THRESHOLD OF RESPONSE OF THE CEREBRAL VESSELS OF MAN TO INCREASE IN BLOOD CARBON DIOXIDE¹

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The level of carbon dioxide in the blood is now generally accepted as one of the major factors in the regulation of the cerebral circulation. It was first shown in experimental animals that increase in blood carbon dioxide exerts a vasodilator effect on cerebral blood vessels (1, 2). Similar effects were postulated in man by Lennox and Gibbs (3) on the basis of decrease in the cerebral arteriovenous oxygen difference. Conclusive evidence of the effects of carbon dioxide on cerebral blood flow in man was provided by the experiments of Kety and Schmidt with the nitrous oxide method. Reduction in arterial CO₂ through hyperventilation was shown to produce a decrease in blood flow, (4) whereas increase in arterial CO₂ through inhalation of 5 per cent and 7 per cent carbon dioxide was found to cause a striking increase in blood flow (5).

The above observations on man, which were concerned with large-scale effects, do not in themselves permit a precise formulation of the role of carbon dioxide in the control of the cerebral circulation. The minimal changes in blood CO_2 which will evoke vascular responses must be known, together with the degrees of response which are produced by given increments of change in CO_2 beyond these threshold values. Knowledge of the minimal increase in arterial CO_2 required to dilate cerebral vessels has potential therapeutic application in the treatment of certain states of severe impairment of blood flow to the brain. Carbon dioxide in 5 per cent or greater concentra-

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tion has the disadvantages of raising blood pressure (5, 6) and producing uncomfortable dyspnea within a relatively few minutes (7). It appeared possible, however, that some lower concentration of carbon dioxide might prove more tolerable, while still retaining vasodilator properties.

The present studies were concerned with the threshold of response of the cerebral vessels of man to increase in blood carbon dioxide. Cerebral blood flow determinations were made with the nitrous oxide method, employing concentrations of 2.5 and 3.5 per cent CO_2 in the inspired gas, and the associated changes in blood gases and pH were measured.

METHODS

The subjects for these studies were hospital patients convalescing from a variety of illnesses in which the brain was not involved. Seven patients and five normal volunteer subjects were given 2.5 per cent carbon dioxide by inhalation and 12 patients and seven normal subjects were given 3.5 per cent carbon dioxide. The mean ages of these two groups were 30 and 34 years, respectively. Cerebral blood flow (CBF) before and during carbon dioxide inhalations was determined by the nitrous oxide method (8) with slight modifications (9). Six of the 28 subjects were studied by measurements of cerebral arteriovenous gas differences alone and one subject (H. J.) separately by both techniques. Cerebral oxygen consumption (CMRo₂) was determined from the cerebral blood flow multiplied by the cerebral arteriovenous oxygen difference, (A-V)02. The values for (A-V)₀₂ were obtained from analyses of arterial and internal jugular blood samples drawn just before and just after the cerebral blood flow procedure and pooled. The cerebral vascular resistance (CVR) was calculated by dividing the blood flow into the mean arterial pressure, measured several times during the CBF procedure from either the femoral or brachial arteries with a damped mercury manometer.

Control observations of the cerebral circulation were made with the standard gas mixture for the nitrous oxide method (15 per cent N_2O , 21 per cent O_2 , 64 per cent N_2). Following this the patient was given a mixture contain-

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W. 25	55	52	3.4	3.2	1.6	1.8	91	94	6.2	6.2	41	7.50	7.46	31	34	7.47	7.42	38	41	31
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T. 23	49	63	3.1	2.5	1.5	1.3	72	78	6.2	3.9	37									
	49	53	3.0	2.5	1.9	1.6	91	85	6.2	4.7	40	7.39	7.32	35	45	7.32	7.26	47	57	29
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C. 32	50	54	3.3	3.1	1.8	1.6	91	88	6.7	6.2	40	7.36	7.35	43	44	7.37	7.33	47	51	31
an 35	52	57†	3.0	3.0	2.0	1.8†	98	95	6.0	5.4†	39	7.40	7.35	39.4	44.7	7.35	3.32	48.8	53.8	31.0

TABLE I

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ing 2.5 per cent or 3.5 per cent CO_2 , with 21 per cent O_2 and the remainder N_2 . At the end of 15 to 20 minutes this mixture was changed to gas containing the same percentage of CO_2 and O_2 , together with 15 per cent N_2O , and the experimental blood flow determination carried out.

