Chronic Exposure to Carbon Monoxide at High Altitude: Effects on Mean Electrical Axis

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COOPER, R., J. J. McGRATH, S. DOOLEY AND M. T. KOPETZKY. *Chronic exposure to carbon monoxide at high altitude: Effects on mean electrical axis.* PHYSIOL BEHAV **46**(1) 75–79, 1989.—The effects of breathing CO continuously at high altitude on the mean electrical axis of the heart, hematocrit ratio and body weight were studied in laboratory rats. Laboratory rats were exposed for 6 weeks to: 100 or 500 ppm CO; 15,000 feet simulated high altitude (SHA); or 100 or 500 ppm CO at SHA. SHA decreased body weight significantly; CO and CO-SHA interaction had no significant effect on body weight. CO and SHA increased hematocrit ratio significantly; five hundred ppm CO increased hematocrit ratio to a greater extent than 100 ppm CO. There was a significant interaction between 500 ppm CO and SHA on hematocrit ratio. The mean electrical axis (MEA) was shifted to the right by SHA, and shifted to the left by CO. The effect was dose dependent, with the greater left shift occurring with 500 ppm CO. There was a significant interaction between 500 ppm CO and SHA on the MEA. These results indicate that, in general, the effects produced by 15,000 feet SHA are not intensified by 100 ppm CO, but are intensified by 500 ppm CO.

Carbon Monoxide   High altitude   Electrocardiogram   Hypoxia   Air pollution   Mean electrical axis

THE physiological responses of mammals to chronic high altitude exposure have been well-studied; the most prominent responses include increased blood hemoglobin concentration caused by hypoxia (15), and right ventricular hypertrophy, caused by hypoxic pulmonary vasoconstriction (12). Likewise, the physiological responses to chronic carbon monoxide (CO) exposure have been reasonably well-studied; the most prominent responses include increased blood hemoglobin caused by hypoxia (16), but left ventricular hypertrophy caused by increased cardiac work (9). Due to technical difficulties, there have been few studies of the long term effects of breathing CO at altitude (5). The lack of information in this area is a significant problem because over 2.2 million people living at altitudes in excess of 1524 m (5,000 ft), and countless tourists and other sojourners visiting high altitude areas during both the summer and winter months (8), are exposed to CO from automobiles, fireplaces and smoking.

In this study, we tried to analyze the chronic effects of CO at 15,000 ft on the mean electrical axis (MEA), hematocrit ratio and body weight in the laboratory rat.

METHOD

Exposure System

The altitude chamber system used in these studies has been described previously (6). It consists of 6 cylindrical steel chambers connected to a central air supply duct. Each chamber is fabricated from a 200 l barrel and fitted with a clear, Lucite plastic door for observing the animals. The door is machined and fitted with an 0 ring to ensure a gas tight seal. Air enters the system through a Hepa filter and flows through each chamber (55 l/min or 16 air changes/hr). Altitude, simulated by an Atlantic Fluidic's water-sealed pump (Fluid-Vac, model A10) and a system of adjustable globe valves, is measured by an aircraft altimeter. CO, provided in high-pressure steel cylinders, is introduced into the air-intake side of each chamber via a mass flow controller (Matheson Gas). Chamber atmosphere is sampled sequentially from the outflow duct of each chamber via a switching solenoid (Chronotrol-Lindberg Enterprises, Inc.). CO concentrations are measured continuously for 1 hr with a nondispersive infrared analyzer system (Beckman) and recorded continually on a chart recorder (Houston Instruments).

Animals

Male, Fisher-344 rats (Sasco Inc.) were used in these studies. The rats weighed approximately 135 g and 200 g, respectively, at the beginning of the 100 ppm CO and 500 ppm CO studies. The animals were housed in shoe box cages (6/cage) placed in the exposure chambers; they were fed a commercial diet (Purina Rat

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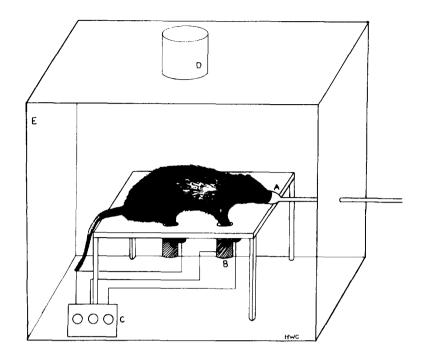[1]Requests for reprints should be addressed to Dr. James J. McGrath.

FIG. 1. ECG recording set ups: (A) Nose cone for administering gas mixture and halothane; (B) Saline-filled containers; (C) ECG panel; (D) Vent; (E) Plastic chamber in Faraday Cage.

