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Effect of prolonged exposure to elevated carbon monoxide and carbon dioxide levels on red blood cell parameters during submarine patrols

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Wilson, A. J., and K. E. Schaefer. 1979. Effect of prolonged exposure to elevated carbon monoxide and carbon dioxide levels on red blood cell parameters during submarine patrols. Undersea Biomed. Res. Sub. Suppl.: S49–S56.—Twenty volunteers were chosen at random from the crew of a Polaris submarine to ascertain the effect of prolonged exposure to elevated levels of carbon monoxide and carbon dioxide on red blood cell parameters during a routine patrol. Measurements were made of hemoglobin (Hb) concentrations, hematocrit (Hct) levels, and red blood cell (RBC) and reticulocyte counts. The average CO concentrations during patrol remained below 20 ppm (range 15–20); the average CO_2 concentration was 0.9%. A base-line study was performed prior to patrol while the subjects were breathing atmospheric air. Three determinations were performed at different times during patrol. These studies revealed a statistically significant rise in Hb, Hct, and RBC counts during the first 32 days of patrol and a subsequent decline almost to base-line levels on the 52nd day of patrol. Chronic exposure to low levels of carbon monoxide (caused by smoking) is known to produce a rise in Hb, Hct, and red cells, to compensate for the anoxic stress induced by higher carboxyhemoglobin levels (HbCO). Inhalation of CO_2 in higher concentrations (5–8% CO_2) causes an increase in ventilation and higher O_2 tensions, which are known to inhibit the erythropoietic response caused by acute or chronic hypoxia. However, the CO_2 concentration of 0.9% found in submarines is apparently too low to compensate for the slight anoxic stress produced by increased levels of CO. Both smokers and non-smokers showed this response; however, only smokers exhibited a rise in reticulocyte counts.

carbon monoxide poisoning
smokers and non-smokers
interaction of CO_2 and carbon monoxide
erythrocytes
hemoglobin
hematocrit

In nuclear-powered submarines, men live in a sealed environment and are continuously exposed to atmospheric contaminants such as carbon dioxide (CO_2) and carbon monoxide (CO). The effects of prolonged exposure to 0.7–1% CO_2 on submariners have been summarized by Schaefer (1979) for 13 patrol studies. Hypercapnic stress causes increases in respiration and changes in the acid-base balance, electrolytes, and calcium-phosphorus metabolism. Findings correspond in general to those obtained in the laboratory during pro-

longed exposure to 1.5% CO_2 (Schaefer, Hastings, Carey, and Nichols 1963a; Schaefer, Nichols, and Carey 1963b; Schaefer, Nichols, and Carey 1964).

Carbon monoxide, caused primarily by smoking, is also present in the submarine atmosphere. Weybrew (1974) reported the results of an evaluation of smoking habits in 347 submariners that was carried out in 1967. It can be assumed that at the time of the present study (1969), submariners had similar smoking habits. Weybrew found 27% non-smokers, 7% occasional smokers, 15% light smokers (¼ package of cigarettes or 1 pipeful/1 cigar a day), 46% moderate smokers (1–1¼ package of cigarettes or 10 pipes/8 cigars/day), and 5% heavy smokers (2+ packages of cigarettes, 12+ pipes, or 9+ cigars/day). According to Lightfoot (1972), catalytic burners have reduced the previously much higher concentrations of CO (about 100 ppm) to 8–10 ppm in present submarine operations.

Schulte (1961) found an average CO concentration of 44 ppm during a U.S. Polaris submarine patrol of 72 days. A continuous exposure to 44 ppm CO would be expected to cause an equilibrium value of 8–10% carboxyhemoglobin (HbCO). Under these conditions, Schulte (1961) did not find any gross changes in behavior or work performance.

The maximum permissible threshold limit value of CO for 90 days' continuous exposure is 25 ppm. Exposure to this level produces a saturation level in non-smokers of 5% carboxyhemoglobin, while exposure to 8–10 ppm results in a saturation level of 1.6% HbCO in the non-smoker. According to Lightfoot (1972), 1.1% HbCO has been found in non-smokers in a British submarine, while smokers (20 cigarettes a day) averaged 8% HbCO and heavy smokers (2 subjects) showed a HbCO level of over 18%.

