Oxygen Toxicity. Arterial and Internal Jugular Blood Gas Composition in Man During Inhalation of Air, 100% O_2 and 2% CO_2 in O_2 at 3.5 Atmospheres Ambient Pressure[1]

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THE ADDITION of carbon dioxide to oxygen inhaled at increased ambient pressure has for many years been known to shorten greatly the latent period preceding the onset of oxygen convulsions (1–3). This undisputed fact has often been advanced as indirect support of Gesell's proposal (4) that autointoxication with carbon dioxide, due to failure of hemoglobin reduction in the presence of large amounts of oxygen physically dissolved in blood, is an important contributing cause of oxygen convulsions. Our recent observations in resting man breathing oxygen at 3.5 atmospheres (5, 6) indicate that the concomitant rise in cerebral venous pCO_2 is only 2–3 mm Hg, and Behnke *et al.* (7) have reported similar findings in the mixed venous blood of anesthetized dogs. The very high tensions of carbon dioxide (71–368 mm Hg) which have been described in subcutaneous gas or fluid depots in small animals breathing oxygen at high pressure (3, 8) we find to occur only after the onset of oxygen convulsions (9). We therefore believe that carbon dioxide retention in the tissues can be excluded as a major cause of the symptoms of oxygen poisoning. The accelerated onset of the latter on the addition of carbon dioxide to oxygen inhaled at high ambient pressures then remains to be explained.

One of the most likely possibilities lies in the well-known cerebral vasodilator effect of carbon dioxide (10, 11). Our earlier studies (5, 6, 12) led us to conclude that the cerebral vasoconstriction associated with inhalation of oxygen (approximately a 50% increase in cerebral vascular resistance of normal men at 3.5 atm.) is primarily due to the lowering of arterial pCO_2 by oxygen-induced hyperventilation. An effective cerebral vasodilator agent, and particularly carbon dioxide, should overcome the cerebral vasoconstriction so produced, and thus bring about a marked rise in the pO_2 in the brain cells. The latent period for the onset of oxygen convulsions should be correspondingly shortened. Such an effect would be evident in the behavior of the pO_2 of cerebral venous blood on the addition of carbon dioxide to oxygen inhaled under high pressure. The experiments now to be reported were intended to test this hypothesis.

METHODS

The data for this investigation were obtained upon four male schizophrenic patients, aged 19–32, during an evaluation of possible therapeutic effects of oxygen convulsions in schizophrenia. Each subject was studied at rest in the supine position during air breathing at 1 atm., and during the breathing of air, 100% O_2, and 2% CO_2 in O_2 at an ambient pressure of 3.5 atm. Since the rates of cerebral blood flow and cerebral O_2 utilization in schizophrenic patients were found by Kety *et al.* (13) to be normal, these subjects were considered suitable for the present study.

The experiments were performed in a compression chamber large enough to accommodate the subject and investigators. Air temperature within the chamber was maintained between 20 and 23°C. At 3.5 atm. variations in pressure did not exceed ±0.3 psi (about ±16 mm Hg in 2660 mm Hg). Barometric pressure ranged from 759.0 to 770.0 mm Hg, averaging 763.3 mm Hg.

All gases were administered by means of a respiratory apparatus consisting of an A-14 aviation mask, breathing valves, and a manifold of 30-liter Douglas bags filled through humidifiers from cylinders of compressed, water-pumped gas. The resistance of this system did not exceed 4 cm of water on inspiration or expiration at the maximum ventilations encountered. The approximately 35 ml dead space of the respiratory appara-

Received for publication July 14, 1955.

[1] This investigation was supported by a research contract between the Office of Naval Research, Dept. of the Navy and the Univ. of Pennsylvania (NR112-279).

