EFFECT OF P_{CO_2} ON TOLERANCE TO SEVERE HYPOXIA IN DOGS

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VAN LIERE and STICKNEY¹⁰⁾ state in their review that CO_2 enhances the tolerance of the organism to hypoxia by increasing cerebral blood flow and arterial oxygen tension. Although a number of experiments have previously been conducted on the P_{CO_2} effect on hypoxia tolerance, their results are conflicting; e. g., HALL and HALL³⁾ and SHOJI et al.⁸⁾ reported beneficial effects on human subjects: on the other hand, OTIS et al.⁶⁾ were unable to find such an advantage. These investigations were performed by adding CO_2 to hypoxic air, and the tolerance to hypoxia was evaluated by the effect on the loss of consciousness. In this experiment the P_{O_2} -ventilation response curves at varying P_{CO_2} levels were investigated with anesthetized dogs, and the P_{O_2} at the peak ventilation in each response curve was taken as an indicator of the hypoxia tolerance.

METHODS

Sixty-one mongrel dogs were used in the experiments. The dog was anesthetized with sodium pentobarbital, injected (30 mg/kg initial dose) intramuscularly. Additional doses of the same anesthetic (20-25 mg) were given intermittently through a branch of the femoral vein to keep a light but uniform anesthesia. The trachea was cannulated in a supine position and connected to a respiratory valve. After a control period, the dog rebreathed air of 14-16 l which was stored in a Benedict-Roth respirometer. A bypass containing CO_2 absorber was set in the rebreathing circuit. Experiments were performed in the following three different series; Series A: Hypocapnic hypoxia; Series B: Normocapnic hypoxia and Series C: Hypercapnic hypoxia. In series A, all of the expired air was introduced into the bypass, so that the experimental animal was submitted to an increasing degree of hypocapnia and hypoxia as the time lapsed. In series B, alveolar P_{CO_2} , P_{ACO_2} , was maintained at a control level by adjusting the volume of the expired air to be introduced into the bypass. This was performed by monitoring an infra-red CO_2 analyzer (BECKMAN LB-1). In series C, rebreathing was conducted without introducing the expired air to the bypass, and thus hypercapnia was produced in increasing degree with the development of hypoxia. Series A and C were performed with most of dogs and series A, B and C were performed on the

Received for publication February 23, 1965

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remaining dogs.

Ventilatory minute volume was estimated from the tracing on respirometer and expressed as a ratio of observed ventilation to the control value of ventilation (VR). As the level of alveolar P_O, P_{AO}, was gradually lowered by rebreathing, ventilation increased and reached a maximum at an extremely low P_O level. Then, the respiration began to decrease; gradually in normocapnic and hypercapnic hypoxia, while rapidly in hypocapnic hypoxia. Thus, the experiment of hypocapnic hypoxia inevitably resulted in death of the animal unless some restorative measures for the animals were immediately instituted. Consequently, the experiment had to be stopped when the ventilation began to decrease. The P_{AO} at maximum ventilation was defined as a critical point (C.P.) for tolerance to hypoxia. Alveolar air was endtidally collected into a 2 ml oiled syringe through a narrow vinyl tube placed in the trachea and was analyzed by the Scholander method. Blood was drawn into a syringe through an indwelling needle which was inserted into a branch of the femoral artery. To prevent glycolysis and blood clotting, a dead space of the syringe was filled with heparin-fluoride solution (heparin 10 mg+fluoride 40 mg/ml). The blood used for Hb estimation was separately collected in a test tube containing a mixture of dry ammonium and potassium oxalate. The blood sample was used for the following determinations: pH by a glass electrode⁷⁾, Hb by cyanment-Hb method⁸⁾, oxygen content by the manometric method of VAN SLYKE and NEIL, and arterial oxygen pressure, P_{aO}, by the Beckman gas analyzer (Model 160). The P_{aO} analyzer was calibrated by the water equilibrated with the gas of known P_O at body temperature. Admitting that 1 gm. of Hb combines with 1.34 ml. of oxygen, the oxygen capacity of the blood was estimated from its Hb concentration. From the oxygen capacity and content of the arterial blood, its oxygen saturation was calculated. Both alveolar air and arterial blood were collected just at the end of each one minute period during which the ventilation was measured successively. To economize the quantity of blood in one sampling, oxygen saturation, blood pH, and oxygen pressure were measured separately with different blood samples collected from the respective animals. Control ventilation of each experimental animal was maintained as constant as possible in all series of experiment by injected the minimum necessary amount of anesthetic. This was also conducted by continuously referring to the P_{ACO} level read from an infra-red CO₂ analyzer.