Impairment of performance (visual discrimination time-interval estimation and complex task performance) has been observed at levels of 2–10% HbCO (Beard and Grandstaff 1970). However, other researchers have not been able to confirm these results (Mikulka 1970). Carbon monoxide interfered significantly with the oxygen supply (Ayres, Giannelli, and Muellett 1970) at a HbCO level of 9%. These workers observed an increase averaging 8% HbCO in the blood of patients after administration of 5% CO in air for 30–120 s and 0.1% CO (1000 ppm) in air for 8–15 min; this resulted in a reduction of 8 mmHg in the venous oxygen tension, increased minute ventilation, a 44% rise in coronary blood flow, and reduced myocardial oxygen uptake. Changes could be identified at a level of HbCO as low as 4%.

Permutt and Farhi (1969) have calculated that exposure to 70 ppm CO for a period long enough to reach a steady state would result in a HbCO concentration of 9%. Assuming that there would be no change in blood flow, Hb concentration, or alveolar ventilation, the venous P_{O_2} would be lowered by 4–6 mmHg, which may be equivalent to a 37% reduction of Hb concentration or a 46% decrease of arterial P_{O_2}. It seems, therefore, that a rather small amount of HbCO can produce a significant reduction in the oxygen supply to the tissues. In persons with decreased arterial P_{O_2} from chronic lung disease or anemia, the decrease in tissue oxygenation caused by exposure to CO would be even greater. The effects of exposure to different concentrations of CO can be summarized according to Stewart (1974). Carboxyhemoglobin levels of 1–5% cause an increased blood flow to vital organs, which compensates for the loss of oxygen-carrying capacity of the blood caused by the binding of CO on Hb. Carboxyhemoglobin levels of 2–9% reduce exercise tolerance, increase visual light thresholds, and have other CNS effects. At HbCO levels higher than 9%, symptoms of headache occur (Stewart 1974).

The most sensitive indicators of the anoxic stress produced by exposure to CO appear to be increases in hematocrit and red cell mass, which were found to correlate very well with the levels of HbCO in the blood of 29,000 blood donors (smokers and non-smokers) (Stewart, Baretta, Platte, Stewart, Kalbfleisch, van Yserloo, and Rimm 1974).

The present report deals with a study of red cell parameters, made during a 1969 patrol, which demonstrated increases in red cell parameters in both smokers and non-smokers exposed to CO levels ranging between 15 and 20 ppm and at an average CO_2 concentration of 0.9%.

MATERIALS AND METHODS

Twenty volunteers were chosen at random from the crew of a Polaris submarine. The subjects ranged in age from 20 to 37 years. All were considered to be in good health, as evidenced by recent physical examinations that included blood counts, urine analysis, and chest X rays.

The following procedures were used before and during patrol. Blood was collected by venipuncture in Vacutainer tubes; disodium ethylenediamine tetracetate was used as an anticoagulant. Hemoglobin determinations were performed in duplicate with the Sahli-Haden Hemoglobinometer, using an Ulrich pipette, and 0.1 N HC1 as the diluting fluid. Hematocrit values were determined in duplicate, using capillary hematocrit tubes and a microhematocrit centrifuge. Red blood cell counting determinations were performed with Thoma glass pipettes and using Gower's solution as a diluting fluid; a Spencer Bright Line counting chamber was used. All erythrocyte counting determinations were duplicated. Reticulocytes were stained with methylene blue; 1,000 red blood cells were counted.

Determinations were performed on the following schedule: 1) seven days before patrol while all volunteers were breathing atmospheric air, and 2) during the 6th, 32nd, and 52nd days of an approximately 8-week patrol.

All determinations were performed within 24 h of venipuncture. If there was any significant delay between venipuncture and the determination, the blood was refrigerated at 4–6°C to prevent lysing of the cells. The Student's *t*-test was used for statistical analysis. Carbon dioxide and CO concentrations in the submarine atmosphere were monitored with infrared CO_2 and CO analyzers.

RESULTS

Carbon monoxide concentrations in the submarine atmosphere were always below 20 ppm and ranged between 15 and 20 ppm. Ambient CO_2 levels were 6.63, 6.43, and 6.52 mmHg, respectively, on the days blood determinations were made. These percentages correspond to an average CO concentration of 0.9%. During the patrol, CO_2 levels consistently remained between 5.0 and 9.0 mmHg. Atmospheric pressure on board approximated 760 mmHg. Oxygen levels ranged between 140 and 160 mmHg.

