Electrolyte Changes with Chronic Passive Hyperventilation in Man[1]

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ALTHOUGH THE EFFECTS of chronic hyperventilation in the presence of low oxygen tension have been studied exhaustively by many investigators, a search of the literature fails to reveal comparable studies of chronic overventilation at normal oxygen tensions. Several studies (1–6) have been made of electrolyte and water metabolism during short periods of voluntary hyperventilation. The present study was undertaken to ascertain the consequences of prolonged passive hyperventilation in man with particular reference to the composition of the blood and urine. The study was stimulated by the observation that patients maintained in body-type respirators for long periods were frequently hyperventilated. It therefore seemed important to study the basic physiological alterations in prolonged simple passive hyperventilation.

Previous studies of short periods of voluntary hyperventilation in man have shown increased volume, decreased titratable acidity, decreased excretion of ammonia (1, 2) and decreased excretion of phosphates (3) in the urine. Furthermore, decreased CO_2 content, decreased CO_2 capacity, increased *p*H and decreased inorganic phosphate in the blood have been reported (3, 4, 5). A comprehensive analysis of the blood electrolyte changes with voluntary hyperventilation has been reported by Rapoport *et al.* (6). In these and other previous studies the overventilation was carried out for periods of time ranging from 6 to 90 minutes.

PROCEDURE

In this study 8 young, healthy, male subjects were hyperventilated in a body-type respirator[2] for periods of 8 or 24 hours. At least 48 hours prior to the beginning of the period of hyperventilation the subjects were placed on a diet consisting of University of Minnesota Hospital Diet II (as described by Varco, 7), milk and water *ad libitum*. This diet was continued until 24 hours after completion of the period of overventilation. Urine samples were saved

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for the 24 hours before, for the period of hyperventilation, and for the 24 hours after the experimental period. These samples were refrigerated immediately after being voided and analyses were made after the 24-hour or 8-hour sample was completed. No precautions were taken to prevent loss of CO_2 from the samples.

The ventilation rate employed for a given subject was established by setting the respirator at the subject's normal respiratory rate and increasing the pressure gradient within the respirator until the subject exhibited symptoms of tetany. In every instance this occurred when the ventilation ratio (defined as minute volume divided by the normal resting minute volume) was between 2 and 3. When carpopedal spasm appeared or the subject complained of tingling, drawing, or other skin sensations the pressure gradient was reduced until symptoms abated. An attempt was then made to maintain this ventilation rate during the remainder of the hyperventilation period. Measurements of ventilation rate were made at intervals throughout the time the subject was in the respirator, but these recorded values are sample measurements and do not necessarily represent the average ventilation over the hyperventilation period. After the respirator was stopped and opened, the subject remained resting for one and one half hours while ventilation records were made and the first post-hyperventilation blood was drawn. *Subjects 3, 4,* and *5* were hyperventilated 8 hours; the other 5 subjects, 24 hours.

The methods of measuring ventilation and the treatment of arterial blood samples for CO_2 content and CO_2 capacity determinations have been described previously (8). Whole blood was used for the CO_2 content and capacity determinations for the first 5 subjects, and true separated plasma was used for these measurements for the last 3 subjects. Sodium heparin solution in an amount of 0.01 ml/ml. of blood was used as anticoagulant. Since all samples are subject to the same error no correction has been made in the reported analyses for this dilution nor for the addition of sodium, which amounted to 1.8 milliequivalents per liter of blood. Control blood samples were drawn 24 hours before, and usually a second sample 1 or 2 hours before the hyperventilation started. During hyperventilation, 2 to 4 blood samples were obtained, and at 1 hour and 24 hours after stopping the overventilation additional samples were drawn. Only CO_2 content and capacity were measured on the blood of *subjects 1* and *2*; additional determinations were made in the case of the other 6 subjects as indicated in table 2.

