EFFECT OF PROLONGED HYPERVENTILATION ON THRESHOLD P_{CO_2} FOR RESPIRATORY SYSTEM OF DOGS

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A number of investigations¹⁻¹⁰⁾ have demonstrated that prolonged hypocapnia from various means caused readjustment of the respiratory response to CO_2 , i. e., an increased sensitivity slope of the P_{CO_2} -ventilation response curve as well as decreased threshold P_{CO_2} (hereafter defined as P_{TCO_2}) for respiration. There still seems to remain some uncertainty in the numerical values of P_{TCO_2} , because P_{TCO_2} presented heretofore was inferred by extrapolating stimulus-response curve to P_{CO_2} axis.

By taking phrenic nerve discharges as a direct indicator of respiratory activity, it was shown in the preceding paper¹¹⁾ that the P_{TCO_2} is obtainable with small experimental error (± 0.48 mm Hg of S.D.). Therefore, further observations were made in the present experiment to get exact levels of P_{TCO_2} during the course of passive hyperventilation in dogs.

METHODS

Nine dogs weighing 7.5-13.2 kg were used as experimental animals. Anesthesia was initially given by intramuscular injection of 30 mg per kg of sodium pentobarbital. Additional doses of the same anesthetic were given once every 2 or 3 hours to keep a light but uniform anesthesia. After exposing the first branch of the phrenic nerve in the cervical region in a supine position, the experimental animal was ventilated by a positive pressure ventilator pump with room air and was immobilized with Flaxedil. The general outline of the experimental setup, which was also presented in our previous paper¹¹⁾, is shown in FIG. 1. The exposed phrenic nerve was severed and its centrifugal discharges were picked up with bipolar silver electrodes. The action currents were recorded by a two beam cathode-ray oscilloscope, an inkwriter, and listened to with a loudspeaker.

The alveolar P_{CO_2} was continuously recorded in the expired air by an infra-red CO_2 analyzer (Beckman LB-1) which was connected to a small tube inserted in a tracheal cannula. For pH and CO_2 content measurement, 1 ml of blood was drawn into a syringe from an indwelling needle which was placed at a branch of the femoral artery. A

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FIG. 1. Schematic representation of general experimental setup.

small amount of heparin solution (10 mg/ml) with sodium fluoride (added 40 mg to 1 ml heparin solution) was contained in the dead space of the sampling syringe to prevent glycolysis and blood clotting. From an indwelling needle inserted in a branch of the femoral vein, Flaxedil and pentobarbital were introduced as necessary. The pH of arterial blood was measured by our own glasselectrode assembly¹²⁾, and plasma CO_2 content was analyzed by Copp-Natelson's apparatus¹³⁾. Then arterial PCO_2 and plasma bicarbonate were calculated by means of the Henderson-Hasselbalch equation ($\text{pK}' = 6.10$).

To record respiratory movement electrically, we used a rubber tube containing a saturated ZnSO_4 solution and Zn electrodes as one arm of a wheatstone-bridge. This was placed on the thorax and its resistance change due to respiratory movements was recorded.

The PTCO_2 for the respiratory system was detected in the following manner: The level of alveolar PCO_2 was altered arbitrarily by varying the amount of ventilation; as ventilation increased, alveolar PCO_2 decreased and it was followed by a gradual suppression of phrenic activity. When phrenic nerve discharges disappeared, alveolar PCO_2 was decided to be the threshold value for the respiratory system. However, a delay of 1-2 minutes was required to attain a steady state of phrenic activity at any given level of alveolar PCO_2 . Taking this time delay into consideration, the PTCO_2 was decided. Simultaneously with this a blood sample was drawn from the femoral artery to measure pH and plasma CO_2 . The PTCO_2 of the control period was at first observed before the onset of hyperventilation. The degree of hyperventilation was three times greater than that at which the control PTCO_2 was observed, and maintained for 4-8 hours. In order to get the PTCO_2 during the course of hyperventilation, ventilation was reduced to the control level at every two hours and the PTCO_2 was again examined by the method described above. The time required for the determination of PTCO_2 at these occasions was approximately 20 minutes.