The effect of prolonged exposure to 15–20 ppm CO and 6.6 mmHg CO_2 (0.9% CO_2) on Hb, Hct, RBC, and reticulocytes for various periods during patrol are presented in Table 1. Hemoglobin, Hct, and RBC showed a statistically significant rise during the first 32 days of patrol and a gradual return to base-line levels during the last week of patrol. The only exception to this pattern occurred with the hemoglobin level, which continued to show a statistically significant elevation during the last week of patrol (52nd day, 15.50 g), but was falling compared with earlier patrol levels (6th day, 15.71 g; 32nd day, 15.75 g).

The reticulocyte response showed an upward trend in the first two patrol determinations and then fell to base-line level late in patrol, but this elevation was not statistically significant (Table 1).

TABLE 1
EFFECT OF PROLONGED EXPOSURE TO ELEVATED CO AND CO_2 CONCENTRATION ON RED CELL PARAMETERS (ALL SUBJECTS)

		Pre-Patrol	Patrol		
			6th Day	32nd Day	52nd Day
		Atmospheric Conditions			
CO, ppm		0	Below 20 ppm (Range 15–20)	Below 20 ppm (Range 15–20)	Below 20 ppm (Range 15–20)
CO_2, mmHg	Mean	0	6.63	6.43	6.52
	SE		0.18	0.09	0.09
	n		(12)	(12)	(12)
		Red Cell Parameters			
Hb, g	Mean	15.08	15.71	15.75	15.58
	SE	0.120	0.124	0.150	0.150
	n	(20)	(19)	(20)	(20)
	P	—	<0.001	<0.005	<0.02
Hct, vol %	Mean	47.3	48.6	48.6	47.1
	SE	0.449	0.467	0.419	0.478
	n	(20)	(19)	(20)	(20)
	P	—	—	<0.05	—
RBC, millions/mm³	Mean	4.71	5.23	5.15	4.89
	SE	0.126	0.105	0.168	0.116
	n	(20)	(19)	(20)	(20)
	P	—	<0.005	<0.05	—
Reticulocytes, /100 RBC	Mean	1.02	1.16	1.16	0.95
	SE	0.114	0.106	0.096	0.072
	n	(20)	(19)	(20)	(20)
	P	—	—	—	—

In the statistical analysis, pre-patrol samples were compared with the 6-day, 32-day, and 52-day patrol samples. Only statistically significant *P* values are listed.

When the group was further divided into smokers and non-smokers, essentially the same responses occurred, except that the rise in the reticulocyte counts occurred only in the smokers' group (Tables 2 and 3).

DISCUSSION

Carbon monoxide has a much higher affinity for hemoglobin than oxygen. The most significant physiological effects of CO are therefore related to the formation of HbCO, which decreases oxygen transport capacity and also makes it more difficult to unload the oxygen carried by the blood in the tissues (Otis 1970). Hypoxia caused by CO resembles that produced by exposure to a low-oxygen gas mixture or to altitude. Acclimatization to hypoxia such as occurs in exposure to CO at altitude involves a marked increase in red cell mass (Otis 1970).

TABLE 2
EFFECT OF PROLONGED EXPOSURE TO ELEVATED CO AND CO_2 CONCENTRATION ON RED CELL PARAMETERS (SMOKERS)

		Pre-Patrol	Patrol		
			6th Day	32nd Day	52nd Day
		Atmospheric Conditions			
CO, ppm		0	Below 20 ppm (Range 15–20)	Below 20 ppm (Range 15–20)	Below 20 ppm (Range 15–20)
CO_2, mmHg	Mean	0	6.63	6.43	6.52
	SE		0.18	0.09	0.09
	n		(12)	(12)	(12)
		Red Cell Parameters			
Hb, g	Mean	14.94	15.75	15.78	15.66
	SE	0.225	0.186	0.168	0.224
	n	(9)	(8)	(9)	(9)
	P	—	<0.02	<0.01	—
Hct, vol %	Mean	47.2	49.2	48.4	47.6
	SE	0.518	0.708	0.583	0.461
	n	(9)	(8)	(9)	(9)
	P	—	<0.02	—	—
RBC, millions/mm^3	Mean	4.71	5.26	5.23	4.88
	SE	0.140	0.079	0.273	0.131
	n	(9)	(8)	(9)	(9)
	P	—	<0.005	—	—
Reticulocytes, /100 RBC	Mean	0.79	1.24	1.12	0.87
	SE	0.213	0.211	0.157	0.101
	n	(9)	(8)	(9)	(9)
	P	—	—	—	—

In the statistical analysis, pre-patrol samples were compared with the 6-day, 32-day, and 52-day patrol samples. Only statistically significant *P* values are listed.

