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Calcium, magnesium, and phosphorus metabolism, and parathyroid-calcitonin function during prolonged exposure to elevated CO_2 concentrations on submarines

A. A. MESSIER, E. HEYDER, W. R. BRAITHWAITE, C. McCLUGGAGE, A. PECK, and K. E. SCHAEFER

Naval Submarine Medical Research Laboratory, Naval Submarine Base, Groton, CT 06340

Messier, A. A., E. Heyder, W. R. Braithwaite, C. McCluggage, A. Peck, and K. E. Schaefer. 1979. Calcium, magnesium, and phosphorus metabolism, and parathyroid-calcitonin function during prolonged exposure to elevated CO_2 concentrations on submarines. Undersea Biomed. Res. Sub. Suppl.: S57–S70.—Studies of calcium and phosphorus metabolism and acid-base balance were carried out on three Fleet Ballistic Missile (FBM) submarines during prolonged exposure to elevated concentrations of CO_2. The average CO_2 concentration in the submarine atmosphere during patrols ranged from 0.85% to 1% CO_2. In the three studies, in which 9–15 subjects participated, the urinary excretion of calcium and phosphate fell during the first three weeks to a level commensurate with a decrease in plasma calcium and increase in phosphorus. In the fourth week of one patrol, a marked increase was found in urinary calcium excretion, associated with a rise in blood P_{CO_2} and bicarbonate. Urinary calcium excretion decreased again during the 5th to 8th week, with a secondary decrease in blood pH and plasma calcium. During the third patrol, the time course of acid-base changes corresponded well with that found during the second patrol. There was a trend toward an increase in plasma calcium between the fourth and fifth week commensurate with the transient rise in pH and bicarbonate. Plasma parathyroid and calcitonin hormone activities were measured in two patrols and no significant changes were found. Hydroxyproline excretion decreased in the three-week study and remained unchanged in the second patrol, which lasted 57 days. It is suggested that during prolonged exposure to low levels of CO_2 (up to 1% CO_2), calcium metabolism is controlled by the uptake and release of CO_2 in the bones. The resulting phases in bone buffering, rather than renal regulation, determine acid-base balance.

calcitonin activity
calcium excretion
chronic hypercapnia
magnesium
parathyroid
phosphorus
submarine patrols

Prolonged exposure to low levels of CO_2 (1.5% CO_2) has been found to cause a transient hypocalcinuria and hypocalcemia, which have been interpreted as calcium retention occurring

in conjunction with CO_2 storage in the bones (Schaefer, Nichols, and Carey 1963b). Similar observations have been made more recently by Gray, Lambert, and Morris (1969) and Gray, Morris, and Brooks (1973) during submarine studies. This report deals with three submarine studies in which the average CO_2 concentration ranged between 0.85 and 1%CO_2. Calcium and phosphorus metabolism were investigated and the blood samples obtained during patrol were also analyzed for parathyroid and calcitonin activity. The changes in calcium metabolism observed during prolonged exposure to 0.85–1% CO_2 did not involve any significant alterations in parathyroid and calcitonin activity.

MATERIALS AND METHODS

During the first patrol, the subjects were seven members of a Fleet Ballistic Missile (FBM) submarine crew. All men were in good health and had no history of pulmonary, renal, or skeletal disease. All were experienced submariners and had been on previous FBM patrols. Oxygen, carbon dioxide, and carbon monoxide were measured at 4-h intervals in three of the ship's compartments and average values were recorded. On a daily basis, the level of CO_2 varied from 0.8 to 1.2% CO_2, with a mean of 0.98% CO_2 for the 57 days under study. Oxygen concentration was maintained between 19% and 21%. Carbon monoxide was maintained at less than 25 ppm. No dietary restrictions or measurements were in effect during the study. Drinking water was distilled and no minerals were added. At no time during the data collection was the submarine environment ventilated with outside air.

Samples of blood were collected during Days 1, 8, 15, 22, 29, 36, 51, and 57 of patrol. Because of operational limitations, controls were not collected until 9 months after the patrol. However, this period coincided seasonally with the time which would have been the pre-patrol portion of the exposure, i.e., no seasonal variation was introduced. Venous samples were collected in 7-ml heparinized Vacutainers, spun down immediately, and separated anaerobically. The separated plasma and red cell fractions were then anaerobically transferred to fill a 2-ml test tube completely and were then frozen at −15°C. After completion of the patrol, the samples were returned to the laboratory for analysis. The analyses of blood samples were staggered in order that each group of samples would be frozen for approximately the same period (100–110 days). In addition, a control study was performed using blood obtained from the subjects of this study. The blood was analyzed immediately and an aliquot was treated identically to the blood samples of the submarine study: each sample was reanalyzed after being frozen for 106 days. Any plasma samples with an elevation of $Po_2 > 50$ mmHg that showed evidence of air venting were not used. Venous Po_2 ranged from 40–50 mmHg for all exposure periods, indicating valid readings for typical venous samples. During a previous patrol study (Peck 1971), blood samples were analyzed for venous Po_2 immediately after the blood was drawn. The range of Po_2 values (Po_2 = 30–42 mmHg) approximated those obtained in the present study.