[2] Work performed during period as John and Mary R. Markle Foundation Scholar in Medical Science.

tus was limited to that within the mask. Femoral arterial and internal jugular venous blood samples were collected via indwelling needles inserted after infiltration of each puncture site with about 3 ml of 1% procaine solution. All blood specimens were placed in salted, iced water immediately on sampling and were processed anaerobically, using the previously described (5), special procedures for samples collected at increased ambient pressure. The CO_2 and O_2 contents of whole blood were measured in duplicate by the manometric method of Van Slyke and Neill (14) within 3 hours of withdrawal. Total hemoglobin concentration was measured spectrophotometrically in duplicate by the cyanomethemoglobin method (15), and an approximation of O_2 capacity was calculated on the assumption that 1.34 cc of O_2 combines with each gram of active hemoglobin (16). Measurement of pH of blood samples was completed in duplicate at ambient temperature within 1 hour of sampling, by means of a McInnes-Belcher type of glass electrode and a Cambridge Model R pH meter. The observed values were converted to their equivalents at 37°C by the use of Rosenthal's temperature coefficient (17). Standardization procedures, buffers and precautions for pH measurement at high ambient pressure were identical with those previously described (5). Blood CO_2 tension was calculated with the Henderson-Hasselbalch equation from observations of CO_2 content and pH of whole blood, hemoglobin concentration, and O_2 saturation of whole blood after using the nomogram of Sendroy, Dillon and Van Slyke (18) to estimate the corresponding content of CO_2 in serum. As previously described (5) a pK of 6.105 and a Bunsen solubility coefficient of 0.520 for CO_2 in blood were employed in order to refer all data to a body temperature of 37.0°C. Since earlier studies have indicated that the indirect procedure for estimating blood pCO_2 consistently gave results averaging about 3 mm Hg too high (5, 19), this amount was subtracted from each calculated value for CO_2 tension. The use of a correction factor in this manner affects absolute values but not the data relating to changes in blood pCO_2 observed. The O_2 tensions of blood specimens in which hemoglobin was not completely saturated were estimated from the O_2 saturation on the dissociation curves of Bock (20, 21) with suitable corrections for pH and physically dissolved oxygen. When the inspired O_2 tension was high enough to produce essentially 100% hemoglobin saturation, blood pO_2 was calculated from the solubility coefficient for O_2 in blood at 37°C and the O_2 physically dissolved. The latter was estimated by subtracting the calculated hemoglobin O_2 capacity from the observed total O_2 content of whole blood. This procedure has an error of approximately ±100 mm Hg or about 5% of the arterial O_2 tension (average about 2000 mm Hg) associated with O_2 breathing at 3.5 atm. (5).

The experiments were carried out as follows: during air breathing at 1 atm. arterial and internal jugular venous blood samples were withdrawn simultaneously over a 1-minute period. Then, with the subject still breathing air, chamber pressure was raised to 3.5 atm. (45 psi gauge pressure), taking about 15 minutes to do so. Arterial and cerebral venous blood samples were again withdrawn simultaneously after 5 minutes of breathing air at 3.5 atm. Oxygen was then administered and blood samples were again obtained 10 minutes after initiation of O_2 breathing. The CO_2-O_2 mixture was then substituted without intervening exposure to air. When toxic symptoms became evident the last pair of blood samples were drawn. In several preliminary experiments at 3.5 atm. the CO_2-O_2 mixture was administered immediately following air breathing, but in these the rapid onset of O_2 toxicity precluded subsequent measurements on O_2 alone and the sequence described above therefore was adopted as a routine procedure.

RESULTS

The individual measurements obtained in four schizophrenic patients breathing air at 1 atm., and air, commercial O_2 and 2% CO_2 in oxygen at 3.5 atm. pressure, are shown in table 1, the average values in table 2. In view of the small number of patients available for the study, no statistical analysis has been carried out on these data. Findings which appear to deserve special mention are as follows:

Air and O_2 Breathing at 3.5 Atmospheres. The changes in arterial and venous blood gases during air breathing at 3.5 atm. are smaller than, but qualitatively similar to, those produced by O_2 breathing at the same pressure. The findings relating to blood gas changes in both situations are consistent with our previous studies of the respiratory effects of air breathing at 3.5 atm. (12), and the effects of O_2 breathing at 3.0 and 3.5 atm. upon respiration, blood gas transport and cerebral circulation (5, 6, 12). Together with our earlier results, these data suggest that increasing the pO_2 of the inspired air leads first to cerebral venous hypercapnia (through interference with CO_2 transport), which in turn (through rise in the pCO_2 in the respiratory centers) causes hyperventilation, arterial hypocapnia and increase in cerebral vascular resistance. This concept is in harmony with the observed increases in the cerebral arteriovenous pCO_2 difference from 8 mm Hg during air breathing at sea level to 13 mm Hg on air breathing at 3.5 atm. and to 17 mm Hg on O_2 inhalation at the increased pressure (table 2). The corresponding increases in the cerebral arteriovenous O_2 tension difference were from 51 mm Hg at sea level to 146 (air breathing) and 1824 mm Hg (O_2 inhalation) at 3.5 atm. (table 2). The relative stability of cerebral

