conditions. By means of the Kr⁷⁹ method, which permits continuous minute-by-minute measurement of cerebral blood flow in man, Lewis and his co-workers¹⁴ have been able to follow the cerebral circulatory changes occurring in the first few minutes immediately following the onset of either CO₂ inhalation or hyperventilation. Their results are graphically illustrated in figure 1. It is

seen that 7 per cent CO₂ produces slight but detectable changes in cerebral blood flow within the first minute following the onset of its inhalation; cerebral blood flow then rises rapidly and continues to rise even after 4 minutes of inhalation. Similarly, hyperventilation in room air at a rate of 30 liters per minute, or about three times the control level, is only slightly less rapid in producing an effect. A reduction in cerebral blood flow is first detected after about 1.5 minutes of such hyperventilation, but, thereafter, the blood flow declines rapidly, almost linearly with time, and is still falling after 6 minutes of hyperventilation. Since most of the latency in the above responses can be attributed to the approximately one minute resolution time of the method, it can be concluded that the reactivity of the cerebral circulation to altered arterial P_{CO₂} is prompt, almost immediate; the delay in achieving a steady state reflects the time required for the alveolar and arterial P_{CO₂} to reach their equilibrium value.

EFFECTS OF CARBON DIOXIDE ON LOCAL CEREBRAL BLOOD FLOW

Blood flow differs considerably in the various component structures of the brain,²⁸ and local differences in physiological and pharmacological responses are often observed.¹⁷ Methods for the measurement of local human cere-

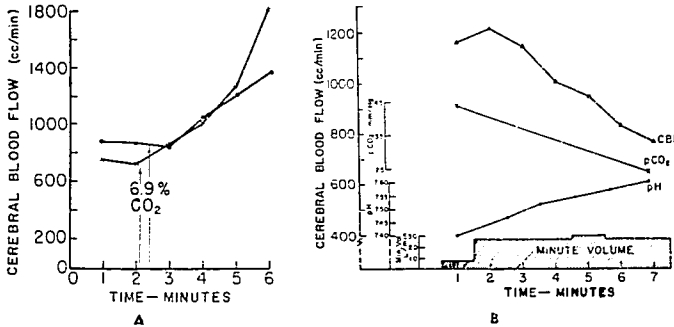


FIG. 1. Time course of changes in cerebral blood flow in response to alterations in arterial P_{CO_2} . A, two studies during the inhalation of 7 per cent CO_2 ; B, during hyperventilation of room air at a rate of approximately 30 liters per minute [from Lewis, *et al.*¹⁴].

bral blood flow are not yet available, but Kety and his associates^{17, 22, 28} have recently developed a technique for the simultaneous quantitative determination of blood flow in, at least, 28 structures of the cat brain. Hansen and his co-workers^{17, 24} have studied the effects of CO_2 inhalation in unanesthetized cats by means of this technique. Although there were quantitative differences in response in the various areas, all structures studied revealed increases in blood flow. The increases were somewhat greater in gray matter than in white matter. For example, the average responses to 5 per cent CO_2 were +67 per cent in gray matter and +54 per cent in white matter; 10 per cent CO_2 caused considerably greater increases in both types of tissues, particularly the gray matter.

EFFECTS OF CARBON DIOXIDE ON CEREBRAL METABOLIC RATE

Carbon dioxide is known to alter central nervous system functions.^{19, 29, 32, 43} The prolonged breathing of 10 per cent or even lower concentrations of CO_2 can depress the central nervous system and may result in unconsciousness. Higher concentrations of CO_2 may cause convulsions. Measurements of cerebral metabolic rate during CO_2 induced unconsciousness or convulsive seizures have not been reported, but it is likely that it would be found to be altered in these conditions. Cerebral oxygen consumption is reduced in all pathological

