Changes in Response to Inhalation of CO_2 Before and After 24 Hours of Hyperventilation in Man[1]

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IN STUDIES ON THE EFFECTS of prolonged periods of hyperventilation in human subjects, it was observed that after 24 hours of hyperventilation in a body respirator subjects not only failed to show apnea, but spontaneously overventilated for several hours. This reaction is comparable to the phenomenon of continued overventilation following descent to sea level in persons who have become acclimatized to high altitude (1). On the basis of calculations utilizing the equations derived as part of his multiple factor theory of respiratory regulation (2), Gray has suggested that this continued increased ventilation is due to a change in sensitivity of the respiratory center to arterial pCO_2 (3). In an attempt to help elucidate this question, respiratory ventilation responses to 2.5 per cent, 5 per cent and 7.5 per cent CO_2 in oxygen were determined before and after 24 hours of hyperventilation.

EXPERIMENTAL PROCEDURE

Three young, healthy, male medical students were ventilated at a rate approximately two to three times normal for 24 hours in a body respirator.[2] Two days prior to the day of hyperventilation, subjects were placed on a diet consisting of University of Minnesota Hospitals diet II (4), milk and water *ad libitum*. This diet was maintained until 24 hours after completion of the hyperventilation period. On each of the two days prior to the experimental period the subject came to the laboratory for ventilation studies. After the subject had rested in the supine position for 30 minutes, respiratory minute volume and respiratory rate were determined with the subject breathing 100 per cent oxygen, 2.5 per cent CO_2 in oxygen, 5 per cent CO_2 in oxygen and 7.5 per cent CO_2 in oxygen, in that order. Resting ventilation and CO_2 response determinations were repeated one hour after the 24 hours of hyperventilation, and at daily intervals for several days, or until the response had returned to the control level. Minute volumes were measured

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[2] The respirator employed was the commercial model of the J. H. Emerson Company, to whom we are indebted for its loan.

by the open circuit method using a modified, tightly fitting A-15 Army aviation mask and collecting the exhaled air in a 100-liter balanced spirometer. Subjects noticed no resistance to breathing with this system except at very high rates of flow, i.e. 60 to 80 liters per minute. Normal resting minute volumes were measured by allowing the subject to breathe 100 per cent oxygen from a 5-liter rubber bag which was continuously filled from a cylinder of compressed oxygen. It has recently been shown that changing normal human subjects from air to 100 per cent oxygen at sea level has little or no effect on ventilation rate (5). Ventilation response to CO_2 was determined using the same apparatus and filling the bag from a cylinder containing the proper mixture of CO_2 and oxygen.

Blood samples were drawn from either the brachial or femoral artery before each series of ventilation determinations. Precautions were observed to prevent exposure of the blood to air, and .01 ml. of sodium heparin solution per ml. of blood to be drawn was used as an anticoagulant. No correction has been made in the data for this dilution. Immediately after drawing the blood, one ml. was introduced anaerobically into a specially constructed glass electrode pH meter maintained at 38° C. and the pH was determined. This instrument uses the circuit described by Burr *et al* (6). Plasma from 10 ml. of blood was separated by centrifugation under oil which had been previously equilibrated with a mixture of gas containing CO_2 at a tension of 40 mm. Hg at 38° C., and the plasma CO_2 content was determined with the Van Slyke manometric apparatus.

Carbon dioxide capacity (T_{40}) was similarly determined on plasma separated from blood which had been equilibrated for 30 minutes at 38° C. with a gas mixture containing CO_2 at a pressure of 40 mm. Hg and oxygen at a pressure of approximately 150 mm. Hg.

RESULTS

Respiratory minute volumes, blood pH, plasma CO_2 content and CO_2 capacity as determined before, during and after 24 hours of hyperventilation are presented in table 1. Arterial plasma CO_2 content decreased an average of 8.9 vols. per cent in one hour of hyperventilation and an average maximum of 18 vols. per cent during the 24-hour period. This represents a reduction of 14.2 per cent and 29 per cent of the average control values, respectively. With this fall in CO_2 content, arterial pH increased an average of 0.10 pH units in one hour, 0.16 pH units in 12 hours, and 0.12 pH units in 24 hours as compared with the average control arterial blood pH.