TABLE 1. EFFECTS OF INHALING AIR, OXYGEN AND 2% CO_2 IN OXYGEN UPON ARTERIAL AND INTERNAL JUGULAR VENOUS BLOOD GAS COMPOSITION (INDIVIDUAL VALUES)

Inspired gas	Ambient Pressure	Subject	Time	CO_2 Content		CO_2 Tension		pH		O_2 Content		O_2 Capacity		Hb Saturation		CBF Index †	O_2 Tension	
				Art	Int Jug	Art	Int Jug	Art	Int Jug	Art	Int Jug	Art	Int Jug	Art	Int Jug		Art	Int Jug
	atms		mins	vols%		mmHg				vols%		vols%		%		ΔA-V O_2 ratio	mmHg	
Air	1.0	W.K.		49.8	55.2	43	51	7.35	7.32	18.8	13.3	19.2	19.2	96	69	1.00	97	40
		D.L.		49.3	55.5	41	50	7.38	7.34	19.0	12.7	19.8	19.7	94	64	1.00	95	38
		R.M.		48.8	52.6	38	46	7.40	7.35	17.7	13.3	19.2	19.4	91	68	1.00	65	39
		W.B.		49.9	55.7	40	48	7.39	7.36	18.0	12.3	18.8	18.9	98	65	1.00	97	35
Air	3.5	W.K.		49.8	55.7	40	52	7.39	7.32	19.8	15.1	19.1	19.1	100	78	1.17	230	47
		D.L.		49.8	56.7	40	53	7.40	7.32	20.2	13.4	19.8	19.7	100	68	0.93	130	45
		R.M.		49.1	54.5	41	52	7.37	7.31	19.8	14.2	19.2	19.4	100	73	0.79	200	43
		W.B.		48.3	55.9	40	55	7.37	7.29	19.3	12.2	18.6	18.7	100	65	0.80	200	39
Oxygen	3.5	W.K.	10	49.3	55.2	39	51	7.39	7.32	25.5	19.2	19.2	19.2	100	98	0.87	2000	95
		D.L.	14	48.3	55.4	37	53	7.42	7.32	25.4	18.4	19.8	19.7	100	92	0.90	1800	70
		R.M.	11	46.8	54.4	33	53	7.45	7.31	26.1	19.0	20.2	20.7	100	90	0.80	1800	70
		W.B.	12	48.1	56.6	39	60	7.38	7.26	24.5	16.7	18.5	18.6	100	89	0.73	2000	68
2% CO_2 in Oxygen	3.5	W.K.	6	53.6	57.3	52	61	7.30	7.26	25.2	22.4	19.4	19.4	100	100	1.96	1900	1000
		D.L.	8	55.2	58.1	60	67	7.26	7.23	26.6	22.6	19.8	19.8	100	100	1.58	2200	900
		R.M.	7	55.2	57.3	61	72	7.25	7.19	25.4	22.9	19.2	19.4	100	100	1.76	2000	1100
		R.M.*	12	55.8	57.5	64	69	7.23	7.21	25.6	22.9	19.2	19.4	100	100	1.63	2100	1100
		W.B.	6	54.1	57.3	59	68	7.25	7.21	24.0	21.3	18.4	18.5	100	100	2.11	1800	900

† Indicates ratio of A-V O_2 difference during control period of air breathing at 1.0 atm. to A-V O_2 difference in experimental situation. * Indicates second experiment on subject *R. M.* in which CO_2-O_2 mixture was administered without preceding period of O_2 breathing. Not included in average values of table 2.