RESULTS

The preliminary experiment showed that, when repeating the experiment with short interval in the same series, the magnitude of ventilation decreased successively with a relatively small fluctuation of P_{AO} at C.P. (a few mmHg). Decreased ventilation at C.P. was considered to be due to the reduced sensitivity of the respiratory system to hypoxia, resulting from severe hypoxia successively introduced. Therefore, in the present experiments, a recovery period of about two hours was interposed between the successive experiments; during the first one hour of experiment, the ventilation was maintained 1.5 times as large as that in the resting period by administering oxygen air rich (about 60% O₂) through a positive pressure ventilator pump; during the second hour, the dog was subjected to spontaneous breathing of room air. By this means, the P_O-ventilation response curve could be obtained reproducibly without a significant change in the maximal ventilation and P_{AO} at C.P. If this procedure

FIG. 1. P_{aO_2} -ventilation response curve obtained from six dogs in three experimental series. An arrow on each response curve shows the point of maximum ventilation, and this point is defined as C.P. (Critical Point).

Δ : Hypocapnic hypoxia, $\circ$: Normocapnic hypoxia, $\bullet$: Hypercapnic hypoxia.

was not taken, the inhalation of room air for at least six hours should be required to attain a recovery of the sensitivity of the respiratory system to the normal level. By applying the above procedure, the sequence of the three different series of experiment could be performed at will. Usually, however, the present experiment was conducted in the order of series A, B and C. Each of those series of experiments lasted for 25 to 50 minutes.

FIG. 1 shows the results obtained from six dogs, each of which was subjected to the three series of experiments. The ventilation ratio was plotted against the P_{AO₂}. Open triangles, open circles and solid circles represent the data of experiments of series A, B and C respectively. The arrow on each response curve indicates the maximum ventilation i.e., C.P. It is obvious that the P_{O₂}-ventilation response curve tends to shift to the right with an increasing P_{ACO₂} level and the magnitude of ventilation depends on the P_{ACO₂} level, i.e., the higher the P_{ACO₂}, the larger is the ventilation at C.P. Consequently, the magnitude of maximum ventilation is the largest in hypercapnic hypoxia and the smallest in hypocapnic hypoxia; the value of P_{AO₂} at C.P. is the lowest in hypocapnic hypoxia and the highest in hypercapnic hypoxia. The results of the experiments on six dogs were also summarized in TABLE 1, showing the P_{AO₂} and P_{ACO₂} level, and the VR at C.P. The VR at C.P. in the table are represented as percentage of that obtained by the experiment normocapnia which is taken as 100%. The average values of P_{AO₂} at C.P. in six dogs were 18.6 mmHg in the hypocapnia series, 24.4 mmHg in the normocapnia series, and 35.7 mmHg in the hypercapnia series. The figures in the

TABLE 1.

P_{AO₂}, P_{ACO₂} and VR at C.P. in hypocapnic, normocapnic and hypercapnic hypoxia. The VR obtained from the normocapnia series was taken as 100%. Figures on the bottom line show the average values of P_{AO₂} with S.D., obtained from all of the present experiments. Figures in parentheses represent the number of experiment.