Plasma CO_2 capacity showed no consistent change in the first hour of hyperventilation, then fell steadily until sometime between one hour and 24 hours after artificial hyperventilation was discontinued. The lowest value recorded at one hour after hyperventilation, averaged 8.8 per cent below

the pre-hyperventilation level. Twenty-four hours later CO_2 capacity had increased, but was still 6.7 per cent below the control average.

It should be pointed out that the minute volumes measured with the subject in the respirator were sample values and not continuous measurements of ventilation over the 24-hour period. The ventilation volume depends upon several factors in addition to the pressure gradients set up by the respirator.[3] *Subject W. F.* exhibited marked signs of tetany when, in the initial setting of the respirator pressure gradient, his ventilation ratio

TABLE 1. RESPIRATORY MINUTE VOLUME AND PLASMA CO_2 CONTENT, pH, AND CO_2 CAPACITY (T_{40}) BEFORE, DURING AND AFTER 24 HOURS OF HYPERVENTILATION

SUBJECT	*H. B.*				*W. F.*				*C. B.*			
	Minute Vol.	Plasma			Minute Vol.	Plasma			Minute Vol.	Plasma		
		CO_2	pH	T_{40}		CO_2	pH	T_{40}		CO_2	pH	T_{40}
	l.	*vol. %*		*vol. %*	*l.*	*vol. %*		*vol. %*	*l.*	*vol. %*		*vol. %*
Before hypervent...	6.9	59.9	7.40	59.8	7.7	64.4	7.36	64.5	7.8	59.2	7.36	62.7
1 hr. hypervent.....	14.3	50.8	7.51	63.3	12.3	56.5	7.42	60.4	26.5	49.7	7.50	64.0
12 hr. hypervent....	19.5	48.7	7.52	62.9	12.7	40.5	7.56	61.1	25.0	48.7	7.52	59.0
24 hr. hypervent....	18.7	44.0	7.50	57.2	17.0	45.0	7.47	59.6	21.1	44.9	7.52	59.0
1 hr. after hypervent.....	10.2	50.5	7.42	56.4	6.7	53.4	7.37	57.9	9.1	50.6	7.36	56.2
24 hr. after hypervent.....	7.1	50.1	7.36	56.8	6.9	58.3	7.37	60.0	7.0	51.2	7.40	57.6

exceeded 2 for any length of time. As a result he probably was overventilated less than the other 2 subjects. *Subject H. B.* was uncomfortable in the respirator and slept little or none during the 24 hours.

Table 2 gives normal resting ventilation and ventilation response to the three mixtures of CO_2 in oxygen before and after 24 hours of hyperventilation. Ventilation ratio is expressed as the ratio of minute volume to the resting minute volume breathing oxygen before hyperventilation. The response of *subjects H. B.* and *C. B.* before hyperventilation fall within the normal range as reported by Peabody (7), but after 24 hours of overventilation the responses of these 2 subjects were markedly elevated. The control response of *W. F.* is somewhat below Peabody's range of normals and following the stay in the respirator he showed an increased response only on the highest concentration of CO_2 used. This increase in response, however, continued for 72 hours.

[3] It was observed, for example, that *subject C.B.'s* respiratory minute volume fell markedly during sleep. Attention was called to this phenomenon by the occurrence of laryngeal stridor when this subject fell asleep. By using a mask that allowed the subject to sleep while ventilation records were being made, it was demonstrated that while asleep he was being ventilated very little in excess of his normal resting rate, regardless of the pressure differential being imposed by the respirator. The mechanism of this closure of the airway is entirely unknown. It became necessary to keep *subject C.B.* awake during the remaining 18 hours of the time in the respirator in order to insure that he was being hyperventilated.