Exposure to 15–20 ppm CO would produce an equilibrium level of 2.5–3.2% HbCO, according to the frequently used equation: HbCO saturation (%) = 0.6 × ambient CO (parts/10^6). At these levels of HbCO, increases in red cell parameters compensating for slight anoxic stress have been found in both smokers and non-smokers (Stewart et al. 1974). Prolonged exposure to 15–20 ppm CO during the submarine patrol can, therefore, be considered to have caused the observed increases in Hct, Hb, and erythrocytes.

Data obtained during the patrol clearly demonstrate that both smokers and non-smokers responded to the chronic exposure to increased levels of CO (15–20 ppm) in the submarine atmosphere. However, the trend toward a rise in reticulocytes was present only in the smokers, which indicates greater anoxic stress. Evidence of adaptation to CO has been obtained by Wilks, Tomashefski, and Clark (1959) and Gorbatow and Noro (1948); these latter authors observed that the adaptation to CO was particularly noticeable after the fall in intravascular Hb concentration. This agrees with our data, which also provide evidence for adaptation to

TABLE 3
EFFECT OF PROLONGED EXPOSURE TO ELEVATED CO AND CO_2 CONCENTRATION ON RED CELL PARAMETERS (NON-SMOKERS)

		Pre-Patrol	Patrol		
			6th Day	32nd Day	52nd Day
		Atmospheric Conditions			
CO, ppm		0	Below 20 ppm (Range 15–20)	Below 20 ppm (Range 15–20)	Below 20 ppm (Range 15–20)
CO_2, mmHg	Mean	0	6.63	6.43	6.52
	SE		0.18	0.09	0.09
	n		(12)	(12)	(12)
		Red Cell Parameters			
Hb, g	Mean	15.18	15.18	15.73	15.59
	SE	0.143	0.190	0.238	0.238
	n	(11)	(11)	(11)	(11)
	P	—	<0.05	—	—
Hct, vol %	Mean	47.4	48.1	48.7	46.7
	SE	0.380	0.713	0.665	0.760
	n	(11)	(11)	(11)	(11)
	P	—	—	—	—
RBC, millions/mm^3	Mean	4.70	5.20	5.09	4.90
	SE	0.015	0.161	0.199	0.164
	n	(11)	(11)	(11)	(11)
	P	—	—	—	—
Reticulocytes, /100 RBC	Mean	1.20	1.10	1.19	1.01
	SE	0.171	0.057	0.143	0.105
	n	(11)	(11)	(11)	(11)
	P	—	—	—	—

In the statistical analysis, pre-patrol samples were compared with the 6-day, 32-day, and 52-day patrol samples. Only statistically significant *P* values are listed.

CO, since the increase in Hb, Hct, and RBC found in smokers and non-smokers during patrol was limited to the first 32 days on patrol. On the 52nd day of patrol, the Hb, Hct, and RBC values decreased again.

To evaluate the influence of the increased level of CO_2 (0.9%), two mechanisms producing increased red cell parameters should be discussed, a decrease in plasma volume and an increase in red cell mass due to stimulation of the erythropoietic system by hypoxia. The first of these reactions has been observed during the initial stages of hypoxia prior to the slower responses of the erythropoietic system, which produces a sustained increase in red cell volume during adaptation to hypoxia (Mylrea and Abbrecht 1970).

Acute exposure to 1% CO_2 did not affect either intra- or extracellular fluid shifts in guinea pigs and rats (Murray, Abbott, and Schaefer 1975), and prolonged exposure (1–4 weeks) did not cause significant changes in hematocrit. These findings are in line with observations made

on human subjects during 42 days of exposure to 1.5% CO_2, in which RBC, Hct, and Hb did not change significantly, except for a transient fall in Hb (Schaefer et al. 1964).