states of unconsciousness thus far studied,^{21, 29} and increased cerebral oxygen consumption has been observed in convulsions induced by electrical stimulation and a variety of drugs.^{8-10, 29, 41} In the absence of these gross functional disturbances, changes in the P_{CO_2} of the blood and cerebral tissues still have profound effects on the EEG,^{19, 29, 43} but they do not then appear to affect cerebral oxygen consumption. In numerous studies in man on the effects of the inhalation of 2.5 to 7 per cent CO_2 ,^{12, 14, 23, 26, 47, 48} no significant changes in cerebral metabolic rate have been observed. Gibbs and co-workers²¹ have reported that 10 per cent CO_2 reduces human cerebral oxygen consumption, but the method employed by them was the dye dilution technique with unilateral internal jugular venous sampling, and this method has been found to have doubtful reliability.²⁰ Kety and Schmidt,²⁴ employing the nitrous oxide method, found increases in cerebral oxygen consumption during active hyperventilation, but the significance of this finding is uncertain since the same degree of hypocapnia produced by passive hyperventilation had no such effect.²⁴ Also, others have failed to observe any effects on cerebral metabolic rate during comparable degrees of voluntary hyperventilation.^{14, 21}

MECHANISM OF ACTION

Changes in arterial blood pressure frequently accompany the effects of altered arterial P_{CO_2} on the cerebral circulation (table 1), but these

changes are often absent or in the opposite direction and never of sufficient magnitude to explain the effects. Carbon dioxide alters cerebral blood flow almost entirely by its action on the cerebrovascular resistance (table 2). Of the various factors which contribute to this function, only two are appreciably influenced by carbon dioxide. One, the intracranial pressure, is raised by carbon dioxide,^{4, 69} a change which would increase rather than lower cerebrovascular resistance. The other, the diameter of the cerebral vessels, must, therefore, be decreased, and indeed active dilatation of pial vessels by CO₂ and constriction by hyperventilation have been directly visualized.^{60, 71} The rise in intracranial pressure caused by CO₂ inhalation is secondary to the effects of the cerebral vasodilatation, for example, increases in the blood content,⁶⁸ volume,^{65, 69} and blood flow^{51, 52} of the brain.

Neurogenic mechanisms do not appear to be involved in the cerebral vasodilator response to carbon dioxide. Spinal transection, decerebration, section of the sixth, seventh, and eighth cranial nerves, and cervical sympathectomy, operations which interrupt all known vasomotor pathways to the cerebral vessels, do not prevent the rise in cerebral blood flow caused by CO₂ administration.⁷⁰ Local vasodilator reflexes of the axon type would not be interrupted by these procedures, but there is no evidence that carbon dioxide is capable of activating axon reflexes in any vascular bed. Furthermore, CO₂ administration causes simultaneously with the increased cerebral blood flow a depression of the circulation in the extracranial⁵⁸ and peripheral tissues;^{5, 25, 29, 42, 43} a reduction in blood P_{CO₂} by hyperventilation does the opposite.^{5, 29, 42, 43} Following interruption of their vasomotor innervations, however, these other vascular beds respond to CO₂ exactly like the cerebral circulation.^{19, 51, 63} The fact that the cerebral vessels normally respond to CO₂ like other vascular beds do only after denervation is further evidence that the CO₂ effect on the cerebral vessels is not mediated by nervous mechanisms but is a direct action on the smooth muscle of the vessel walls. Indeed, isolated strips of carotid artery have been observed to dilate when CO₂ is dissolved in the Ringer solution in which they are immersed.⁷

The question is frequently raised whether the action of CO₂ on the cerebral circulation might not be explained by its effect on pH, particularly since acids have been reported to dilate^{18, 19, 55, 71} and alkalis to constrict^{18, 43, 55, 71} the cerebral vessels. The effects of pH are, however, weak and inconstant compared to those of carbon dioxide. Furthermore, there have been observations of decreases in cerebral blood flow caused by acids⁵⁵ and increases caused by alkalis.⁵⁵ Such contrary effects might be expected in partially compensated metabolic acidosis or alkalosis in which, if the actions of CO₂ and pH are truly independent, their effects on the cerebral circulation conflict. There is then acidosis with decreased blood P_{CO₂} or alkalosis with increased P_{CO₂}, and depending on the degree of acidosis or alkalosis and the extent of compensation, either pH or P_{CO₂} may dominate. It is only in respiratory acidosis and alkalosis that the effects of the changes in pH and P_{CO₂} on the cerebral circulation augment each other. Schieve and Wilson⁵⁵ have studied carefully the effects of experimental metabolic acidosis and alkalosis on the cerebral circulation in man. Their results clearly dissociate the actions of CO₂ from those of pH, more or less prove that the CO₂ effects are not indirectly mediated through changes in pH, and demonstrate that within blood pH ranges not two distant from normal, P_{CO₂} is a more potent regulator of cerebrovascular tone than pH.