Twenty-four hour urine samples were collected, under oil, throughout the patrol and control periods. At the end of each 24-h period, the urine volume was measured and a 10% aliquot of the sample was frozen at −15°C. No preservatives were used. Analysis of pH was made on a pH blood gas analyzer (I.L. 113-S1, Instrumentation Laboratory, Inc.); Na and K were analyzed on a flame photometer (I.L. 343, Instrumentation Laboratory, Inc.); Cl was measured with a chloridometer; Ca and Mg by atomic absorption spectrophotometry (Perkin Elmer, Model 206); hydroxyproline and inorganic phosphorus by autoanalyzer (Technicon Corporation); and urinary HCO_3 by manometric procedures (Van Slyke Magne-matic, A. H. Thomas Co.). Plasma levels of parathyroid hormone and calcitonin were determined by

radioimmunoassay at the Endocrine Laboratory of Massachusetts General Hospital, Boston. Statistical analyses were performed using paired *t*-tests. Differences with $P \leq 0.05$ were considered significant. The F-test for sample variance was also performed.

The same methods were employed in two other patrol studies in which 9 and 15 subjects participated, respectively.

Diet

The average daily intake of food during patrols is about 3600 kcal/person. Schulte (1950) conducted a dietary study aboard a submarine deployed in the Arctic and measured an average daily intake of 3800 kcal/person. The protein content of this diet was 120 g. Although Schulte's study was made on a Diesel submarine, it can be assumed that a similar intake occurred on nuclear submarines. Dietary habits investigated during patrols on nuclear-powered submarines were found not to change in any significant way from those of patrols on Diesel-powered submarines. There was, however, a decrease in the number of regular meals and an increase in the number of between-meal snacks (Kropp and Shiller 1968; Summitt and Shiller 1968). The average daily intake on British nuclear-powered submarines is about 3400 kcal/person (Southgate and Stirling 1966).

RESULTS

Table 1 presents blood gas data from a controlled study using the subjects' venous plasma; blood was immediately analyzed and was then stored for 106 days at −15°C in completely filled 2-ml glass tubes. The data indicate minimal changes in the acid-base parameters after storage for 106 days. The greatest change, which was not significant ($0.2 < P < 0.1$), was an elevation of P_{O_2} of 5 mmHg that was probably caused by the sampling procedure.

Table 2 presents a summary of the data obtained from the frozen venous samples taken throughout an 8-week exposure to a submarine atmosphere containing 1% CO_2. Note the immediate increase in P_{CO_2} and slight increase in bicarbonate during the first 22 days of the

TABLE 1
CONTROL STUDY TO ESTABLISH VALIDITY OF FROZEN PLASMA SAMPLES

Sample	Immediate Analysis				Stored at −15°C for 106 Days			
	pH	P_{CO_2}, mmHg	P_{O_2}, mmHg	Act HCO_3, mM/liter	pH	P_{CO_2}, mmHg	P_{O_2}, mmHg	Act HCO_3, mM/liter
1	7.445	44.6	59.0	29.3	7.439	42.8	65.0	27.7
2	7.415	50.6	59.0	30.8	7.415	49.0	66.0	30.0
3	7.444	37.2	65.0	24.3	7.469	35.8	74.0	24.8
4	7.465	37.9	58.5	26.2	7.472	39.8	63.0	27.8
5	7.409	46.3	56.0	27.8	7.420	42.5	63.0	26.4
6	7.406	43.2	62.8	25.8	7.390	37.0	69.0	21.4
7	7.388	52.0	53.0	29.8	7.373	55.0	50.8	30.6
Mean	7.425	44.5	59.1	27.7	7.425	43.1	64.4	27.0
SD	0.027	5.7	4.0	2.4	0.037	6.8	7.1	3.2
SE	0.010	2.2	1.5	0.9	0.014	2.6	2.7	1.2

TABLE 2
EFFECT OF EXPOSURE TO 1% CO_2 ON VENOUS BLOOD GAS PARAMETERS

		Control	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 51	Day 57
pH	Mean	7.425	7.417	7.413	7.408	7.418	7.419	7.411	7.390*	7.404
	SE	0.014	0.013	0.006	0.008	0.006	0.005	0.009	0.008	0.011
P_{CO_2},	Mean	43.1	46.0	46.6	46.6	47.4	52.6*	55.9*	48.3	47.5
mmHg	SE	2.6	1.5	1.6	1.5	1.1	1.5	0.9	1.5	1.7
HCO_3,	Mean	27.0	28.3	28.9	28.1	29.3	32.7*	33.2*	28.2	28.3
mM/liter	SE	1.2	0.8	0.8	0.9	0.9	0.9	0.5	1.1	0.8

*Statistically significant at 5% level, paired t-test; $n = 7$.

exposure, followed by a significant increase in P_{CO_2} and bicarbonate during the fourth and fifth weeks of the patrol. Throughout the exposure, pH was below the control level and was significantly decreased at the seventh week.