TABLE 2. EFFECTS OF INHALING AIR, OXYGEN AND 2% CO_2 IN OXYGEN UPON ARTERIAL AND INTERNAL JUGULAR VENOUS BLOOD GAS COMPOSITION (AVERAGE VALUES IN 4 SUBJECTS)

Inspired gas	Ambient pressure	Time	CO_2 Content		CO_2 Tension		pH		O_2 Content		O_2 Capacity		Hb Saturation		CBF index	O_2 Tension	
			Art	Int Jug	Art	Int Jug	Art	Int Jug	Art	Int Jug	Art	Int Jug	Art	Int Jug		Art	Int Jug
	Atms	mins	vols %		mmHg				vols %		vols %		%		$\Delta A-V\ O_2$ ratio	mmHg	
Air	1.0		49.5	54.9	41	49	7.38	7.34	18.4	12.9	19.3	19.3	95	67	1.00	89	38
Air	3.5		49.2	55.7	40	53	7.38	7.31	19.8	13.7	19.2	19.2	100	71	0.92	190	44
Oxygen	3.5	12	48.1	55.4	37	54	7.41	7.30	25.4	18.3	19.5	19.6	100	92	0.83	1900	76
2% CO_2 in Oxygen	3.5	7	54.5	57.5	58	67	7.27	7.22	25.3	22.3	19.2	19.3	100	100	1.85	2000	1000

venous pO_2 (38, 44 and 76 mm Hg) probably reflects, not an active homeostatic mechanism, but the O_2 reservoir function of hemoglobin after loss of physically dissolved O_2 to the tissues.

2% CO_2 in O_2 at 3.5 Atmospheres. On substituting 2% CO_2 in O_2 for pure O_2, the expected increases in arterial and cerebral venous pCO_2 and cH occurred (table 2). Neither the content nor tension of O_2 in arterial blood was appreciably altered but the cerebral arteriovenous O_2 difference was decreased from 7 to 3 volumes % (table 2). As a consequence of the diminished extraction of O_2, the average cerebral venous pO_2 was elevated by CO_2 breathing to 1000 mm Hg.

DISCUSSION

The most striking result of these experiments was the elevation of cerebral venous pO_2 from less than 100 mm Hg to approximately 1000 mm Hg on the addition of 2% CO_2 to O_2 inspired at 3.5 atm. (table 2). The magnitude of this change seems to us to justify the belief that the ability of CO_2 to shorten the latent period of O_2 toxicity may be attributed entirely to a simple increase in the tissue pressure of oxygen.

Cause of Increased Internal Jugular pO_2. The observed gross elevation of the O_2 tension of blood leaving the brain could have been brought about by one or more of several factors including *a*) an increase of arterial O_2 content, *b*) a decrease in the rate of utilization of O_2 by brain tissue and *c*) an increase in the volume of blood (O_2) flow through the brain. The first possibility can be dismissed at once because in these experiments no significant change in *arterial* pO_2 occurred on changing from O_2 breathing to inhalation of 2% CO_2 in O_2 at 3.5 atm. (table 2). The indicated average rise from 1900 to 2000 mm Hg on administration of CO_2 with O_2 is probably a reflection of experimental error in the small number of subjects available; in any case this small change could not of itself account for a rise of 1000 mm Hg in the venous pO_2. Actually, hyperventilation during O_2 breathing should not alter alveolar O_2 tension excepting in the amount by which alveolar pCO_2 is changed. With hyperventilation produced by CO_2 in

subjects breathing O_2 alveolar pO_2 might therefore be expected to decrease, not rise.

The second possibility could not be investigated directly here because the impracticability of maintaining a steady respiratory state in our schizophrenic subjects made it unfeasible to determine cerebral O_2 consumption by the nitrous oxide method (22). Our earlier studies established that O_2 inhalation at 3.5 atm. does not measurably alter cerebral O_2 consumption (5) and the experiments of Kety and Schmidt (11) revealed no decrease in the rate of O_2 utilization by the brain when 5% CO_2 was inhaled with 21% O_2. In the same study (11) two subjects who inhaled 7% CO_2 (corresponding to 2% CO_2 at 3.5 atm.) showed only a small decrease in cerebral O_2 consumption. Additional measurements are necessary to establish whether these changes were significant; certainly they were not large enough to explain the greatly decreased arteriovenous O_2 difference observed in this series (from 7.1 to 3 vol. %) on the addition of 2% CO_2 to O_2 at 3.5 atm.

It is possible that a combined action of increased CO_2 and O_2 tensions may result in depression of brain metabolism not predictable from the effects of either alone, but to account thus for all of the increase in cerebral venous pO_2 observed in the present study, oxygen uptake by the brain would have to be reduced to less than one-half the normal rate. According to existing information (23) an impairment of this magnitude would be associated with deep coma and the manifestations of O_2 toxicity would differ considerably from those ordinarily encountered. This was not the case. The pattern of O_2 toxicity when CO_2 was added to O_2 differed only in greater respiratory activity and shortened latent period from that observed with O_2 alone. For these reasons we consider a marked depression of cerebral O_2 consumption by the combined action of high CO_2 and O_2 tensions as a highly improbable cause of the elevated internal jugular venous pO_2.