THE ROLE OF CARBON DIOXIDE IN THE NORMAL REGULATION OF THE CEREBRAL CIRCULATION

Since CO₂ is constantly being produced by the metabolism of the brain and removed by its circulation, the changes in cerebral blood flow induced by altered blood P_{CO₂} are in a direction tending to maintain a constancy of the tissue P_{CO₂}. Thus, increased arterial P_{CO₂} results in an increased blood flow which tends to remove the CO₂ produced by metabolism more rapidly from the tissues; reduced arterial P_{CO₂} does the opposite. The efficacy of this homeostatic mechanism is evident in the changes observed in the P_{CO₂} of the cerebral venous blood, which reflects more closely than arterial blood the conditions in the cerebral tissues.^{5, 19, 26, 42} Alterations in arterial P_{CO₂}, produced either by CO₂ inhalation or hyperventilation, are

greatly damped and only partially reflected in the $P_{T_{CO_2}}$ changes in the cerebral venous blood^{19, 26, 42} because of the compensatory effect of the concomitant changes in cerebral blood flow. A mechanism which regulates blood flow so as to maintain homeostasis in the tissues in regard to CO_2 would, by virtue of the relationship between CO_2 production and metabolic rate, serve also to adjust the blood flow to the metabolic demands and functional activity of the tissue. The assumption is made, of course, that CO_2 in the surrounding tissues is just as effective in dilating cerebral vessels as the CO_2 in the blood. It was just such a chemical mechanism mediated by the action of a metabolite which Roy and Sherrington⁵⁰ first proposed for the regulation of cerebral blood flow. Because its action under normal circumstances is so much more potent than that of any other chemical agent,^{29, 61, 70} carbon dioxide has gained recognition as the metabolite most prominently involved.^{16, 19, 29, 38, 61, 62, 70} Indeed, in the absence of any clear demonstration of significant neurogenic control of the cerebral vasculature,^{21, 29, 61, 62, 70} it is this chemical mechanism, the modulation of the continuous action of CO_2 on the cerebral vessels, which is currently believed to be the chief means for the normal regulation of the cerebral circulation.^{16, 19, 29, 38, 61, 62, 70} There may be conditions in which the effects of CO_2 may be superseded by the action of other chemical factors, such as low oxygen tension in anoxia^{19, 29, 36} or pH in metabolic acidosis,²² but under normal circumstances the influence of CO_2 appears to be predominant.

EFFECTS OF CARBON DIOXIDE ON CEREBRAL CIRCULATION IN VARIOUS PHYSIOLOGICAL AND PATHOLOGICAL STATES

Hypoxemia. There have been numerous studies on the effects on the cerebral circulation of simultaneous alterations in both the CO_2 and O_2 tensions of the blood.^{19, 29, 33, 36, 38, 42, 16} Although the threshold of the cerebral circulatory response to increased CO_2 may be reduced when it is combined with a low oxygen content of the inspired air, there is evidence that a cerebral blood flow already increased by hypoxemia is less altered by changes in arterial $P_{T_{CO_2}}$ than normally. Lennox and Gibbs¹² have found that the combined effects