A comparison of results of three separate studies of the time course of the arterial and venous acid-base status of submariners exposed to approximately 1% CO_2 for periods of up to eight weeks' duration is presented in Table 3. The studies of Peck (1971) and Pingree (1977) involved immediate on-board analyses of samples. The arterial and venous samples have basic similarities. There is a slight decrease in pH, along with an initial rise in P_{CO_2} during the first

TABLE 3
TIME COURSE OF ARTERIAL AND VENOUS ACID-BASE STATUS OF SUBMARINERS EXPOSED TO 0.85–1.00% CO_2

				Time, Weeks							
			Control	1	2	3	4	5	6	7	8
Peck		arterial	7.46	7.43*	7.45	7.46	7.46	–	7.44	–	7.42*
(1971)	Mean	venous	7.42	7.42	7.40	7.41	7.42	–	7.42	–	7.39*
Pingree (1977)	pH	arterial	7.40	7.38*	7.38*	7.38*	7.38*	7.38*	–	–	–
This study (1979)		venous	7.43	7.42	7.41	7.42	7.42	7.41	–	7.39*	7.40
Pingree	Mean	arterial	38.3	39.0*	39.8*	39.0*	40.7*	41.7*	–	–	–
This study	P_{CO_2}, mmHg	venous	44.5	46.0	46.6	47.4	52.6*	55.9*	–	48.3	47.5
Pingree	Mean	arterial	23.5	22.6	22.8	23.0	24.5*	24.5*	–	–	–
This study	HCO_3, mM/liter	venous	27.8	28.6	28.1	29.3	32.7*	33.2*	–	28.2	28.3

Peck (1971)-15 subjects; arterial = arterialized capillary blood analyzed immediately after sampling; venous = whole blood analyzed immediately after sampling. Pingree (1977)-15 subjects; arterial = whole blood analyzed immediately after sampling. This study (1979)-7 subjects; venous = plasma anaerobically separated from whole blood, frozen at −15°C and analyzed in the laboratory. *$P \leq 0.05$.

three weeks of exposure, followed by a secondary increase in P_{CO_2} and an increase in bicarbonate during the fourth and fifth week of the patrol.

Figure 1 shows data on pH, P_{CO_2}, and HCO_3 levels of plasma obtained during the patrol. A decrease in pH and a significant increase in the P_{CO_2} and bicarbonate level in plasma developed by approximately the fourth week of exposure, indicating a mild respiratory acidosis. Chloride changes in plasma and red cells served as independent indicators of respiratory acidosis. The decrease in plasma chloride and concomitant increase of red blood cell chloride on Days 29 through 51 are in agreement with the measured pH changes. The acidosis appears to have been compensated for by Day 57, when it returned to control levels.

The effects upon plasma electrolytes of prolonged exposure to 1% CO_2 during patrols are presented in Table 4. Plasma sodium increased and plasma potassium decreased. The plasma calcium data demonstrated an immediate decrease, beginning on Day 1 of the exposure. Plasma phosphorus levels did not change significantly. Plasma magnesium exhibited an increase only on Day 51 of the exposure.

The preceding figure and table present evidence suggesting the development of a mild respiratory acidosis during the fourth week of exposure. However, the plasma electrolytes, Ca and Na, differed significantly by the first day of exposure (Table 4).