Sodium and potassium concentrations in plasma and urine were determined with the flame photometer[3], using LiCl as an internal standard (9). The method of Van Slyke (10) was used for chloride determinations, and

[3] The Internal Standard Flame Photometer used was loaned by Dr. R. B. Barnes, Director of Research, American Cyanamid Company. Thanks are due to Dr. W. D. Armstrong and Mrs. Mary Smersh for assistance with the analyses of sodium and potassium.

phosphates were determined by the method of Fisk and SubbaRow (11). Urine acidity was assayed by titration with 0.1N NaOH to a phenolphthalein end point, and urine *p*H was measured with a glass electrode *p*H meter. Intake of sodium, potassium, chloride and phosphates in the diet was estimated on the basis of calculations from analyses of aliquots of the milk and University Hospital Diet II.

TABLE 1. AVERAGE HOURLY URINARY EXCRETION FOR THE 24 HOURS BEFORE, FOR THE TIME DURING, AND FOR THE 24 HOURS AFTER PASSIVELY INDUCED HYPERVENTILATION FOR 8 SUBJECTS

	URINE *ml.*	MILLIEQUIVALENTS TITRATABLE ACID *mEq.*	pH	Na *mEq.*	K *mEq.*	Cl *mEq.*	P *mmol.*
Before.....	49.0	2.17	5.7	5.1	3.7	6.1	1.89
During.....	68.0	−0.09	7.7	10.3	5.1	5.6	0.52
After.....	27.8	2.54	5.4	3.3	3.4	3.2	2.10

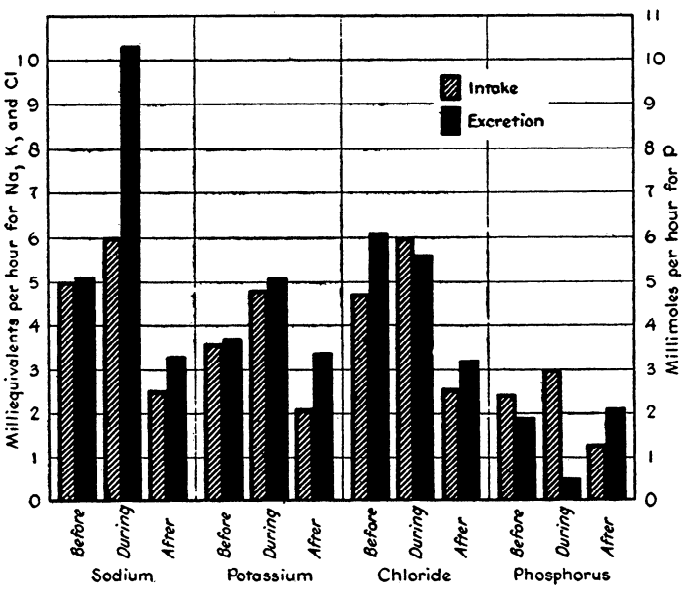

Fig. 1. INTAKE AND URINARY EXCRETION of sodium, potassium, chloride, and phosphorus for the 24 hours before hyperventilation, for the period of hyperventilation, and for the 24 hours following hyperventilation.

RESULTS

Averages of urinary volume, acid, sodium, potassium, chloride and phosphates excreted per hour before, during, and after hyperventilation are presented in table 1. The diuresis, decrease in acidity and decreased excretion of phosphates reported for short periods of overventilation are also evident here. In addition, a marked increase in excretion of sodium and a smaller

increase in excretion of potassium are shown. The excretion values cannot be interpreted properly without comparison with the simultaneous intakes. Such comparisons are presented in figure 1. If excretion of these electrolytes by other routes remains relatively constant, there would appear to be a significant loss of sodium and a retention of phosphates by the body during prolonged hyperventilation. There is no great change in chloride or potassium balance, although it is possible that a slight retention of chloride occurred during hyperventilation.