The most likely explanation of this phenomenon, in our opinion, is an increase in the rate of cerebral blood flow, brought about by arterial hypercapnia. An increase in arterial pCO_2 has been firmly established as a highly potent dilator of cerebral blood vessels (10, 11). On the other hand, O_2 breathing at pressures up to 3.5 atm. causes cerebral vasoconstriction (5, 11). In the absence of a measurable effect of high O_2 tension upon the cerebral metabolic rate (5), the cerebral blood flow index of table 2 indicates that in these studies O_2 breathing without added CO_2 lowered cerebral blood flow. Our earlier studies suggest that this constriction is probably not due to a direct action of high O_2 tensions on the vessels, but is secondary to the arterial hypocapnia associated with inhalation of O_2 (5, 6). The values for arterial pCO_2 in tables 1 and 2 indicate the same tendency toward hypocapnia during O_2 breathing observed in our earlier, more extensive studies (6, 12). It is likely, then, that the decreased rate of cerebral blood flow accompanying O_2 breathing should be readily overcome or even replaced by cerebral vasodilatation when sufficient CO_2 is added to the inspired O_2.

In these experiments at 3.5 atm., arterial pCO_2 was raised 21 mm Hg, from the level of about 37 mm Hg associated with O_2 breathing to about 58 mm Hg on the addition of 2% CO_2. This increase in arterial pCO_2 is more than twice as large as the 9 mm Hg found by Kety and Schmidt (11) to coincide with about a 75% increase in cerebral blood flow on administration of 5–7% CO_2 in 21% O_2. The A-V O_2 ratio (tables 1 and 2) rose from .83 to 1.85 upon adding CO_2 to O_2 at the increased ambient pressure. At present we consider this change to indicate a doubling of cerebral blood flow, an effect proportional to the degree of arterial hypercapnia.

Relationships of Arterial and Cerebral Venous pO_2 to Brain Tissue pO_2. In the present experiments at 3.5 atm. inspired O_2 pressure the amount of O_2 carried in physical solution in arterial blood was about 6 volumes %. The volume of O_2 extracted from the blood by the brain during inhalation of O_2 (without CO_2) was about 7 volumes % (table 2). Since the physically dissolved O_2 of arterial blood was insufficient to meet the brain tissue requirement, the capillary pO_2 evidently fell to the point at which hemoglobin yielded some of its O_2 and the venous blood emerged with a pO_2 of 76 mm Hg and a saturation of 92% (fig. 1). These are not very much higher than the corresponding values (44 mm Hg and 71%) encountered during O_2 inhalation at