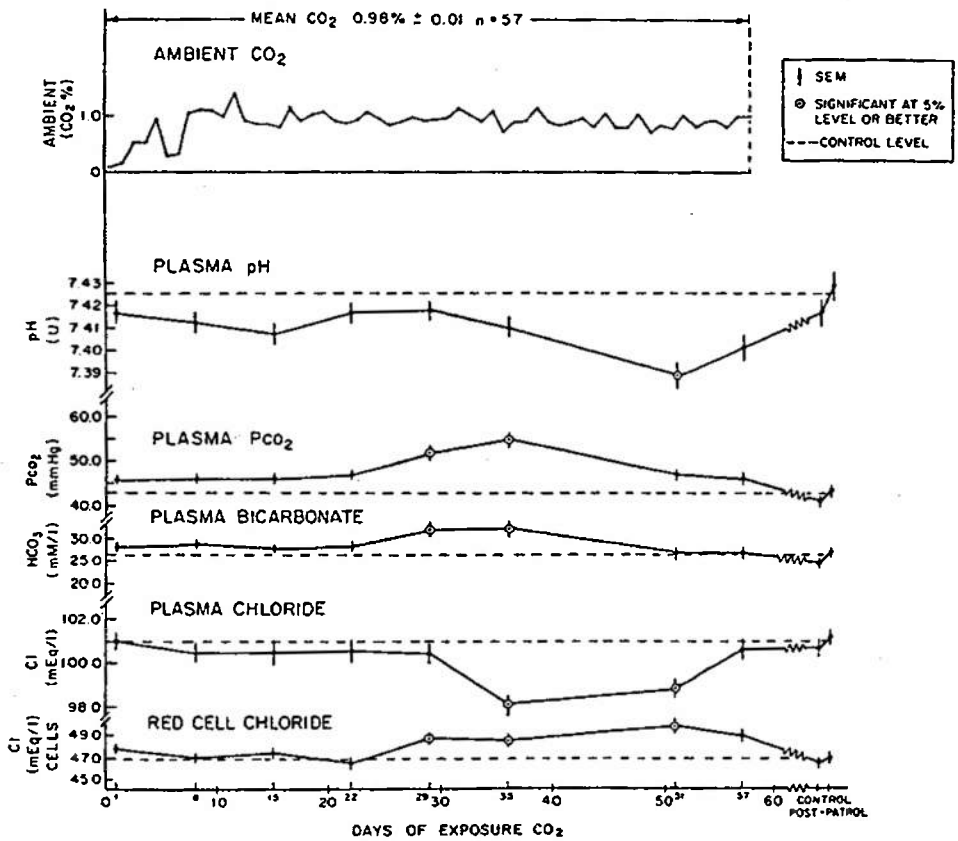

Fig. 1. Effect of prolonged exposure to 1% CO_2 during patrol on acid-base status of blood. Paired *t*-test, $n = 7$.

TABLE 4
EFFECT OF PROLONGED EXPOSURE TO 1% CO_2 ON PLASMA ELECTROLYTES

		Post-Patrol Control	Day 7	Day 8	Day 15	Day 22	Day 29	Day 36	Day 51	Day 57
Plasma	$\bar{X}$	131.2	136.3	136.3	136.6	137.3	135.9	136.0	136.9	136.9
Sodium,	SEM	1.5	0.9	0.7	0.7	2.1	0.6	0.7	0.3	0.4
mEq/liter	P*	–	<0.025	<0.01	<0.01	<0.05	<0.025	<0.025	<0.005	<0.005
Plasma	$\bar{X}$	4.3	4.4	4.1	4.1	3.9	3.7	3.7	4.0	3.8
Potassium,	SEM	0.07	0.09	0.12	0.19	0.06	0.07	0.08	0.08	0.06
mEq/liter	P	–	NS	NS	NS	<0.001	<0.001	<0.001	<0.025	<0.001
Plasma	$\bar{X}$	2.2	2.3	2.3	2.3	2.3	2.2	2.1	2.3	2.3
Phosphorus,	SEM	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1
mEq/liter	P	–	NS	NS	NS	NS	NS	NS	NS	NS
Plasma	$\bar{X}$	5.0	4.3	4.4	4.5	4.4	4.3	4.6	4.8	4.5
Calcium,	SEM	0.1	0.1	0.05	0.1	0.1	0.1	0.2	0.1	0.05
mEq/liter	P	–	<0.001	<0.001	<0.025	<0.005	<0.001	<0.05	NS	<0.001
Plasma	$\bar{X}$	1.65	1.69	1.74	1.70	1.75	1.65	1.70	1.80	1.72
Magnesium,	SEM	0.03	0.02	0.06	0.06	0.05	0.05	0.05	0.03	0.03
mEq/liter	P	–	NS	NS	NS	NS	NS	NS	<0.025	NS
Plasma	$\bar{X}$	101.3	101.1	100.6	100.8	99.7	99.7	97.7	98.6	99.4
Chloride,	SEM	0.9	1.1	0.8	0.8	0.8	0.8	0.7	0.6	0.8
mEq/liter	P	–	NS	NS	NS	NS	NS	<0.005	<0.025	NS

*Statistical analyses by paired t-test; $n = 7$.

Erythrocyte electrolyte data are presented in Table 5. Red cell sodium increased and was associated with an immediate decrease of red blood cell potassium. Erythrocyte calcium was also immediately elevated; red blood cell magnesium decreased by Day 51, the same day that plasma Mg increased.

An important aspect of acid-base and electrolyte balance is the renal handling of an acid load. Figure 2 presents data on urine electrolyte excretion during the patrol. Urine pH was elevated throughout the patrol. Urine calcium, phosphorus, and magnesium levels were all depressed. Although urine bicarbonate concentration showed considerable variation, with the only significant differences occurring on Days 29, 51, and 57, it was elevated throughout the exposure. Urinary hydroxyproline values did not change significantly throughout the exposure.

Parathyroid hormone and calcitonin activity were determined on 68 plasma samples. There was no demonstrable increase in the level of either hormone.

Figure 3 shows the results of a second patrol study in which pH measurements were made on 15 subjects. The decline in blood pH during the first 20 days was attributed to metabolic acidosis (Schaefer 1979). After about 3 weeks, pH began to rise, reaching a peak at Day 30. This period of a compensated respiratory acidosis was followed by a decline, which was most pronounced on Day 52 of the patrol.

Data on serum calcium and phosphorus were obtained only on three occasions during this patrol; measurements were taken in the period of acidosis marked by a decline in pH. Plasma calcium decreased during these periods and phosphorus increased. The decrease in serum

calcium was associated with a decrease in calcium excretion in the urine, which suggests a retention of calcium. There was, however, a marked rise in calcium excretion on Day 30, commensurate with the pH and bicarbonate rise in the blood. Unfortunately, no blood calcium data were obtained at this point.