The pooled blood samples of arterial and venous blood were analyzed for oxygen and carbon dioxide content by the combined procedure for both gases described by Peters and Van Slyke (10), as modified for the presence of nitrous oxide by Kety and Schmidt (8). Oxygen capacity of the blood samples was determined by the method of Roughton, Darling, and Root (11). Blood pH was measured with a Cambridge Model R. pH meter, with appropriate corrections to body temperature (12). Carbon dioxide tensions (pCO_2) were obtained from the pH, CO₂ content and hematocrit by means of the nomogram of Singer and Hastings (13). The individual pCO₂ values were estimated to the nearest 0.1 mm. Hg from an enlarged print of this nomogram. This was done to define as precisely as possible the blood flow-pCO₂ relations over a narrow range of CO₂ increase. No implication is intended, however, that the method possesses such accuracy in terms of the absolute magnitude of individual determinations. Venous oxygen tension was determined from the pH and the per cent of oxygen saturation, using the oxygen-hemoglobin dissociation curves of Dill (14). Observations were made on the character of the subject's breathing, but respiratory minute volumes were not measured.

RESULTS

Inhalation of 2.5 per cent carbon dioxide produced very little change in the mean values of the cerebral blood flow, cerebral oxygen consumption or vascular resistance (Table I). The mean arterial pH and pCO₂ values with air and CO₂ breathing were respectively: 7.44 and 7.39, 38.4 and 42.5 mm. Hg. A comparable group of seven subjects given 2.5 per cent CO₂ for 15 minutes showed a decrease in the mean value for arterial pH from 7.37 to 7.34 and an increase in arterial pCO₂ from 41.3 to 45.6 mm. Hg. Dyspnea and increase in rate or depth of the subjects' breathing were either slight or not detectable. The same concentration of carbon dioxide was also well tolerated by 10 patients with cerebral vascular accidents (7) for periods of 30 minutes to one hour.

Inhalation of carbon dioxide in 3.5 per cent concentration was associated with a mean increase of 10 per cent (p < .05) in cerebral blood flow and a comparable decrease in cerebral vascular resistance (p < .05). There was no change in cerebral oxygen consumption. There was, however, a decrease in the cerebral arteriovenous oxygen difference. The mean values of $(A-V)_{o2}$ for air and CO_2 breathing in the patients studied by the nitrous oxide method were 6.0 and 5.4 volumes per cent (p = .05), respectively. In the larger group comprising 16 observations on 15 subjects, the mean value for (A-V)₀₂ was 6.4 volumes per cent with air and 5.5 volumes per cent with CO₂ breathing (p < .01). In 12 of these observations there was a fall in $(A-V)_{02}$ of 0.5 volumes per cent or more during CO₂ inhalation, and in four there was little change (Table II). Changes in the blood gas tensions and pH in the eight patients of the nitrous oxide group in whom these functions were studied were almost identical with those in the larger group of 15 subjects. In these 15 individuals 3.5 per cent carbon dioxide produced the following increases: arterial pCO₂, 5.3 mm. Hg; jugular venous pCO₂, 4.3 mm. Hg; jugular venous pO₂, 4.7 mm. Hg. Arterial pH fell .04 unit and jugular venous pH .03 unit with this concentration of carbon dioxide.

The relation between increase in arterial CO_2 tension and the corresponding change in two different measures of cerebral blood flow is shown in Figure 1. These measures are the cerebral blood flow as determined by the nitrous oxide method, and the cerebral blood flow as indicated by the reciprocal of the arteriovenous oxygen difference. In order to make them comparable, the values for both determinations during carbon dioxide inhalation are shown as percentage of control. Each of the points as plotted represents the mean obtained with a given concentration of inspired CO_2 in those subjects on whom both the CBF_{N2O} and

 $\frac{1}{(A-V)o_3}$ measurements were made. The function

 $\frac{1}{(A-V)_{O_2}}$ represents a valid measure of changes in blood flow where O_2 consumption is constant. The data for 5 per cent and 7 per cent CO_2 are taken from the work of Kety and Schmidt (5). However, supplementary observations made with 5 per cent CO_2 in our laboratory (7) in four patients with cerebral vascular accidents showed a decrease in the cerebral arteriovenous oxygen difference only slightly less than that observed by Kety and Schmidt in normal subjects.