Blood data for the 8 subjects are presented in table 2. With the degree of hyperventilation imposed, arterial blood CO_2 content decreased an average of about 15 per cent in one hour, 25 per cent in 8 to 12 hours, and remained practically unchanged thereafter. One hour after termination of the imposed hyperventilation, the arterial CO_2 content was still 14 to 16 per cent below normal, and 24 hours after artificial hyperventilation was discontinued the arterial CO_2 content was still depressed in all subjects.

Although the arterial CO_2 capacity changes were not consistent from subject to subject during the first hour of overventilation, the average shows a slight increase. From one hour of hyperventilation until some time between one and 24 hours after termination of artificial hyperventilation, the average CO_2 capacity fell. It should be noted that in the first hour after turning off the respirator, this value decreased in 7 of 8 subjects and in the 8th no change occurred. Changes in CO_2 content and capacity with time are presented in figure 2. Both the whole blood (first 5 subjects) and plasma (last 3 subjects) CO_2 capacity curves show a slight rise during the first hour, a steady fall during the remainder of the hyperventilation period and a marked increase in the slope of this fall during the first hour after hyperventilation. Twenty-four hours later, CO_2 capacity had increased but was still below normal in 7 subjects.

Potassium was measured in the plasma of 2 subjects and no consistent change was found. Rapoport *et al.* (6) found a small but significant increase in the level of serum potassium with 6 minutes of voluntary hyperventilation. They mention increased secretion of adrenalin as a possible explanation for this change in potassium level.

Plasma sodium concentration decreased early in hyperventilation in 4 of 5 subjects. The average fall was 3.8 mEq. per liter during the first hour of hyperventilation. Insufficient data are available to draw conclusions about the behavior of the plasma sodium during the remainder of the experimental period. In *subject 3* the plasma sodium level fell steadily during the overbreathing and was still somewhat low 24 hours later. In other subjects the changes were erratic.

Plasma chloride levels showed no consistent change. Three of the five subjects showed a fall in chloride during hyperventilation, a change which is