Data on plasma calcium and phosphorus and red cell calcium obtained on a third patrol are presented in Fig. 4. The patrol lasted only three weeks. There was a decline of plasma calcium and an increase in red cell calcium, which became statistically significant after 3 weeks of exposure to the submarine atmosphere. These changes are in agreement with the findings obtained on the other patrols. After one week of recovery on air, red cell calcium values had returned to initial levels. Parathyroid activity was also measured (Endocrine Laboratory, Massachusetts General Hospital). There were no statistically significant changes in the hormone activity.

As shown in Fig. 5, urinary excretion of calcium, phosphorus, and hydroxyproline declined during the three weeks of exposure. The decrease was statistically significant after 3 weeks. Urinary volume did not change in this period. Sodium, K, and Cl excretion also decreased during the exposure period.

DISCUSSION

The results of this study show three phases of urinary calcium excretion: a marked decrease during the first three weeks, followed by a rise that does not exceed control levels during the fourth and fifth weeks, and a subsequent decline between the 6th and 9th weeks. A similar pattern has been observed in British submarine studies during prolonged exposure to 1% CO_2 and 0.7% CO_2, respectively (Gray et al. 1969, 1973).

Plasma calcium was measured in two patrol studies, the one reported in this paper and the study of Gray et al. (1973). Moreover, plasma calcium data were obtained in two laboratory

TABLE 5
EFFECT OF PROLONGED EXPOSURE TO 1% CO_2 ON RED CELL ELECTROLYTES

		Post-Patrol Control	Day 1	Day 2	Day 15	Day 22	Day 29	Day 36	Day 51	Day 57
RBC	$\bar{X}$	0.29	0.65	0.57	0.57	0.52	0.42	0.57	0.41	0.47
Calcium,	SEM	0.01	0.05	0.05	0.05	0.05	0.03	0.05	0.03	0.04
mEq/liter	*P*	–	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RBC	$\bar{X}$	11.1	22.5	17.4	18.8	16.0	18.3	19.8	16.2	17.5
Sodium,	SEM	0.2	1.5	1.5	0.9	1.1	0.7	0.8	0.5	0.7
mEq/liter	*P*	–	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RBC	$\bar{X}$	72.2	61.1	67.1	67.5	68.1	67.8	65.1	67.9	67.5
Potassium,	SEM	1.3	1.0	1.7	0.7	0.5	0.9	0.7	0.4	0.6
mEq/liter	*P*	–	<0.001	<0.05	<0.01	<0.01	<0.025	<0.001	<0.01	<0.01
RBC	$\bar{X}$	45.9	47.8	46.7	47.4	46.0	48.1	47.8	50.4	47.9
Chloride,	SEM	0.7	0.6	0.5	0.9	0.8	0.6	0.4	0.8	0.6
mEq/liter	*P*	NS	NS	NS	NS	NS	<0.05	<0.05	<0.001	NS

*P; statistical analyses by paired t-test; $n = 7$.

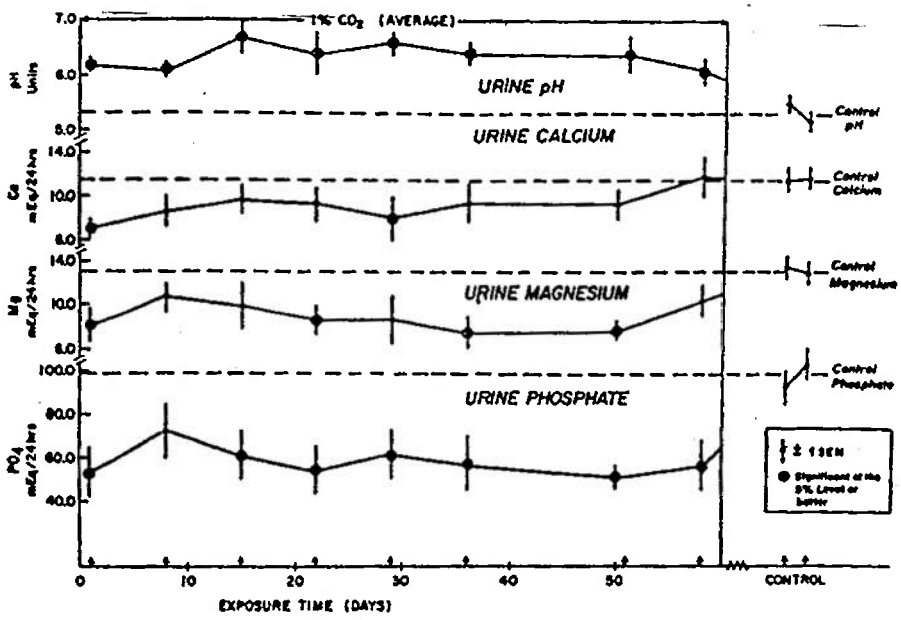

Fig. 2. Effect of prolonged exposure to 1% CO_2 during patrol on urine electrolytes; $n = 7$.