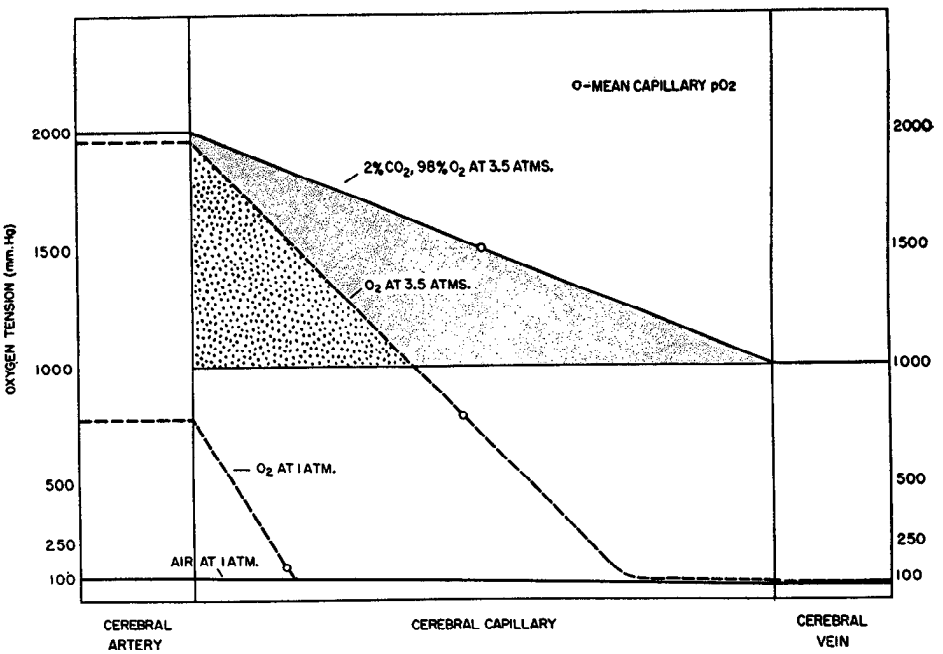

FIG. 1. Effects of breathing O_2 alone and with CO_2 upon arterial, cerebral venous and cerebral capillary pO_2. Data for O_2 breathing at 1.0 atm. obtained from previous study (5). If the rate of O_2 loss to the tissues were uniform, flowing capillary blood would reach its mean pO_2 near the arterial end of the capillary with normal arterial pO_2 and would approach the mid-capillary position as arterial pO_2 or blood flow was increased. Due to relatively great decreases in blood pO_2 when physically dissolved O_2 supplies the tissues, very high arterial pO_2 is associated with only a small increase of venous pO_2. Arbitrarily designating 1000 mm Hg as a minimal 'toxic' level for capillary pO_2, it can be seen that administration of CO_2 with O_2 could increase both the magnitude of mean pO_2 and the mass of tissue exposed to tensions above the minimal toxic level.

1 atm. (5, 11). Nevertheless, the latter procedure never induces O_2 convulsions.

When CO_2 is added to O_2 at 3.5 atm. the situation is profoundly altered. The volume of O_2 carried physically dissolved in arterial blood (6 vols. %) now is greater than can be extracted by the brain (3 vols. %). The venous blood therefore leaves the brain with its hemoglobin still 100% saturated, and with a pO_2 of about 1000 mm Hg.

The observed decrease in extraction of O_2 from blood must have resulted in an increase in brain tissue pO_2. Bohr (24) first expressed the relationships between the O_2 tensions of the blood and tissues by the formula

$$O_2 \text{ consumption} = (\text{mean capillary } pO_2 - \text{mean tissue } pO_2)DO_2$$

DO_2 is the diffusion coefficient of the tissue for O_2 and should depend, in addition to the solubility and molecular weight of O_2, upon the distances over which diffusion of O_2 must take place in the tissues (distribution of capillaries, vessel size, relative direction of blood flow). Mean capillary pO_2 is normally not an arithmetic mean of the arterial and venous tensions, due to the effect of the hemoglobin dissociation curve upon the rate of fall of pO_2 as O_2 leaves the flowing capillary blood (24). Its value can be roughly estimated by an integration procedure from knowledge of arterial and venous O_2 tension and capacity (table 3). In the special circumstance of $CO_2 - O_2$ inhalation at high ambient pressure, the fall in pO_2 along the capillary would be unaffected by the characteristics of hemoglobin dissociation. Ideally, depending only upon the solubility coefficient, rate of blood flow and rate of O_2 consumption, it would be linear and an arithmetic mean capillary pO_2 could be calculated (table 3, fig. 1). Even in this unique situation, however, practical considerations such as uneven rates of blood flow and O_2 consumption, pO_2 gradients parallel to the capillary and effects of randomly distributed, adjacent capillaries render

assumption of a regular, linear fall in pO_2 in capillary blood invalid. Nevertheless, the same objections apply to estimation of mean capillary pO_2 by integration and this would appear to be the first occasion in which the arithmetic average of arterial and venous tensions offers a closer index of mean capillary pO_2 than does integration. It can be seen from the estimated values of mean brain capillary pO_2 in table 3 that at sea level even O_2 breathing does not produce a mean capillary pO_2 much in excess of 100 mm Hg. At 3.5 atm. the inspired pO_2 of about 2660 mm Hg results in a mean capillary pO_2 of only about 780 mm Hg and the addition of CO_2 essentially doubles this value.