It is evident in Figure 1 that a rather abrupt change in the slope of both curves must occur between the 2.5 per cent and 3.5 per cent inspired

TABLE I

		Art. p mm.	CO ₂ Hg	Art	. pH	Ven. j mm.	PCO2 Hg	Ven.	рH	Ven. mm.	pO2 Hg	(A-V Vol	V) 01 . %	$\frac{1}{(A-V)_{02}}$ as % of control (air)
Patient	Age	Air	CO2	Air	CO2	Air	CO2	Air	CO2	Air	CO2	Air	CO2	CO ₂
<u>C. C.</u>	33	35	45	7.39	7.32	47	57	7.32	7.26	29	37	6.2	4.7	132
W. McL.	25	47	55	7.38	7.30	61	70	7.30	7.25	33	35	6.5	6.4	102
G. G.	40	43	47	7.40	7.36	52	55	7.34	7.32	34	37	4.8	4.7	102
W. M. J.	36	37	39	7.42	7.40	46	47	7.37	7.36	35	35	5.1	5.3	96
G. M.	52	41	45	7.40	7.35	52	54	7.33	7.29	26	27	8.6	8.3	104
C. P.	22	40	40	7.38	7.38	48	49	7.32	7.32	27	32	4.9	3.8	129
J. S.	25	42	49	7.39	7.38	51	55	7.35	7.34	35	38	5.3	4.8	110
С. Н.	58	48	55	7.31	7.27	58	61	7.28	7.24	30	41	5.4	3.9	138
E. C.	37	37	45	7.43	7.37	52	57	7.35	7.32	24	28	9.6	7.8	123
H. J.	33	37	42	7.39	7.35	43	48	7.38	7.33	32	38	5.4	4.9	110
Н. Ŵ.	25	32	41	7.43	7.38	42	48	7.41	7.36	28	37	7.5	5.1	147
D. C.	32	43	44	7.36	7.35	47	51	7.37	7.33	31	35	6.7	6.2	108
H. I.	33	38	44	7.40	7.35	46	50	7.37	7.33	38	46	4.6	3.6	126
B. G.	27	40	47	7.41	7.35	48	53	7.38	7.34	30	34	7.2	6.2	116
C. W.	26	41	4 2	7.39	7.36	51	53	7.35	7.32	32	35	7.7	7.2	108
G. H.	31	39	44	7.42	7.37	47	51	7.38	7.35	31	34	7.4	5.7	129
Mean	33	40.0	45.3†	7.39	7.35	49.4	53.7	7.35	7.32	30.9	35.6	6.4	5.5†	117.5

Arterial and internal jugular blood gas and pH determinations in sixteen observations on fifteen subjects during air and 3.5 per cent carbon dioxide inhalation *

* Individual pCO₂ values are rounded to nearest whole number. Figures for mean pCO₂ obtained from unrounded individual values (see Methods).

† Tested by analysis of variance and found significantly different (p<.01) from mean value with air breathing.



FIG. 1. RELATION BETWEEN THE CEREBRAL BLOOD FLOW AND RECIPROCAL OF THE CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCE AND THE INCREASE IN ARTERIAL CARBON DIOXIDE TENSION

carbon dioxide concentrations, and likewise between the increases in arterial pCO₂ produced by these concentrations. The progressive rise in both measures of cerebral blood flow with further increments in the inspired CO, concentration and the arterial pCO₂ is also readily apparent. A 12 to 13 per cent increase in blood flow in these subjects is indicated for a 5.3 mm. rise in pCO₂, and a doubling of blood flow is predicted for a 10 to 11 mm. Hg increase in CO₂ tension. In the larger group of 15 subjects, 3.5 per cent CO₂ produced a mean increase in $\frac{1}{(A-V)o_1}$ of 17 per cent. The mean changes in arterial pCO2 shown in this figure for the 2.5, 3.5, 5, and 7 per cent CO₂ concentrations are respectively: 4.1, 5.3, 7.0, and 14 mm. Hg. A scatter plot of the individual data shows no tendency for the value of $\frac{1}{(A-V)_{0_1}}$ to rise with increases in arterial pCO₂ smaller than 5 mm. Hg, but a clearly evident tendency for this function to rise with increases of pCO₂ of 5 mm. or greater. The same can be said for the individual CBF_{N20} data, although there are fewer points to indicate the trend of the relationship.