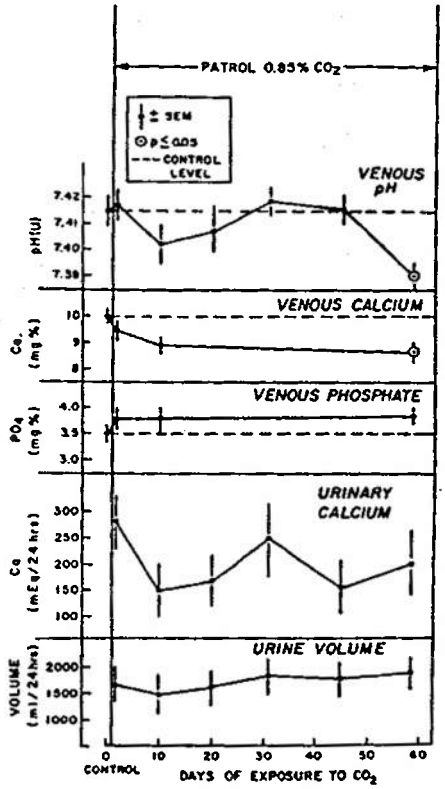

Fig. 3. Effect of 56 days of exposure to 0.85% CO_2 on pH, blood calcium, phosphorus and urinary calcium, and urine volume; $n = 15$.

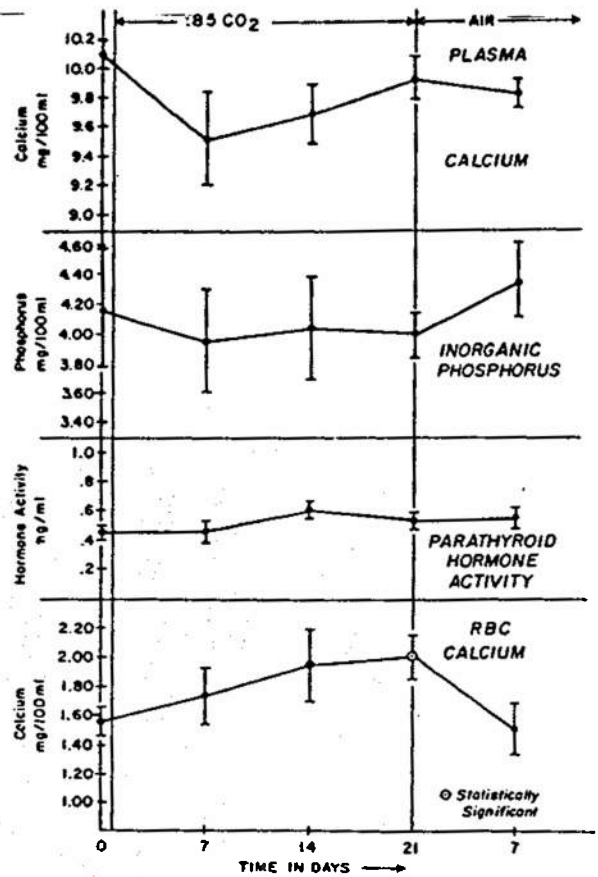

Fig. 4. Effect of 3 weeks of exposure to 0.85% CO_2 on plasma calcium and phosphorus, parathyroid hormone activity, and red cell calcium; $n = 9$.

simulation studies involving exposure to 1% CO_2 for 90 days (McDonnell 1971) and to 1.5% CO_2 for 42 days (Schaefer et al. 1963b). When these plasma calcium data were plotted together, clearly pronounced cyclic changes were observed: a fall of plasma calcium during the first 20 days, followed by a marked rise during the second 20-day period (Schaefer 1979). The peaks of plasma calcium fell around the 40th day, with the exception of one value on Day 51 that has been reported in this paper. A second decline in plasma calcium occurred between 40 and 60 days of exposure to low levels of CO_2.

The periods of peak blood calcium levels did not correspond with the times of highest urinary calcium excretion, which occurred in later time periods. This process may be related to the interaction of parathyroid hormone and calcitonin. According to Peacock, Robertson, and Nordin (1969), these hormones influence the threshold of urinary calcium excretion inversely.

The activity of parathyroid hormone and calcitonin was measured in samples obtained in two patrol studies. As shown in Fig. 4, an increase in these factors was observed in one of the studies after two and three weeks of exposure to 1% CO_2, but the changes were not statistically significant compared with control levels. In the second study, blood from a large number of samples showed no measurable hormone activity at all. In view of the fact that the accuracy