of high CO_2 and low O_2 contents in the inspired air are not entirely additive; they are less than the sum of their individual action and, in fact, no greater than that of the increased CO_2 alone. Similarly, a given reduction in arterial $P_{T_{CO_2}}$ by means of hyperventilation causes a lesser reduction in cerebral blood flow during hypoxemia than under normal conditions.^{19, 42} The cerebral vasodilatation already produced by hypoxemia^{6, 29, 36, 42, 61, 70, 71} appears, therefore, to represent a contributory part of that which would result from the raised $P_{T_{CO_2}}$ alone and tends to combat the vasoconstrictor effect of a reduction in $P_{T_{CO_2}}$. One might expect a point of lowered oxygen tension at which the effects of CO_2 are negligible. Indeed, Noell and Schneider⁴⁵ have found in dogs that the lower limit of cerebral blood flow resulting from hypocapnia occurs when the cerebral venous $P_{T_{CO_2}}$ falls to about 19 mm. of mercury; at this point cerebral blood flow cannot be further reduced by additional lowering of arterial $P_{T_{CO_2}}$ because of the vasodilator effects of the low tissue O_2 tension. Evidence for a similar phenomenon has been obtained in man.¹⁹

The relative importance of blood $P_{T_{CO_2}}$ and $P_{T_{O_2}}$ in regulating the cerebral blood flow appears to vary with the blood tensions of both gases. Carbon dioxide becomes progressively less effective as the blood $P_{T_{CO_2}}$ deviates more and more from the normal level.¹⁶ On the other hand, at elevated, normal, or even slightly reduced levels of blood $P_{T_{O_2}}$, oxygen has relatively negligible effects compared to those of CO_2 . Courtice⁶ has found in chloralosed cats that the breathing of low O_2 mixtures does not increase cerebral blood flow until the concentration in the inspired air is reduced below 15 per cent. With increasing hypoxemia, the effectiveness of reduced oxygen tension increases progressively,⁶ and the relative importance of O_2 and CO_2 undergoes a gradual reversal. For example, the breathing of 10 per cent O_2 results in considerable increases in cerebral blood flow despite the hypocapnia resulting from the associated hyperventilation.²⁶ Ultimately, at a critical level of hypoxemia,¹⁶ the influence of O_2 is paramount and that of CO_2 negligible. In the transitional zone between mild and extreme hypoxemia, cerebral blood flow is adjusted by

the blood and brain tensions of both gases, and its level is determined more or less by their net effect. In general, the evidence supports the view expressed by Gibbs and his co-workers^{19, 21} that cerebral blood flow is normally regulated chiefly by carbon dioxide to maintain homeostasis as regards brain tissue P_{CO_2} ; a similar homeostatic mechanism for oxygen exists, but it is primarily an emergency one that becomes important only when adequate oxygenation of the brain is threatened.

Increased Blood P_{O_2} . The action of CO_2 on the cerebral circulation is altered very little, if at all, by elevated blood P_{O_2} .¹² This is probably because of the relatively weak cerebral vasoconstrictor effect of increased oxygen.^{25, 26, 35, 42, 65} The combination of high O_2 and high CO_2 concentrations in inspired air so frequently employed clinically is, therefore, associated with almost the same degree of augmentation of the cerebral blood flow as obtained with increased CO_2 alone.

Acidosis and Alkalosis. Acids dilate cerebral vessels,^{18, 45, 57, 71} and cerebral vessels already dilated in acidosis might be expected, as in hypoxemia, to be less responsive to change in the P_{CO_2} of the blood. With severe enough acidosis, the vasodilator effect may be sufficient to supersede the vasoconstrictor effects of even pronounced reductions in the arterial P_{CO_2} .²³ Conversely, in metabolic acidosis a compensatory reduction in blood P_{CO_2} may be sufficient to overcome the effects of low pH and cause cerebral vasoconstriction; in such circumstances the administration of 5 per cent CO_2 in the inspired air has been found to be as effective as normally in increasing the cerebral blood flow.²⁵ Normal cerebral circulatory responses to CO_2 have also been observed in metabolic alkalosis induced by bicarbonate infusions.²⁵

Anesthesia. Except for thiopental, there are almost no reliable data available on the effects of general anesthetics on the cerebral circulation.⁶¹ In thiopental anesthesia^{56, 69} there appears to be a slight but significant decrease in the responsiveness of the cerebral circulation to the administration of CO_2 in the inspired air. However, arterial P_{CO_2} is frequently already elevated during deep thiopental anesthesia because of the respiratory depression,^{67, 69} and the reduced reactivity to additional CO_2 may reflect only the decreasing effectiveness of

the gas as its blood tension deviates further from its normal physiological levels.⁶⁶