Dog Weight, kg	Hypocapnic Hypoxia			Normocapnic Hypoxia		Hypercapnic Hypoxia		
	P _{AO₂} , mmHg	P _{ACO₂} , mmHg	VR %	P _{AO₂} , mmHg	P _{ACO₂} , mmHg	P _{AO₂} , mmHg	P _{ACO₂} , mmHg	VR %
11.7	13.6	17.9	63.9	19.5	32.8	29.8	76.6	165.9
12.8	17.3	17.4	61.3	24.6	34.3	39.6	63.7	125.6
13.3	19.2	18.6	66.9	30.7	41.2	39.9	67.5	116.2
9.4	20.3	14.1	60.4	24.1	36.3	45.0	75.3	134.4
11.7	18.7	15.6	66.7	21.5	44.2	31.8	79.6	185.7
13.8	22.2	19.6	58.3	26.0	42.6	28.0	78.0	139.7
Mean	18.6	17.2	62.9	24.4	38.6	35.7	73.5	144.6
Mean P _{AO₂}	19.9±3.49 (46)			23.6±3.97 (57)		32.6±6.64 (32)		

bottom line are the average values of P_{AO_2} with S.D., obtained from all the experiments performed with 32-57 dogs: 19.9 ± 3.49 mmHg in hypocapnia series, 23.6 ± 3.97 mmHg in normocapnia series and 32.6 ± 6.64 mmHg in hypercapnia series. The numbers of the experiments performed are shown in parentheses. It can be seen from TABLE 1 that P_{AO_2} at C. P. in hypercapnic hypoxia is more than 10 mmHg higher than that in hypocapnic hypoxia. P_{ACO_2} at C. P. can also be seen to be about 20 mmHg in hypocapnic hypoxia, and 80 mmHg in hypercapnic hypoxia.

TABLE 2 shows the P_{AO_2} and arterial oxygen saturation at C. P. obtained from six dogs in the hypocapnic and hypercapnic series. The values of P_{AO_2} in this table except for the dog weighing 7.0 kg, show similar tendencies to those in TABLE 1. As seen from TABLE 2, despite of the marked difference (over than 10 mmHg) of P_{AO_2} , arterial oxygen saturation at C. P. in the two series did not differ significantly; ranging 20-25% in both series. The average

TABLE 2.
Alveolar P_{O_2} , P_{AO_2} , and arterial oxygen saturation, So_2 , at C. P. in hypocapnic and hypercapnic hypoxia.

Dog Weight, kg	P_{AO_2} , mmHg		So_2 , %	
	Hypocapnic Hypoxia	Hypercapnic Hypoxia	Hypocapnic Hypoxia	Hypercapnic Hypoxia
14.2	20.4	30.1	23.7	21.6
7.0	34.5	42.3	25.7	20.4
11.5	19.5	35.4	20.8	24.8
10.5	21.7	32.8	24.3	24.9
10.5	20.1	31.8	20.7	22.8
11.5	20.6	31.2	21.0	22.0
Mean			22.7	22.8

TABLE 3.
Alveolar P_{O_2} , P_{AO_2} , arterial P_{O_2} , P_{aO_2} , and alveolar-arterial P_{O_2} difference, $A-aDO_2$, at C. P. in hypocapnic and hypercapnic hypoxia.

Dog Weight, kg	Hypocapnic Hypoxia			Hypercapnic Hypoxia		
	P_{AO_2} , mmHg	P_{aO_2} , mmHg	$A-aDO_2$, mmHg	P_{AO_2} , mmHg	P_{aO_2} , mmHg	$A-aDO_2$, mmHg
9.5	22.6	15.0	7.6	32.3	25.5	6.8
11.5	21.9	19.2	2.7	30.1	25.9	4.2
12.0	15.3	10.8	4.5	27.0	23.9	3.1
9.8	15.6	11.9	3.7	35.8	31.5	4.3
Mean	18.9	14.3	4.6	31.3	26.7	4.6

saturation was 22.7% in the hypocapnia experiment and 22.8% in the hypercapnic experiment. Although the dog weighing 7.0 kg exhibited an especially high P_{AO₂} level as compared to those in other dogs, the oxygen saturation was found to be 25.7% and 20.4% in both series. From these results, the respiratory depression observed in the present experiment seems to be closely associated with the level of arterial oxygen saturation which has decreased lower than a certain value at C.P. (22.7%, in TABLE 2).

TABLE 3 shows the results of P_{AO₂} and P_{aO₂} at C.P. obtained from four dogs in hypocapnic and hypercapnic hypoxia. The alveolar-arterial oxygen difference, A-aD_{O₂}, at C.P. was maintained approximately constant, and its mean value was 4.6 mmHg P_{O₂} in both series of experiments.