RESULTS

An illustration of gradual disappearance of phrenic nerve discharges accompanied by lowering of alveolar P_{CO_2} is shown in FIG. 2. In order to ascertain constancy of the control P_{TCO_2} , the P_{TCO_2} was repeatedly examined for 8 hours in dogs under normal ventilation. The result is shown in FIG. 3. Average values of the alveolar P_{TCO_2} obtained on two dogs were $31.7 (\pm 0.37)$, $28.0 (\pm 0.74)$ mmHg, respectively (figures in parentheses are S.D.). As it is obvious in FIG. 3, the variation of P_{TCO_2} was within 1-2 mmHg during 8 hours observation.

The control values of P_{TCO_2} , arterial pH, and plasma bicarbonate simul-

FIG. 2. An illustration for disappearance of phrenic nerve discharges due to gradual lowering of alveolar P_{CO_2} .

FIG. 3. Serial estimation of P_{TCO_2} on two dogs maintained in a normocapnic condition during 8 hours.

taneously estimated, are seen in the second line of TABLE 1. These values were the averages obtained from 9 dogs before the experimental animal was put in a state of forced hyperventilation. As is seen from the standard deviation of these figures, in parentheses, considerable individual differences were found in these estimations.

Average values of arterial pH, plasma bicarbonate, and arterial and alveolar P_{CO_2} , observed in 9 dogs during the course of forced passive hyperventilation, are presented in the third line of TABLE 1. These observations were made just before each P_{TCO_2} determination. During the first two hours in hyperventilation, arterial and alveolar P_{CO_2} and plasma bicarbonate were remarkably decreased by the amount of 18.9 mmHg, 20.4 mmHg, and 6.7 mM/L from the control values respectively, while arterial pH was elevated from 7.42 to 7.63. Thereafter, these values decreased by small amounts over the remainder of the

TABLE 1
Arterial pH, plasma bicarbonate and P_{CO_2} observed every two hours in the course of 8 hours hyperventilation in comparison with the values obtained at threshold condition before hyperventilation.
Figures in parentheses represent S. D.

Duration of hyperventilation	Art. pH	Plasma $BHCO_3$	Art. P_{CO_2}	Alv. P_{CO_2}
Threshold condition before hyperventilation	7.42 (± 0.069)	mm/L 20.0 (± 1.31)	mmHg 32.1 (± 5.07)	mmHg 30.6 (± 5.13)
2 hours	7.63 (± 0.062)	13.3 (± 2.10)	13.2 (± 2.47)	10.2 (± 2.00)
4 hours	7.62 (± 0.089)	11.9 (± 1.61)	12.0 (± 1.52)	9.1 (± 2.24)
6 hours	7.62 (± 0.080)	10.5 (± 2.35)	10.4 (± 1.94)	7.9 (± 1.44)
8 hours	7.57 (± 0.095)	10.6 (± 3.23)	12.3 (± 5.01)	7.7 (± 1.51)

FIG. 4. An illustration of alveolar P_{TCO_2} drop observed in the course of 8 hours hyperventilation.

experiment. It must be noted that the degree of passive hyperventilation was so great that alveolar and arterial P_{CO_2} were lowered to about 10 mmHg.

An illustration of changes of the alveolar P_{TCO_2} observed in the course of this experiment is shown in FIG. 4. It is obvious that the P_{TCO_2} remarkably decreases lower than the control value after 4 to 8 hours forced ventilation. The relationship between arterial and alveolar P_{TCO_2} and duration of hyperventilation observed in 9 dogs are presented in FIGS. 5 and 6. The P_{TCO_2} was

FIG. 5. Relationship between P_{TaCO_2} and duration of passive hyperventilation. Solid line represents regression line. P_{TaCO_2} ; arterial P_{TCO_2} . Points with same symbol were obtained from same dog.