The frequent use of passive hyperventilation during surgical anesthesia raises a relevant question about the effects of hypocapnia on the cerebral circulation in that condition. Although the data are sparse, there is evidence to suggest that most volatile general anesthetics dilate cerebral vessels.⁶¹ In the case of diethyl ether, the effect is almost certain and probably direct;^{61, 70} as regards most other anesthetics, the evidence is inconclusive, and the cerebral vasodilatation may be only a secondary effect of a respiratory depression produced by the drug.⁶¹ In the anesthetized state achieved by anesthetic agents which themselves dilate the cerebral vessels, it is likely that this vasodilator action would tend to combat the vasoconstrictor effects of low P_{CO_2} and reduce the cerebral circulatory response to hypocapnia. Furthermore, the profound reduction in cerebral metabolic rate during anesthesia^{27, 56, 67, 69} probably allows the brain to withstand lower levels of blood flow without damage than under normal circumstances. There is an additional factor which must be considered, however. Carbon dioxide itself has tonic effects on the cerebral tissues, as manifested, for example, by its actions on the functional activity of the medullary centers and the electrical activity of the cortex;^{19, 26} it is not inconceivable that prolonged reductions in P_{CO_2} may have direct deleterious effects on the cerebral tissues.

Cerebrovascular Disease. Studies on the effects of altered arterial CO_2 tensions on the cerebral circulation of elderly subjects and patients with vascular disease are summarized in table I. The data indicate that the responses of the cerebral circulation in these patients are, at least, qualitatively like those in normal young subjects, but there has been some disagreement concerning the quantitative aspects of these responses.^{10, 14, 23, 39, 41, 47, 53, 56, 61} There have been reports that the effects of CO_2 inhalation on cerebrovascular resistance and cerebral blood flow are less in patients with vascular disease.^{10, 14, 23, 47, 56} It has, in fact, been suggested that the cerebrovascular response to CO_2 be employed clinically to evaluate the relative proportions of functional vasoconstriction and fixed organic narrowing of the cerebral vessels⁴⁷ or to distinguish between senile

dementia arising from primary parenchymatous brain degeneration or from the effects of cerebrovascular disease.⁵⁶ Others, however, have failed to observe in these conditions any noteworthy decrease in the cerebral vascular reactivity to changes in blood P_{CO_2} in either direction.^{14, 29, 41, 57} From a recent review of the literature, Lassen⁵⁸ has concluded that cerebrovascular disease may lead to absolute decreases in the responses of the cerebral circulation to CO_2 , but because of the high cerebral vascular resistance and low cerebral blood flow normally present in these patients, the changes elicited by CO_2 are percentage-wise equal to those in normal subjects.

APPLICATIONS OF THE CEREBRAL CIRCULATORY EFFECTS OF CARBON DIOXIDE

Recovery from Anesthesia. Carbon dioxide is frequently used postoperatively to hasten recovery from general anesthesia. It not only stimulates the respiratory elimination of volatile anesthetics, but also clears the anesthetic agent from the tissues of the central nervous system more rapidly as a result of the accelerated blood flow through them.

Protection Against Deleterious Effects of Hypoxemia on Central Nervous System Functions. Gibbs and his associates²⁹ found the addition of 5 per cent CO_2 to the inspired air to be effective in counteracting the deleterious effects of low oxygen on intellectual functions, electroencephalographic tracings, and cerebral oxygen tension. In their studies, the breathing of 6 per cent O_2 in nitrogen was normally accompanied within a few minutes by mental confusion or unconsciousness, a shift to slow, high voltage waves in the electroencephalogram, and a marked fall in the O_2 saturation of the cerebral venous blood. The addition of 5 per cent CO_2 to the inspired air restored the mental functions and the electroencephalographic tracings to normal and improved the cerebral venous O_2 saturation by an amount equivalent to that achieved by raising the O_2 concentration in the inspired air 2 volumes per cent. Gibbs and his co-workers²⁹ suggest that CO_2 is beneficial when the inspired air is low in oxygen because of two major effects: (1) improvement in oxygenation of the brain resulting from stimulation of pulmonary ventilation, redistribution of the cardiac output in