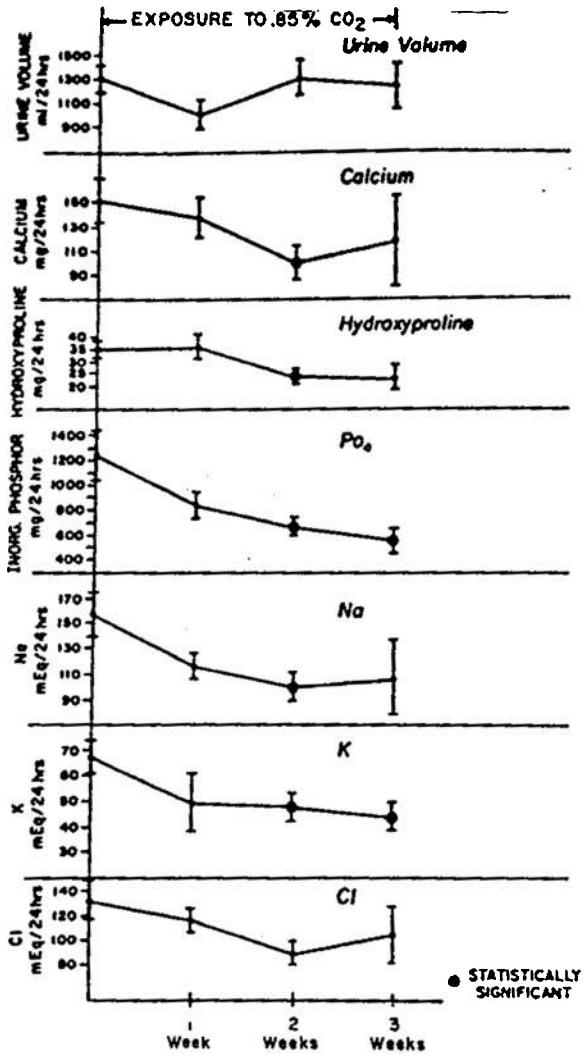

Fig. 5. Effect of 3 weeks of exposure to 0.85% CO_2 on urine volume, urine calcium and phosphorus, hydroxyproline, and electrolytes (Na, K, Cl); $n = 9$.

of the radioimmunoassays had about a 15% variability, it is difficult to establish statistically whether minor but physiologically significant increases in PTH and calcitonin activity occurred under patrol conditions.

Exposure to higher CO_2 concentrations (3%, 10%, and 15% CO_2) produces a hypercalcemia and hypercalcinuria (Schaefer, Hasson, and Niemoeller 1961; Stanmeyer, King, Scofield, and Colby 1962; Heyder 1972; Giannetta and Castleberry 1974); stimulation of parathyroid hormone activity has been considered responsible for this effect (Schaefer et al. 1961; Stanmeyer et al. 1962).

The cycles in plasma calcium and urine calcium of approximately 20 days during prolonged exposure to low levels of CO_2 appear to be related to the 20-day cycles of acid-base balance observed under the same conditions (Schaefer 1979).

The time course of pH, bicarbonate, and $\overline{Pco_2}$ observed during three patrols involving prolonged exposure to 0.85–1% CO_2 and during laboratory simulation experiments with ambient levels of 1.0% CO_2 showed alterations between a metabolic acidosis during the first 15–20 days, followed by a respiratory acidosis (20–40 days), and a subsequent metabolic acidosis during the period between 40 and 60 days.

Moreover, Gray et al. (1973) observed cyclic changes in urinary net acid excretion and ammonia excretion during 7 weeks of exposure to 0.7% CO_2 on submarines. Under these conditions, which are similar to those reported in this paper, net acid and NH_4 excretion decreased below control levels during the first two weeks; this was followed by a rise to control levels, which lasted for 10 days (up to Day 24), and a subsequent decline until the end of the exposure.

The predominant feature of acid-base balance during the first three weeks of exposure to 0.85–1% CO_2 in submarines is a metabolic acidosis (Schaefer 1979). Pingree (1977) has also noted a decrease in bicarbonate during the first three weeks, followed by an elevation in the latter portion of a six-week exposure to 1% CO_2. The blood bicarbonate decrease during this period is in marked contrast to the typical increase in blood bicarbonate observed during exposure to 1.5% CO_2 (Schaefer, Nichols, and Carey 1964) and to higher concentrations of CO_2 (Brackett, Cohen, and Schwartz 1965; Clark, Sinclair, and Welch 1971) and in patients with chronic hypercapnia (van Ypersele, Brasseur, and DeConincok 1966). The increase in blood bicarbonate that occurs in response to an increase in Pco_2 is accomplished through renal regulatory mechanisms and involves increased acid secretion and bicarbonate reabsorption (Pitts 1968; Rector 1974). Findings obtained during the patrol studies indicate that these renal regulatory mechanisms do not operate during the first three weeks of prolonged exposure to 0.85–1% CO_2. The hypothesis has been advanced by Schaefer (1979) that during the first three weeks, CO_2 is taken up in bone, mainly in the fast exchanging bone CO_2 fraction (bicarbonate) that comprises 30% of the total bone CO_2. During this period urinary calcium excretion is reduced and plasma calcium levels are low, except for an early, transient plasma increase during the first few days. These effects may be so strong that the influence of the high protein intake in the submariner's diet (120 g) does not come into play. According to Johnson, Alcantara, and Linkswiler (1970) and Walker and Linkswiler (1972), a high protein intake causes a hypercalcinuria within 24 h after a change in the intake of protein. However, high protein intake had no effect on serum calcium during the patrol.