Chow, Ralston Purina Co., St. Louis, MO) and provided tap water ad lib. Water was supplied in standard watering bottles and care was taken to fill the bottles completely so that air could not displace water from the bottles during the ascent to SHA.

There were two parts to this study: In the first, the animals were exposed to ambient (AMB), AMB + 100 ppm CO, 15,000 ft altitude (SHA) and SHA + 100 ppm CO; in the second, the animals were exposed to AMB, AMB + 500 ppm CO, SHA, and SHA + 500 ppm CO.

Analytical Methods

Blood samples obtained from the tail were used to measure hematocrit ratios, by the microhematocrit technique, and carboxyhemoglobin (COHb) concentrations by the method of Small *et al.* (13). One hundred ppm CO caused a COHb concentration of $8.4 \pm 0.5\%$ (Mean $\pm$ SE), whereas 500 ppm CO caused a COHb concentration of $39.0 \pm 1.7\%$.

At the end of six weeks, ECG's were measured on each rat. All rats were treated equally during the ECG recordings, and the time required to remove the rat from the chamber and begin recording did not exceed 15 minutes.

The rats were anesthetized with halothane administered via a nose cone (Fig. 1); the cone, fabricated from silicone rubber fit loosely over the rat's nose. A vented box was used to contain the rat and the apparatus required for recording the ECG. A vacuum line was attached to a port on top of the box and the box was placed in an aluminum Faraday cage. The animal and the apparatus could be manipulated via an opening in the side of the box; the opening was covered with a screen during the exposure.

To record the ECG, the rat was placed on a platform and its legs were placed into containers filled with a 10% NaCl solution. Individual wires from three of the leg containers (right front leg, left front leg, left rear leg) were fastened to a panel; the panel had connectors to which the corresponding leads from the ECG

recorder were attached. The ground lead from the ECG recorder was attached to the Faraday cage.

The ECG recordings were taken in a standard sequence (lead I, lead II, lead III). The mean electrical axis obtained from the recordings of the three common leads was determined by the common triaxial reference system according to the method of Burch and Winsor (2).

The effects of altitude and CO were assessed by two-way analysis of variance (ANOVA) with the Stats Plus ANOVA procedure (Human Systems Dynamics, Northridge, CA). A *p* value of less than 0.05 was the minimal level of significance.

RESULTS

Body weights increased in all groups throughout the 6-week exposure (Fig. 2). At the end of the experiment, body weights in both the 100 and 500 ppm CO studies were significantly lower ($p < 0.001$) in the SHA than in the AMB groups. There were no significant differences in body weight between groups due to CO treatment nor was there a significant interaction between SHA and CO on body weight.

Hematocrit ratios increased with both CO and SHA (Fig. 3). At the end of the experiment, hematocrit ratios were significantly higher in the SHA ($p < 0.001$) than in the AMB groups, and significantly higher ($p < 0.001$) in both the 100 and 500 ppm CO groups than in the 0 ppm CO groups. Although there was no significant interaction between SHA and 100 ppm CO on hematocrit ratio, there was a significant interaction ($p < 0.001$) between SHA and 500 ppm CO.

The MEA was shifted to the right by SHA, and shifted to the left by CO (Table 1; Fig. 4 A,B). The MEA was significantly greater ($p < 0.001$) in the SHA compared to the AMB groups, in both the 100 and 500 ppm CO Studies. The magnitude of the MEA was less in the 100 and 500 ppm CO groups than in the 0 ppm CO groups, but the differences were not statistically significant. There
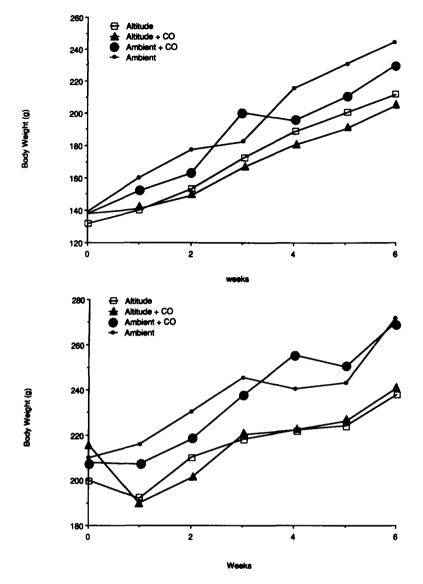
FIG. 2. Effects on body weight of exposure to (upper) 100 ppm CO, and (lower) 500 ppm CO, at 15,000 feet.

was a significant interaction ($p<0.05$) between SHA and 500 ppm CO on the magnitude of the MEA.

DISCUSSION

Body weight, decreased significantly by SHA, was unaffected by either 100 or 500 ppm CO. This observation is in accord with others who report that altitude, depending on the intensity of the exposure, depresses body weight by decreasing both caloric intake and food utilization (1). The decrease in body weight at SHA was not intensified by simultaneous exposure to CO.