Figure 1 presents stimulus response curves for the three subjects in which calculated alveolar pCO_2 is plotted against the alveolar ventilation ratio. Although data for *H. B.* breathing 7.5 per cent CO_2 are included in table 2, they have been omitted from figure 1. It was difficult to obtain reliable values on this subject breathing 7.5 per cent CO_2 since he suffered headache and respiratory distress when he remained on this mixture long enough to reach a steady state.

DISCUSSION

It is apparent from the data presented that a 24-hour period of hyperventilation in man produces a state of increased responsiveness of the respiratory control mechanism to carbon dioxide. The change in the response to CO_2 in *subjects H. B.* and *C. B.* is seen most clearly when the alveolar pCO_2 is plotted against the alveolar ventilation ratios. In order to treat the data

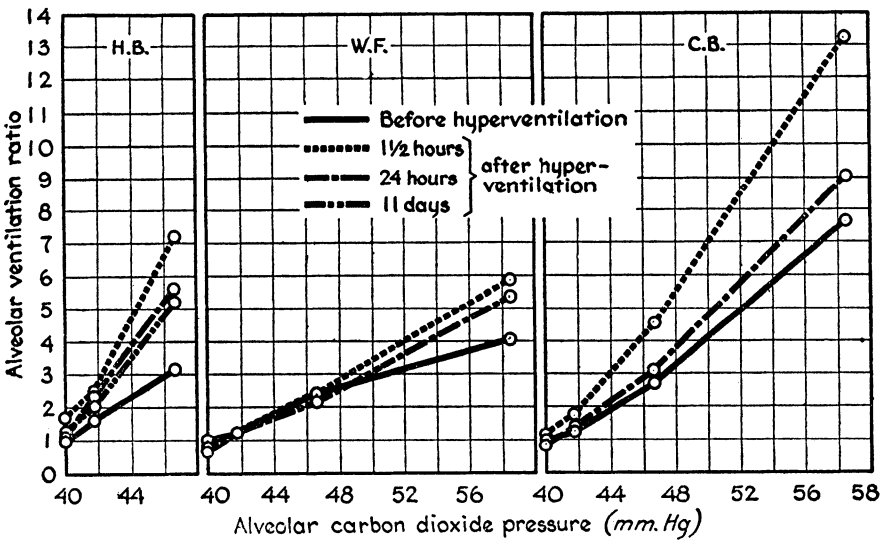

Fig. 1. ALVEOLAR VENTILATION RESPONSES to increasing alveolar pCO_2 before and after 24 hours of hyperventilation.

in this fashion, an estimate of alveolar ventilation was made by assuming a dead space of 150 cc., using the determined respiratory rate and correcting the total ventilation per minute accordingly. Alveolar pCO_2 at steady state, breathing the various CO_2 mixtures, was calculated by means of Gray's equation 23 (3).[4] These data are presented as stimulus-response curves in figure 1.

It is apparent that the slopes of the curves at $1\frac{1}{2}$ hours and 24 hours

[4] $\frac{40 + 7FCO_2}{pCO_2 - 713\ FCO_2} = 0.4p\ CO_2 - 15$ in which F CO_2 is the fraction of CO_2 in inspired air and pCO_2 is alveolar CO_2 tension.

after hyperventilation for *C. B.* are steeper than the slopes of the curves obtained before hyperventilation. Within 48 hours the response of this subject to CO_2 had returned to normal. The same kind of change can be seen in the response curves of *subject H. B.*, but in this case the greater increase in response to a given increase in pCO_2 is still present after 11 days. This subject was not followed further at this time but 6 weeks later he returned to the laboratory for other respiration studies, and at this time his resting ventilation rate had returned to normal.