While capillary pO_2 can be roughly approximated, it has thus far been impossible to measure or calculate either the mean tissue pO_2 or DO_2 *in vivo* for any organ excepting in the peculiar situation provided in the lung by its gas phase. Should the tissue O_2 diffusion coefficient be constant and O_2 consumption also be constant the mean gradient between cerebral capillary pO_2 and brain tissue must remain the same while inspired O_2 tension and cerebral O_2 flow are altered. Under these conditions any rise in mean capillary pO_2 will be accompanied by an equal elevation of the mean pO_2 in the perfused tissue. It is completely unlikely that in a situation such as CO_2 breathing, associated with gross cerebral vasodilatation and a probability of major alterations of vessel size and diffusion distances, the DO_2 should remain the same as during air breathing. However, such effects of CO_2 on cerebral vasculature would be expected to increase, not decrease, the DO_2 and a change in mean capillary pO_2 should represent a minimum change in tissue pO_2. Moreover, mean tissue pO_2 should also increase if high inspired CO_2 tensions depress O_2 utilization by brain tissue. For these reasons, and regardless of the exact mechanisms involved, it appears likely that on the addition of CO_2 to O_2 inhaled at 3.5 atm. by our subjects, a rise in mean brain pO_2 occurred which was at least as great at the estimated 710 mm Hg increase in cerebral capillary pO_2 (table 3).

Quantitative evaluation of the importance to O_2 toxicity of a 1000 mm Hg rise in venous pO_2 or a 700 mm Hg increase in mean brain tissue pO_2 is not yet possible since it is not known at what tension levels in the tissues O_2 become toxic. *In vitro* studies upon rat brain tissue slices or homogenates exposed to O_2 at 8 atm. (6080 mm Hg) pressure show that O_2 utilization is depressed only after exposures of about 1 hour (26). Under these conditions the cellular pO_2 is presumably close to the ambient pressure. In the same species *in vivo*, O_2 breathing at 8 atm. pressure routinely produces convulsions in about 10 minutes (26). Although latent periods are much shorter *in vivo* the actual exposure of most brain cells in the living animal is not to the ambient pO_2 but to far lower O_2 pressures such as shown in table 3.

In view of the great fall in O_2 tension across the brain tissue capillary during O_2 breathing only a small portion of the cells adjacent to the arterial end of the capillary can be exposed to extremely high O_2 tensions, the remainder to smaller increases in pO_2 (5). It is probable that at 3.5 atm. inspired pO_2 the majority of brain cells never experience toxic levels of O_2 tension, the generalized convulsion representing a spread of excitation to normal cells from the relatively small number actually affected by high pO_2. The higher the arterial pO_2 the larger will be the number of cell components exposed to such tensions

TABLE 3. EFFECTS OF INSPIRED pO_2, AMBIENT PRESSURE AND CO_2 INHALATION UPON MEAN CEREBRAL CAPILLARY AND TISSUE pO_2

Condition		Inspired pO_2	Mean Capillary pO_2	Mean Brain pO_2
Gas breathed	Press.			
	Atm.	*mm Hg*	*mm Hg*	*mm Hg*
Air	1.0	160	60	X
Air	3.5	560	80	X + 20
O_2	1.0	760	130	X + 70
O_2	3.5	2660	780	X + 720
2% CO_2 in O_2	3.5	2600	1490	X + 1430

Approximate values for mean capillary pO_2 are estimated by integration method of Bohr (24) from measurements of the O_2 tension, content and capacity of arterial and cerebral venous blood, the Hb dissociation curve of Bock (20) and the solubility coefficient for O_2 in whole blood at 37°C (25). Data used for O_2 breathing at 1.0 atm. were obtained in a previous study (5).

An unknown mean brain tissue pO_2 during air breathing at sea-level is indicated by X. If the tissue O_2 diffusion coefficient does not decrease and/or the rate of tissue O_2 utilization increase the figures in the last column suggest the minimum rise in mean tissue pO_2 for each experimental condition.

before loss of O_2 lowers the capillary pO_2 to nontoxic levels. A slowing in the rate of blood flow through the capillaries would act in the reverse direction.

The results of these experiments suggest that CO_2 inhalation doubles the mean cerebral capillary pO_2. If the tension of O_2 capable of producing a toxic effect upon brain cells is actually fairly low, the observed elevation of mean capillary pO_2 by CO_2 may signify an exposure of many new cells to an increase in O_2 tension much in excess of that required to produce toxic effects. However, if the cellular pO_2 necessary for toxicity is normally high, the elevated capillary pO_2 may indicate only the exposure of an additional small proportion of the total brain cell population to the toxic O_2 level (fig. 1). It would be expected that at 2.0 atm. O_2, an inspired pCO_2 capable of doubling cerebral blood flow would produce a mean capillary pO_2 as great as that associated with O_2 breathing at 3.5 atmospheres. Whether central nervous system toxicity would develop at rest under these circumstances would shed some light on the question of the minimum tensions required for development of toxic symptoms.