DISCUSSION

P_{ACO₂} in hypercapnic hypoxia was 73.5 mmHg on an average (TABLE 1). It is generally known that P_{CO₂}, at its high level, exerts narcotic effects on the respiratory system. GRAY²⁾ estimated that the narcotic effects of CO₂ became increasingly pronounced when it is above 10% in the inspired air. From a rebreathing experiment in dogs, UENO³⁾ recently reported that a peak of ventilation was observed at 80-100 mmHg P_{ACO₂}. The narcotic effect observed in his experiment was extremely weak at a P_{ACO₂} level of about 80 mmHg. Therefore, it was assumed in the present experiment that the depression of ventilation observed just after C.P. in hypercapnic hypoxia was not due to the narcotic effect of P_{ACO₂}.

It is obvious that P_{AO₂} at C.P. in hypoxia depends on P_{ACO₂} as seen from FIG. 1 and TABLE 1. The present experiment shows that CO₂ does not contribute to increasing the tolerance to hypoxia.

In spite of the marked difference of P_{AO₂} at C.P. between the two series, their oxygen saturation at C.P. did not differ significantly (average: 22.7%, TABLE 2). The difference in P_{AO₂} at C.P. between the two series mentioned above could be explained by the Bohr effect on the oxygen dissociation curve. At a given level of oxygen saturation, the higher the P_{CO₂} level, the higher the P_{O₂} level in hypercapnic hypoxia; the lower the P_{CO₂} level, the lower the P_{O₂} level in hypocapnic hypoxia.

From the value of arterial pH and P_{aO₂} obtained at C.P. in hypocapnic and hypercapnic hypoxia, arterial oxygen saturation was calculated as follows, by adopting the coefficient of the Bohr effect (0.5 log P_{O₂}/ΔpH)⁴⁾ and the oxygen dissociation curve at pH 7.4 reported in dogs¹⁾.

	Mean art. pH	Mean P _{AO₂} mmHg	Mean S _{O₂} %
Hypocapnic hypoxia (12)	7.58	19.5	about 25
Hypercapnic hypoxia (8)	7.07	32.8	about 27.5

In this calculation, P_{aO_2} was inferred from P_{AO_2} by subtracting $A-aDO_2$ (4.6 mmHg, TABLE 3). Figures in the above parentheses represent the numbers of estimations. The average value of oxygen saturation, SO_2 %, calculated was about 25% in hypocapnic hypoxia and 27.5% in hypercapnic hypoxia. These values are nearly equal with that experimentally obtained (TABLE 2). Therefore, it has further been confirmed that an oxygen saturation of 20-25%, experimentally obtained is in the critical level for depression of the respiratory system of dogs. Whether or not this saturation level is associated with the loss of consciousness used as an indicator for the human experiment is not possible to estimate. However, the present experiment suggests that the minimum amount of O_2 required to sustain the activity of the respiratory system is mainly determined by the oxygen saturation of the arterial blood rather than by P_{aO_2} .

SUMMARY

The PO_2 -ventilation response curves in acute hypoxia, obtained by the rebreathing method in dogs, were determined in three series; hypocapnic hypoxia, normocapnic hypoxia and hypercapnic hypoxia. The alveolar PO_2 at maximum ventilation was taken as is critical point (C.P.) for the tolerance to hypoxia.

1. The average values of P_{AO_2} at C.P. were 19.9 (± 3.49) mmHg during hypocapnic hypoxia, 23.6 (± 3.97) mmHg during normocapnic hypoxia and 32.6 (± 6.64) mmHg during hypercapnic hypoxia.
2. In spite of a marked difference in alveolar PO_2 , arterial oxygen saturation at C.P. in hypocapnic hypoxia and hypercapnic hypoxia was of a similar magnitude, and remained at 20 to 25% (an average: 22.7%). It seems most probable that a depression of respiration does not occur as long as the arterial oxygen saturation is above 22.7%.
3. The author explained these differences in P_{AO_2} at C.P. through the three series of experiments as due to the Bohr effect.

The author wishes to thank to Dr. K. SAITO for his advice, to H. YACHI for his valuable technical assistance throughout this experiment, and to Dr. Y. HONDA for his criticism and reading the manuscript.

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