TABLE 2. RESPIRATORY RESPONSES TO INHALATION OF CO_2 BEFORE AND AFTER 24 HOURS OF HYPERVENTILATION

	100% O_2			2.5% CO_2			5% CO_2			7.5% CO_2		
	Min. vol.	Vent. ratio	Resp. rate	Min. vol.	Vent. ratio	Resp. rate	Min. vol.	Vent. ratio	Resp. rate	Min. vol.	Vent. ratio	Resp. rate
Subject H. B.												
	l/min.			*l/min.*			*l/min.*			*l/min.*		
Before	6.9	1.00	14	9.6	1.39	14	17.6	2.47	18	55.0	7.97	25
1½ hr. after	10.2	1.49	14	13.5	1.96	14	37.5	5.43	24	73.5	10.65	36
1 day after	7.1	1.03	10	13.7	1.98	18	30.0	4.35	25	66.0	9.66	40
2 days after	8.1	1.17	17	14.7	2.13	20	29.5	4.26	22	66.1	9.66	40
4 days after	8.8	1.27	14	12.6	1.82	17	27.3	3.96	20	53.2	7.71	30
11 days after	7.5	1.09	10	11.2	1.62	10	27.5	3.96	19	57.0	8.25	28
Subject W. F.												
Before	7.7	1.00	16	9.3	1.21	17	15.2	1.96	17	24.4	3.17	18
1½ hr. after	6.7	0.87	16	9.2	1.20	16	15.4	2.00	18	34.4	4.46	22
1 day after	6.9	0.89	18	9.5	1.23	18	15.1	1.96	20	32.2	4.18	24
3 days after	7.7	1.00	13							26.1	3.39	22
Subject C. B.												
Before	7.8	1.00	14	10.2	1.31	18	18.6	2.38	22	47.5	6.10	27
1½ hr. after	9.1	1.17	19	12.7	1.63	19	29.9	3.85	26	80.0	10.25	32
1 day after	7.0	0.89	14	10.2	1.31	16	20.7	2.65	22	57.0	7.30	36
3 days after	6.8	0.87	13	10.1	1.30	15	18.2	2.33	18	52.0	6.68	30

Since the oxygen tension in all instances was above the level at which it plays any significant rôle in control of respiratory ventilation, it may be disregarded as a responsible factor in this change in response. Carbon dioxide tension and/or pH must be considered as possible explanations for the observed changes in response. Since the blood CO_2 capacity was still low 24 hours after hyperventilation, a given increase in pCO_2 at this time would result in a greater decrease in arterial blood pH. The evaluation of the relative importance of these two factors in accounting for the increase in response to CO_2 after hyperventilation cannot be made, since arterial blood pH with the subject at steady state breathing the different CO_2 mixtures was not obtained. It should be pointed out, however, that in both *H. B.* and

C. B. an increased normal resting ventilation was evident after the arterial pH had returned to its control value.

It is interesting to note the wide variation in effects of 24 hours of hyperventilation on CO_2 responses among the 3 subjects. *W. F.* showed only a small change in response, *H. B.* exhibited a marked increase in response which was still evident after 11 days and *C. B.* gave a moderate response falling between these two extremes. Some of this apparent variation among individuals however may be due to differences in the degree of overventilation imposed during the 24-hour experimental period.

The fact that this increased ventilation does continue following as short a period of hyperventilation as 24 hours should be of some significance to the clinician in the handling of patients in a respirator. It has been observed (8) that poliomyelitis patients in respirators are often ventilated at a rate in excess of normal, according to physiological standards. It has also been noted that some of these patients who have been overventilated, when released from the respirator, maintain this elevated ventilation rate until fatigue occurs. These clinical observations are in line with the findings of this study and serve to emphasize the principle that, in order to avoid additional respiratory embarrassment to the partially paralyzed patient when attempts are made to free the patient from the respirator, ventilation should not be maintained over long periods of time at a rate in excess of that necessary to maintain normal pCO_2 and normal oxygen tension.

SUMMARY

Respiratory ventilation responses to CO_2-oxygen mixtures before and after 24 hours of hyperventilation in a body respiratory were determined on 3 young, healthy, male medical students. Two of the subjects showed an increase in ventilation response to the three concentrations of CO_2 after the hyperventilation, while the third exhibited an increase in response to the highest concentration of CO_2 but not to the two lower concentrations. Stimulus response curves, constructed by plotting alveolar pCO_2 against alveolar ventilation ratio, showed an increase in slope in 2 of the 3 subjects when responses before and after 24 hours of hyperventilation are compared.

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