During the inhalation of 3.5 per cent carbon dioxide a definite deepening and slight increase in rate of respiration were usually observed within 10 to 15 minutes. These were associated with slight dyspnea, which in a few subjects became definitely uncomfortable within 30 minutes.

DISCUSSION

The threshold for cerebral vasodilator effect evidently lies beyond the 2.5 per cent inspired CO₂ concentration and its associated mean increase in arterial CO₂ tension of 4.1 mm. Hg. This conclusion is based on the absence of changes in the cerebral blood flow, vascular resistance and arteriovenous oxygen difference.

In regard to 3.5 per cent CO₂, the validity of the cerebral arteriovenous oxygen difference as a measure of small changes in blood flow, under the conditions of these experiments, should first be considered. Actually, the validity of change in $\frac{1}{(A-V)_{O_2}}$ as a measure of change in CBF rests upon the demonstration that cerebral oxygen consumption, as determined by the nitrous oxide method, is not altered by inhalation of carbon dioxide over the concentration range studied. Since $CBF = \frac{CMR_{o_2}}{(A-V)o_2}$, it is evident that when CMR_{0_2} is a constant the value of $\frac{1}{(A-V)o_1}$ will vary as the blood flow. There seems little reason to doubt the constancy of the CMR₀₂, since the number of subjects in the present series combined with those studied by Kety and Schmidt is relatively large. Random errors in the nitrous oxide method would tend to be averaged out, and even systematic errors would not preclude correct conclusions regarding the constancy of cerebral metabolism. It is quite possible that in a limited series of observations, the change in $\frac{1}{(A-V)o_1}$ might be the more accurate measure of small changes in blood flow. The nitrous oxide method in any given determination contains more possibilities of error, since it involves multiple analyses, the assumption of equilibrium in respect to nitrous oxide between the brain and jugular venous blood, and other potential sources of error. In the present studies, these two measures of blood flow were for the most part in good agreement, although the larger number of oxygen difference determinations gives this measure somewhat greater statistical validity.

The relations shown in Figure 1 suggest that the cerebrovascular response to increase in arterial pCO₂ is a threshold type of phenomenon. The rise from the control level of both the CBF_{N2O} and $\frac{1}{(A-V)o_2}$ evidently occurs over a narrow range of increase in arterial CO₂ tension. Since mean arterial blood pressure was unaffected by 3.5 per cent CO₂ (Table I) and only slightly to moderately affected by 5 per cent and 7 per cent CO₂, (5) the rising curve of cerebral blood flow with increase in arterial CO₂ tension beyond threshold must have been due primarily to progressive dilatation of cerebral blood vessels.

The mean threshold value for increase in arterial pCO_2 , below which there was no effect on cerebral vessels and above which there occurred progressive dilation, was approximately 4.5 mm. Hg. It can be seen that both of the curves of Figure 1 when extrapolated downward intersect the control (100 per cent) level very near this point. In the individual data no pCO_2 values lie between

4.2 and 5.0 mm. Hg, but in each of four subjects who had individual increases of 5.0 mm. Hg in pCO_2 the value of $\frac{1}{(A-V)O_2}$ was considerably elevated above control level. This suggests that the 5.0 mm. Hg increase was beyond threshold. It should be emphasized that the 4.5 mm. Hg increase in pCO_2 represents the average threshold in the subject group studied, and that some individual and group variation would be expected.

It is apparent that inhalation of 3.5 per cent CO₂, with its associated mean increase in arterial pCO₂ of 5.3 mm. Hg, produced significant cerebral vasodilatation, since the CBF_{N_2O} , $\frac{1}{(A-V)O}$ and the calculated CVR all showed statistically significant changes. Only four of 15 subjects, including the only patient with definite hypertension (C. G.) showed an increase in $\frac{1}{(A-V)o_2}$ smaller than eight per cent. The difference between the pCo₂ change with 3.5 per cent CO₂ and that produced by 2.5 per cent appears surprisingly small in relation to the difference in effect. However, the importance of small changes in pCO₂ beyond threshold is emphasized by the increase in blood flow of approximately 50 per cent which is produced by a 7 mm. Hg increase in CO₂ tension (8).