At higher levels, CO_2 is known to counteract hypoxic effects by improving tissue oxygenation caused by hyperventilation. Simultaneous exposure to hypercapnic-hypoxic gas mixtures containing 5–8% CO_2 was found to suppress the erythropoietic response produced by hypoxia (Faura, Gurney, and Fried 1968; Streeter, Pepelko, and Cain 1975). At these concentrations, CO_2 can effectively prevent an increase in the red cell parameters discussed here. However, the 0.9% level of CO_2 measured in the submarine atmosphere is apparently too low to cause a significant increase in respiration or a rise in Po_2 to compensate for the anoxic stress caused by chronic exposure to 15–20 ppm CO.

It is unfortunate that HbCO measurements were not performed during this patrol. The findings in the red cell parameters measured establish the need for systematic patrol studies, where HbCO and red cell parameters could be determined, together with investigation of oxygen transport, including the role of 2,3-Diphosphoglycerate (2,3 DPG). Astrup (1970) observed that 24-h exposure to CO resulting in a 20% HbCO level produced an 8% reduction in 2,3 DPG. This causes the oxygen dissociation curve to shift to the left and reduces oxygen delivery to the tissues.

Interaction of elevated CO_2 and CO during prolonged exposure on submarines has to be taken into account. The findings of Ayres et al. (1970) demonstrating an increase in respiratory minute volume in patients with an 8% increase of HbCO and those of Mills and Edwards (1968) showing a slight increase in alveolar ventilation during CO inhalation suggest that CO_2 and CO may have a synergistic effect on ventilation. This would explain the observations that respiratory minute volume during exposure to 0.9% CO_2 on patrols increased more than during exposures to 1.5% CO_2 in the laboratory (Schaefer 1979). However, this increase in ventilation is apparently not sufficient to reduce the anoxic stress.

It has been suggested that chronically higher HbCO levels play a role in the pathogenesis of atherosclerosis (Astrup and Kjeldsen 1974). Whether long-term exposure to low levels of CO, such as those existing currently on submarines (8–10 ppm) (Lightfoot 1972) have an effect on health, particularly on that of non-smokers, cannot be stated at this time. There are great individual differences in susceptibility. Monitoring HbCO levels during patrols and measuring atmospheric CO concentrations are essential as a base for evaluating any possible health hazards.

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Wilson, A. J., and K. E. Schaefer. 1979. Effets de l'exposition prolongée à de hautes concentrations de monoxyde et dioxyde de carbone sur la globule rouge au cours de voyages en sous-marins. Undersea Biomed. Res. Sub. Suppl.: S49–S56.—Pour préciser les effets sur les érythrocytes d'une exposition prolongée à des concentrations élevées de dioxyde et de monoxyde ce carbone, on a étudié vingt volontaires choisis parmi l'équipage d'un sous-marin du type "Polaris". Des déterminations de l'hématocrite et du taux d'hémoglobine, d'érythrocytes, et de réticulocytes ont été réalisées. La concentration moyenne de CO n'a pas dépassé 20 ppm. (Elle se trouve entre 15 et 20 ppm; celle de CO_2 est environ 0,9%.) Les déterminations sont réalisées avant le voyage, pendant que les sujets respiraient l'air atmosphérique; et à trois reprises pendant le voyage. On a observé une augmentation statistiquement significative du taux d'hémoglobine, de l'hématocrite, et du taux d'érythrocytes pendant la première période du voyage (32 jours), suivi d'une diminution presqu'aux valeurs de départ le 52e jour du voyage. Il est connu que l'exposition chronique à des concentrations modestes de CO (p. ex. chez le fumeur) provoque une hausse de l'hémoglobine, de l'hématocrite, et du taux des érythrocytes pour compenser le stress anoxique des concentrations

augmentées de la carboxyhémoglobine. La respiration de concentrations plus importantes (5–8%) provoque une augmentation de la ventilation et des pressions de O_2, qui tendent à inhiber la réponse érythropoiétique de l'hypoxie aigue ou chronique. Cependant la concentration de CO_2 (0,9%) observée au bord du sous-marin paraît trop modeste pour compenser le stress anoxique dû à la concentration augmentée de CO. Cette réponse s'est manifestée chez le fumeur comme chez le non-fumeur; le taux de réticulocytes n'est augmentée que chez le fumeur cependant.

toxicité du monoxyde de carbone
fumeurs
non-fumeurs
interaction de CO_2 et du monoxyde de carbone
érythrocytes
hémoglobine
hématocrite

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