Measurements of the electrical potential of the cerebral cortex in cats breathing O_2 at 40–75 psi gauge pressure have been made by Gersh *et al.* (27) and Sonnenschein *et al.* (28), using the polarigraphic technique of Davies and Brink (29). In each study a sudden rise in electrode potential to values 10–50 times the control level was observed, the rise usually just preceding the onset of convulsions. This 'spike' was normally of brief duration, the potential returning nearly to the control reading in spite of continued O_2 administration at the high ambient pressure. The relationship of these observations to our findings in the blood of men are not clear. In our studies during O_2 breathing no demonstrable rise in venous pO_2 has ever been found to occur until after the breathholding and exertion associated with an O_2 convulsion. Moreover, an elevation of venous pO_2 once produced by CO_2 administration has not proved transient, but remains high until inspired pCO_2 is lowered.

Relations of Increased Arterial pCO_2 to Variability in Latent Period of O_2 Toxicity. The foregoing discussion emphasized the remarkable elevation of brain pO_2 as an indirect result of arterial hypercapnia. Such an effect should be considered a possible accompaniment of O_2 breathing whether arterial pCO_2 is increased by rebreathing exhaled CO_2 from apparatus dead space, breathholding or other forms of inadequate alveolar ventilation, as well as by inhalation of exogenous CO_2. Hyperventilation with arterial hypocapnia should conversely decrease brain pO_2 by causing cerebral vasoconstriction (5, 30). Experiments indicating that in dogs the latent period of O_2 toxicity is greatly prolonged by hyperventilation were performed by Shaw *et al.* (2) and we have found it possible in men to abort signs of O_2 toxicity by over-breathing.

At 3.5 atm., equivalent to the pressure at about 82 feet of sea water, O_2 convulsions develop in men at rest after a latent period ranging from 10 to more than 120 minutes (31, 32). The considerable variability of O_2 tolerance among different individuals and even within the same individual at different times has been especially emphasized by Donald (32). The addition of 2% CO_2 to inspired O_2 in our experiments at 3.5 atm. markedly shortened the latent period of O_2 toxicity and almost eliminated variability among and within our subjects. It is quite possible that the normal variability in O_2 tolerance is prominently related to the well known ability of small changes in alveolar ventilation to produce considerable alterations of arterial pCO_2, with consequent changes in rate of cerebral blood flow.

Whether elevated blood pCO_2 or acidity contributes to the development of O_2 toxicity in any way excepting by an increase in exposure of brain tissue to high O_2 tensions cannot yet be finally decided. It is remotely possible that CO_2, in itself convulsant at inspired concentrations above 15% (33), may contribute directly to the development of O_2 toxicity at the cellular level. It should nevertheless be stressed that in the 30 years since it was first proposed by Gesell no direct, experimental evidence has been obtained to support the hypothesis that CO_2 is a specific etiologic factor in O_2 toxicity. Demonstration of the extreme sensitivity of brain capillary pO_2 to alterations in cerebral blood flow makes it unnecessary to invoke direct CO_2 effects to

account for the shortened latent periods of O_2 toxicity. The latter appear to us to be the indirect result of the cerebral vasodilatation normally associated with arterial hypercapnia.

SUMMARY

Addition of 2% CO_2 to O_2 inhaled at 3.5 atm. pressure in four subjects caused an average increase of internal jugular venous pO_2 of nearly 1000 mm Hg above the level found during the breathing of O_2 alone. The relationships of this finding to changes in brain pO_2 and to O_2 toxicity are discussed. It is proposed that an increased tension of inspired CO_2 shortens the latent period of O_2 toxicity, not by a direct action upon brain cells, but indirectly through a cerebral vasodilatation and the resulting rise in brain pO_2.

The authors wish to acknowledge the continued encouragement and advice of Dr. Carl F. Schmidt, the considerable clinical assistance provided by Dr. F. A. Freyhan of the Delaware State Hospital, and the skillful technical assistance of Mrs. Betty Hanley.

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