TABLE 2. VENTILATION RATIOS AND BLOOD ELECTROLYTE CHANGES BEFORE, DURING AND AFTER 24 HOURS OF PASSIVE HYPERVENTILATION

		VENT. RATIO	CO_2[1] CONTENT	CO_2[1] CAPACITY	PLASMA Na	PLASMA Cl	PLASMA INORGANIC P
			mM/l	*mM/l*	*mEq/l*	*mEq/l*	*mM/l*
Subj. 1	Before hyperventilation	1.0	20.9	20.6			
24 hrs.	1 hour of hyperventilation	2.5	18.2	22.3			
	24 hours of hyperventilation	2.5	19.5	22.1			
	1 hour after hyperventilation	1.8		20.2			
	24 hours after hyperventilation			18.0			
Subj. 2	Before hyperventilation	1.0	21.5	21.1			
24 hrs.	1 hour of hyperventilation	2.2	16.5	21.2			
	24 hours of hyperventilation	2.2		18.0			
	1 hour after hyperventilation			18.0			
	24 hours after hyperventilation			20.0			
Subj. 3	Before hyperventilation	1.0	21.6	21.0	145.6	104.5	1.62
8 hrs.	½ hr. of hyperventilation	1.9	17.8		142.4	104.8	.45
	2½ hrs. of hyperventilation	2.4	16.5	21.4	140.2	106.8	.53
	8 hours of hyperventilation	2.6	15.1	21.5	136.9	108.8	.58
	1 hour after hyperventilation	.96	19.8	18.8		106.3	
	17 hours after hyperventilation	1.1		21.8	143.5	102.4	1.61
Subj. 4	Before hyperventilation	1.0	22.8	21.6	132.2	103.1	1.48
8 hrs.	½ hour of hyperventilation	2.6	20.0	22.8	133.7	102.2	1.22
	8 hours of hyperventilation	2.8	18.6	20.9	134.4	102.9	1.48
	1 hour after hyperventilation	1.5	19.4	20.1	137.8	107.5	1.87
	23 hours after hyperventilation	1.0	21.2	21.0	130.5	108.1	1.61
Subj. 5	Before hyperventilation	1.0	22.2	22.3	147.8	104.9	1.84
8 hrs.	½ hour of hyperventilation	2.0	14.5	21.8	139.3	98.9	.61
	8 hours of hyperventilation	2.1	15.1	20.8	147.8	99.7	.81
	1 hour after hyperventilation	1.4	17.8	19.3	141.3	100.1	1.58
	23 hours after hyperventilation	1.2	19.0	20.2	138.9	99.9	1.55
Subj. 6	Before hyperventilation	1.0	26.9	26.9		108.5	1.28
24 hrs.	1 hour of hyperventilation	2.1	22.8	28.4		109.6	.55
	12 hours of hyperventilation	2.8	20.6	28.3	145.9	125.2	
	24 hours of hyperventilation	2.7	19.8	25.7	139.1	119.8	1.02
	1 hour after hyperventilation	1.5	22.6	25.4	144.6	118.2	1.36
	24 hours after hyperventilation	1.03	22.5	25.6	145.9	106.5	1.35
Subj. 7	Before hyperventilation	1.0	28.9	29.0	142.2	117.3	1.19
24 hrs.	1 hour of hyperventilation	1.6	25.4	27.1	137.2	108.7	.29
	12 hours of hyperventilation	1.7	18.4	27.4			.63
	24 hours of hyperventilation	2.2	20.2	26.8		115.2	.12
	1 hour after hyperventilation	.87	24.0	26.0	149.1	108.7	1.44
	24 hours after hyperventilation	.90	26.2	27.0	130.0		1.31
Subj. 8	Before hyperventilation	1.0	26.6	28.1			1.50
24 hrs.	1 hour of hyperventilation	3.4	22.3	28.7			.95
	12 hours of hyperventilation	3.1	20.5	26.5			.86
	24 hours of hyperventilation	2.7	20.2	26.5			1.00
	1 hour after hyperventilation	1.2	22.7	25.3			1.44
	24 hours after hyperventilation	.90	23.0	25.9			1.00

[1] *Subjects 1–5* whole blood, *subjects 6–8* true separated plasma.

in the direction opposite to that which might be expected as a compensation for the lowered bicarbonate level. In experiments on himself, Peters (12) found a fall in plasma chloride with voluntary overbreathing which he was unable to explain.

The most striking and consistent change observed in plasma electrolyte concentrations, other than bicarbonate, was that of inorganic phosphate. One hour of hyperventilation resulted in an average decrease of 54 per cent, and the plasma level of this anion remained low during the remainder of the overventilation period, returning to normal within the first hour after hyperventilation was discontinued.

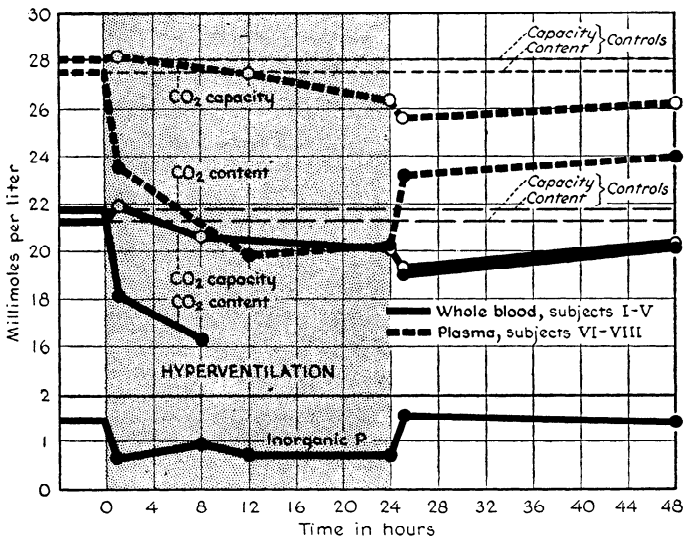

Fig. 2. WHOLE BLOOD AND PLASMA CO_2 CONTENT and capacity, and plasma inorganic phosphorus changes with hyperventilation. The whole blood CO_2 content line is broken between 8 hours of hyperventilation and 1 hour after hyperventilation since no determinations were made on this group of subjects during this interval.