FIG. 6. Relationship between P_{TACO_2} and duration of passive hyperventilation. Solid line represents regression line. P_{TACO_2} ; alveolar P_{TCO_2} .

decreased in approximately linear relation to the period imposed hyperventilation though there were considerable individual differences in degree of lowering. The correlation coefficients (r) were obtained as -0.69 for FIG. 5 and -0.65 for FIG. 6, and regression lines were expressed as following;

$$P_{TaCO_2} = -1.4 H + 29.3 \quad \text{for FIG. 5 and}$$

$$P_{TaCO_2} = -1.2 H + 28.7 \quad \text{for FIG. 6.}$$

Where P_{TaCO_2} and P_{TACO_2} are the arterial and alveolar P_{TCO_2} , and H is duration of hyperventilation in hour.

Arterial pH at the threshold condition in hyperventilation averaged 7.42 (± 0.062) which was nearly equal to that of the control period. Therefore, as is seen from the Henderson-Hasselbalch equation, this means that lowering of the P_{TCO_2} is derived from a decrease in plasma bicarbonate. This relationship between arterial P_{CO_2} and plasma bicarbonate in the threshold condition is demonstrated in FIG. 7. Plasma bicarbonate decreased in proportion to lowering of arterial P_{TCO_2} . The correlation coefficient was 0.79 and the regression line was calculated to be $P_{TaCO_2} = 1.4[BHCO_3]_T + 3.3$. Where $[BHCO_3]_T$ is plasma bicarbonate content at the threshold condition.

FIG. 7. Relationship between arterial P_{TCO_2} and plasma bicarbonate at the threshold condition. Solid line represents regression line. P_{TCO_2} ; threshold P_{CO_2} of arterial blood. $[BHCO_3]_T$; plasma bicarbonate at the threshold condition.

DISCUSSION

Since the first suggestion for decreased P_{TCO_2} in prolonged hypoxic hyperventilation to simulated altitude by NIELSEN¹⁾, several studies have been made

in confirming P_{TCO_2} decreasing by passive hyperventilation³⁻⁵⁾ and by acclimatization to high altitude^{2,6,8-10)}. These authors, however, usually found a decrease of P_{TCO_2} after more than 1 day hypocapnia. The present experiment has shown this occurrence within 8 hours hyperventilation and has presented the average P_{TCO_2} lowering of 1.2-1.4 mmHg per every 1 hour. Perhaps the reason for this is because such a strong hyperventilation, in which the alveolar-arterial P_{CO_2} of the experimental animals was reduced to about 10 mmHg, was used in our experiment.

The explanation for this P_{TCO_2} lowering, as well as increased sensitivity to CO_2 in prolonged hypocapnia, has been searched for by several investigators. NIELSEN et al.⁷⁾ put prime importance on increasing centrogenic drive from the chemosensitive cells of the respiratory center. BROWN^{5,14)} emphasized the decreased buffering capacity of the brain cells, whereas RAHN and OTIS²⁾ have simply ascribed it to the decrease of plasma bicarbonate. Our finding shows the significant relationship between plasma bicarbonate and P_{TCO_2} in FIG. 7.

SUMMARY

By observing phrenic nerve discharges in dogs, the threshold P_{CO_2} (P_{TCO_2}) for the respiratory system was examined during the course of passive hyperventilation lasting for 4-8 hours.

1. The degree of hyperventilation was so strong as to decrease alveolar P_{CO_2} to about 10 mmHg.
2. The P_{TCO_2} was lowered with lapse of time of hyperventilation. The regression line for the relationship between arterial (P_{TaCO_2}) and alveolar (P_{TACO_2}) P_{TCO_2} and duration of hyperventilation in hour (H) were: $P_{TaCO_2} = -1.4H + 29.3$, and $P_{TACO_2} = -1.2H + 28.7$.
3. The regression line for relationship between arterial P_{CO_2} and plasma bicarbonate ($[BHCO_3]$) at the threshold condition was; $P_{TaCO_2} = 1.4[BHCO_3]_T + 3.3$.
4. In spite of decreasing the P_{TCO_2} , arterial pH at the threshold condition was nearly kept constant.

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