favor of the brain because of cerebral vasodilatation and peripheral vasoconstriction, and a shift in the hemoglobin dissociation curve in the direction favoring unloading of O_2 in the tissues; (2) the maintenance of a near optimal brain tissue P_{CO_2} , so essential to normal cerebral functions, despite the hyperventilation associated with the anoxemia.

When anoxemia is complicated by CO_2 retention, as, for example, during asphyxia or enforced rebreathing, the use of CO_2 is probably contraindicated. In such circumstances, the cerebral vessels are already dilated by the combination of the altered gas tensions, and the brain P_{CO_2} is elevated. The addition of CO_2 to the inspired air would then have relatively little further beneficial effect on cerebral blood flow but might raise the brain tissue CO_2 to dangerously high and depressant levels. On the other hand, when cerebral anoxia is caused by ischemia of the brain, as, for example, during circulatory collapse or secondary shock, CO_2 may be beneficial. In these conditions also, the brain tissue P_{CO_2} may be elevated, but only because cerebral blood flow is inadequate. By dilating cerebral vessels, constricting peripheral vessels,^{5, 28, 29, 42, 43, 54, 61} and leaving the coronary vessels unchanged,⁴² CO_2 redistributes the cardiac output to favor the brain at the expense of less vital tissues. It may also combat the arterial hypocapnia resulting from hyperventilation not infrequently seen in secondary shock, and which, when it occurs, further jeopardizes the circulation to the brain. For example, in experimental hemorrhagic shock in man, Stone and his associates⁶¹ found a low cerebral blood flow, attributable not only to the hypotension, but also to a moderate hypocapnia secondary to a hyperventilation of unknown origin. Mental functions were also impaired. The administration of morphine depressed the respiration, restored the arterial P_{CO_2} , and also the cerebral blood flow toward normal, and caused dramatic improvement in the mental state. The beneficial effect of morphine was attributed chiefly to its action in raising arterial P_{CO_2} . It would be of interest to know if the administration of CO_2 alone might have had a similar effect.

Resistance to Positive G. Carbon dioxide has been reported to increase the tolerance to positive radial acceleration^{1, 2, 66} and delay

"blackout." Its beneficial effect is probably related to its peripheral vasoconstrictor and cerebral vasodilator actions, thus reducing peripheral pooling and distribution of blood and aiding in the maintenance of the cerebral circulation under that stress.

SUMMARY

Carbon dioxide occupies a similar role in the regulation of the cerebral circulation as in the control of the respiration. Its vasodilator action on the cerebral circulation is more potent than that of any chemical agent or physiological mechanism yet uncovered. It is tonically active, and changes in the P_{CO_2} of the blood or cerebral tissues alter cerebral blood flow in the manner required to maintain homeostasis with respect to cerebral tissue P_{CO_2} . Since carbon dioxide is a product of cerebral metabolism, it is, in effect, the chemical mediator of the mechanism postulated by Roy and Sherrington⁵⁰ 70 years ago, which adjusts the blood flow of the cerebral tissues to their metabolic rate.

Its role is particularly magnified by the apparent absence of any significant degree of nervous control of the cerebral circulation. This aspect is most obvious in the many unique features of the pharmacology of the cerebral circulation.⁶¹ Drugs which exert powerful effects on other vascular beds through neurogenic mechanisms frequently have either no effects or entirely independent actions on the cerebral vessels as a result of their side effects on the CO_2 tension of the blood. Indeed the nature of the effect of CO_2 , itself, on the cerebral circulation is quite distinct from its action on most other vascular beds. The relationship between CO_2 and the cerebral circulation is so intimate and so fundamental that no physiological or pharmacological study of the circulation of the brain can be considered complete without the simultaneous examination of the effects of the experimental conditions on the state of CO_2 in the blood and cerebral tissues.

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