Although the threshold defined above has been stated in terms of change in arterial pCO₂, it is possible that it actually represents a threshold for the effects of associated change in hydrogen ion or bicarbonate ion concentration. The work of Schieve and Wilson (15) makes it appear unlikely that the H-ion has any cerebral vasodilator effect, but does not exclude the HCO₃-ion. The question must also be raised whether we are dealing with a "pure" CO₂ threshold or whether an increase in oxygen tension as a result of hyperventilation might have exerted opposing (vasoconstrictor) effect. However, cerebral vessels are only slightly constricted by 50 per cent oxygen (16) which, on the basis of the alveolar equation (17) and an assumed alveolar-arterial pO₂ gradient of 20 mm. Hg, should produce an arterial pO₂ of nearly 300 mm. Hg. Since the inspired pO₂ itself in these experiments was not over 159 mm. Hg, the possibility appears remote that change in arterial pO₂ influenced the results.

The site of action of the carbon dioxide in these experiments was probably the blood vessels themselves. Although an autonomic vasodilator innervation has been demonstrated in the experimental animal (18), its functional significance for man is unknown. It is of interest that recent experiments suggest that a threshold concentration of CO₂ is required for respiratory stimulation (19, 20). Observations have been made on the effect of an increase in blood CO₂ on other vessels of the body deprived of their vasomotor innervation. The vessels in sympathectomized upper extremities in man (21) and the hind limb vessels in dogs, given ganglionic-blocking doses of tetraethylammonium (22), respond alike by vasodilatation to increase in blood carbon dioxide.

The CO₂ tension threshold for cerebral vascular effect which is reported in this paper is nonspecific in the sense that it does not indicate which type of vessel was responding: arteries, arterioles, capillaries or venules. Since the increases in venous pCO₂ during 2.5 and 3.5 per cent CO₂ breathing were only slightly smaller than those in arterial pCO₂, the threshold as given would not be greatly in error, regardless of the type of vessel involved. As a corollary we may conclude that, if all of these vessels were responding, the threshold was nearly the same throughout the group. In the case of diseased cerebral blood vessels, or of vessels adapted to chronic abnormality in blood pCO₂, it might be anticipated that the thresholds of response to CO2 change would show some differences from those of normal vessels. In cerebral arteriosclerosis the vascular response to 5 per cent CO₂ inhalation has been shown to be diminished (23).

In the intrinsic control of the cerebral circulation, it appears probable that carbon dioxide and oxygen tension changes operate simultaneously, and usually in the same direction rather than in competition. Thus, with a fall in cerebral blood flow, the resulting fall in capillary and venous pO_2 and rise in pCO_2 both represent vasodilator stimuli. The threshold for the combined vascular effects of fall in pO_2 and rise in pCO_2 quite likely is reached at a smaller value for pCO_2 increase than the threshold reported in this paper. From the Fick equation, and the blood nomogram (13) or the physiological CO_2 absorption curve (24), it can be shown that, with CMR₀₂ constant, cerebral blood flow must fall by approximately 30 per cent to raise venous pCO_2 to the vasodilator threshold. There is some evidence that vessels actually dilate with a smaller reduction in blood flow (25). Studies on such combined thresholds, and on the threshold of cerebral vascular response to reduction in blood CO_2 tension, obviously are needed. The data in the existing literature on the combined effects of arterial pCO_2 and pO_2 on cerebral blood flow have recently been worked into a useful nomogram by Cannon (26).

Therapeutic applications of our findings remain to be explored. Carbon dioxide in 3.5 per cent concentration appears potentially useful for the treatment of cerebral vascular manifestations produced by inadequate blood flow. Although more weakly vasodilator than 5 per cent CO_2 , it is considerably more tolerable from the standpoint of dyspnea and can be given for 30 minutes to most patients without producing excessive dyspnea or increases in arterial blood pressures. Its trial in selected patients with cerebral vascular insufficiency seems indicated.

SUMMARY

1. The vasodilator response of normal cerebral vessels to rapid increase in arterial carbon dioxide tension appears to be a threshold type of phenomenon.

2. In a group of 28 subjects, a mean increase in arterial CO_2 tension of less than 4.5 mm. Hg was without vascular effect, whereas increases greater than this value produced progressive vasodilatation.

3. With constant cerebral metabolism, a reduction in blood flow of approximately 30 per cent would be required to raise end-capillary and venous pCO_2 to the vasodilator threshold for this gas.

4. Inhalation of 3.5 per cent carbon dioxide produced a 10 per cent mean increase in cerebral blood flow, but little change in blood pressure in most subjects. It causes considerably less dyspnea than 5 per cent CO_2 , and may have application in the treatment of states of cerebral vascular insufficiency.

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