DISCUSSION

Changes in the composition of the blood and urine with 8 and 24 hours of passive hyperventilation are in general in the same direction as have been reported previously for short periods of intense voluntary hyperventilation. The blood electrolyte changes noted in this study also follow fairly closely those reported for subjects on mountain climbing expeditions or subjects maintained at low atmospheric pressure over long periods in a low pressure chamber. Dill *et al.* (13) at heights up to 6.14 km. in the Peruvian Andes reported a slight increase in serum chloride, decrease in sodium, a marked decrease in bicarbonate, and no change in protein lactate, potassium and calcium. Serum inorganic phosphates were not measured.

In electrolyte balance studies on himself during a stay at high altitude, Sundstroem (4) found an increased excretion of basic elements and a negative balance of base on moving from sea level to high altitude.

In a 10-hour exposure to simulated altitudes of 8,000 and 10,000 feet, D'Angelo (15) found a significant reduction in renal excretion of inorganic phosphates. Subjects maintained at much higher simulated altitudes in a low-pressure chamber and over much longer periods of time showed a rise in blood *p*H, which was not compensated during the stay of 36 days in the chamber, a fall in CO_2 capacity and no change in plasma chloride or protein during the exposure (16).

In vitro studies on blood indicate that the inorganic phosphate level changes in the same direction as the hydrogen ion concentration (17, 18). The *p*H change may be the controlling factor in the inorganic phosphate shift in the intact body. Shifts into both red blood cells and tissue cells may be controlled by this factor. It may also be noted (fig. 2) that the early shifts in alkali reserve, at one hour of hyperventilation and at one hour post-hyperventilation are opposite to later trends and could be accounted for in part at least by the inorganic phosphate changes.

Although hyperpnea following short periods of voluntary hyperventilation has been observed in a small percentage of individuals (19), the usual result of such forced breathing is a period of apnea. Apnea was not observed in any instance, however, following 8 or 24 hours of passively imposed hyperventilation, and in 6 of 8 subjects an increased ventilation persisted for several hours after termination of the artificial hyperventilation. More extensive studies on respiratory reactions after passive hyperventilation on other subjects, to be reported separately, show that a persistent increase in minute respiratory volume is the more regular occurrence. The subjects whose data are reported here were not 'trained' as well before hyperventilation because the studies were not pointed in the direction of measuring the post-hyperventilation respiratory volume response in this series. In this connection it has been shown that there is an increased response to inhaled CO_2 during this period of spontaneous overventilation following 24 hours of passive hyperventilation (8).

A persistent overventilation has regularly been observed when individuals who have had a prolonged exposure to low oxygen tension are returned to normal oxygen tension (20, 21, 22).

Gray (23) has attributed this maintained overventilation to an increase in the sensitivity of the respiratory center to CO_2.

SUMMARY

Eight, healthy young men were hyperventilated in a body type respirator; 5, for 24 hours and 3, for 8 hours. During the hyperventilation there

was an increase in the volume of urine excreted, an increase in the excretion of urinary sodium and potassium, and a reduction in the excretion of phosphates. Little change in excretion of chloride was observed. A comparison of the intake of sodium, potassium, chloride and phosphates with urinary excretion indicates an overall loss of sodium and a retention of phosphates during prolonged hyperventilation.

Of the plasma electrolytes measured, only bicarbonate and inorganic phosphates showed a consistent change with prolonged passive hyperventilation. Inorganic phosphate level fell rapidly with onset of overventilation. Plasma sodium concentrations regularly fell during the first hour of hyperventilation, but later changes were random. The fall in CO_2 content and capacity accompanying 8 or 24 hours of passive hyperventilation had not been completely repaired in the 24 hours after termination of the hyperventilation.

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