After saturation is reached, which can require several weeks according to Freeman and Fenn (1953), CO_2 could be released from the bone through a shift in the bone CO_2 fractions from bicarbonate to carbonate. According to Poyart, Bursaux, and Freminet (1975), such a shift could free 50% of bicarbonate CO_2 in the form of gaseous CO_2. Schaefer (1979) postulated that this internally released CO_2 could provide the stimulus for activation of the renal bicarbonate reabsorption mechanism, resulting in the phase of respiratory acidosis. During the second 20-day period, calcium excretion is increased and plasma calcium increased. Subsequently, a repetition of the first phase occurs, characterized by a metabolic acidosis. Confirmatory evidence for the existence of 20-day cycles in bone CO_2 uptake and release and associated calcium-phosphorus cycles has recently been obtained during prolonged exposure of guinea pigs to 1% CO_2 (Schaefer, Pasquale, and Messier 1979). It was found that during the first two weeks the bicarbonate fraction of bone CO_2 increased while the carbonate fraction decreased slightly. During the third and fourth weeks, the carbonate fraction rose markedly and bicarbonate fell to control levels; at six and eight weeks, carbonate remained at the level attained at four weeks. However, the bicarbonate fraction rose again. The early part of the rise in bone bicarbonate (first week) was associated with bone CO_2 and phosphorus loss. However, during

the later part of a sustained increase in bone bicarbonate, from the second week on, bone Ca and phosphorus rose again. This rise in both bone Ca and phosphorus fractions was more pronounced during the periods in which bone carbonate increased.

The mechanisms involved in the cyclic bone CO_2 and calcium and phosphorus changes during chronic hypercapnia are far from clear. It is difficult to understand how a small elevation in P_{CO_2} of a few mmHg could cause such cyclic changes, based on a P_{CO_2}-dependent saturation mechanism. However, there are well-known processes in bone CO_2-calcium exchange, such as the increase in bone CO_2 and decrease in bone calcium with aging, which cannot be explained by a P_{CO_2}-dependent saturation mechanism.

Although membrane-bound calcium was not measured in this study, the increase in calcium found in lysed red cells may indicate a pH- or P_{CO_2}-dependent change in red cell permeability. This notion is supported by the simultaneously measured decrease in red cell K and increase in red cell Na (Table 5), generally considered evidence of a change in active transport. Alterations in calcium binding may increase the membrane permeability to water and other ions (Manery 1966). Thus, the alteration in calcium binding at the membrane, under the influence of CO_2 or of decreased pH, may have been sufficient to permit calcium to leak into the cells faster than it could be pumped out.

There is a need to conduct more controlled laboratory studies in both man and animals to delineate the basic mechanisms of long-term adaptation to low levels of carbon dioxide as they relate to bone and perhaps other tissues.

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Messier, A. A., E. Heyder, W. R. Braithwaite, C. McCluggage, A. Peck, and K. E. Schaefer. 1979. Métabolisme du calcium, du magnesium, et du phosphore, et fonctions parathormone-thyrocalcitonine au cours d'une exposition prolongée à des concentrations élevées de CO_2 à bord de sous-marins. Undersea Biomed. Res. Sub. Suppl.: S57–S70.—On a étudié le métabolisme du calcium et du phosphore et l'équilibre acido-basique chez les équipages de trois sous-marins au cours d'une exposition prolongée à des concentrations élevées de CO_2 (concentration moyenne entre 0,85 et 1,0%). Dans les trois séries de sujets, à 9–15 hommes chacune, l'élimination urinaire de calcium et de phosphore a diminué pendant les premières trois semaines; une diminution du calcium plasmatique et une augmentation du phosphore ont été constatées en même temps. Pendant la quatrième semaine d'un voyage, une augmentation importante de la calciurie s'est associée à une augmentation de P_{CO_2} et de bicarbonate sanguins. La calciurie a baissé encore pendant les quatre semaines suivantes, ainsi que le pH sanguin et la calcémie. Pendant le troisième voyage les modifications acidobasiques ressemblaient à celles du deuxième voyage: calcémie accrue pendant les quatrième et cinquième semaines, élevation transitoire de pH et des bicarbonates en même temps. Les déterminations des activités de la parathormone et de la thyrocalcitonine ont été effectuées pendant deux voyages: aucune modification significative n'a été observée. L'élimination de l'hydroxyproline a diminué pendant l'etude de trois semaines, et est restée inchangée pendant le deuxième voyage, qui a duré 57 jours. Il parait que pendant les expositions prolongées à des concentrations basses (jusqu'a 1%) de CO_2, le métabolisme du calcium soit reglé par la consommation et l'élimination osseuses de CO_2. L'équilibre acido-basique serait reglé par les phases de tamponnage osseux, et non pas par le mécanisme regulatoire des reins.

activité de la thyrocalcitonine
calciurie
hypercapnie chronique
magnésium
parathormone
phosphore
sous-mariniers

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