Both SHA and CO increased hematocrit ratio. There was no significant interaction between SHA and 100 ppm CO on hematocrit ratio, but there was a significant interaction between SHA and 500 ppm CO. An increased red blood cell mass maintains oxygen delivery to the tissues during sustained SHA or CO-hypoxia. However, because of the increased work required to pump the more viscous blood, not all investigators agree that this response is beneficial to the organism. Guyton and Richardson (4)

suggest that changes in hematocrit ratio affect not only the oxygen-carrying capacity of blood, but blood flow to the tissues as well. Consequently, if hematocrit ratio increases much above normal, blood flow may decrease and oxygen delivery to the tissues may be reduced. This reduction in blood flow can more than offset the increased oxygen-carrying capacity of the blood. Smith and Crowall (14) conclude that there is an optimum hematocrit ratio at sea level that shifts to a higher value with altitude acclimation. We did not attempt to determine if oxygen delivery to the tissues was compromised by the increased hematocrit ratios observed in these studies.

A major emphasis of this study was to determine if CO shifts the position of the MEA of the heart, and if altitude influences the magnitude of this shift. SHA alone shifted the MEA toward the right; the rightward shift in MEA at altitude is known to be caused by right ventricular hypertrophy. Right ventricular hypertrophy occurs secondarily to the pulmonary hypertension that is common in altitude-exposed animals (3,12). Milledge (7) concludes that pulmonary hypertension along with a high hematocrit leads to
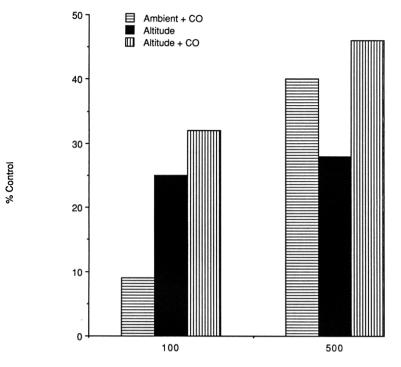
FIG. 3. Effects on hematocrit ratios of exposure to 100 ppm CO, and 500 ppm CO at 15,000 feet. Data expressed as percent of control (ambient + 0 ppm CO).

TABLE 1

MEAN ELECTRICAL AXES[a] IN RATS EXPOSED TO 100 PPM CO, AND 500 PPM CO AT 15,000 FEET

Treatment	100 ppm CO (Degrees)	500 ppm CO (Degrees)
Ambient	40.5 ± 9.1 (12)	48.2 ± 10.9 (6)
Ambient + CO	27.0 ± 4.8 (12)	16.0 ± 10.6 (6)
Altitude	67.1 ± 3.6† (12)	79.7 ± 30.2† (6)
Altitude + CO	65.0 ± 10.3 (12)	164.6 ± 33.1* (5)

[a]Values Mean ± SEM. Numbers of animals shown in parentheses. Two-way ANOVA used to test treatment effects.
*$p < 0.05$; †$p < 0.01$.

increased work for the right ventricle and this results in right ventricle hypertrophy. Milledge's report on the 1960–61 Himalayan Scientific and Mountaineering Expedition examined the ECG changes that occur at altitude. ECG's were taken after the subjects had reached the desired altitude (17,500–19,000 ft), and again while breathing oxygen. When the subjects breathed oxygen the right axis deviation returned to the sea-level position; these workers conclude that there is a critical time of chronic hypoxia, after which changes in the right ventricle or pulmonary circulation are not reversed by relatively short periods of oxygen breathing. We feel that the 6 week exposure for our study was beyond the critical time, and an earlier report on heart weights supports this notion (6). SHA shifted the MEA to the right even in the presence

of 100 ppm CO. This suggests that at 15,000 ft and 100 ppm, right ventricle preponderance is still the dominant feature.

CO shifted the MEA to the left, and the shift was greater with 500 ppm CO than with 100 ppm CO. The leftward shift in the MEA with chronic CO is caused by left ventricular hypertrophy which is produced by a volume overload of the left ventricle. Penney and co-workers (10,11) have shown cardiac enlargement in rats exposed to 500 ppm CO for up to 42 days. At 500 ppm CO, both the right and left ventricles were enlarged and cardiac output was increased by an increased stroke volume. These workers conclude that the greater heart work required to provide adequate oxygenation of the tissues in the presence of CO hypoxia is the major factor responsible for CO-induced cardiomegaly, and that CO produces a volume overload rather than a pressure overload on the heart. The dramatic shift in MEA observed with 500 ppm at SHA is probably caused by the SHA-induced right ventricle hypertrophy combined with the total cardiac hypertrophy induced by 500 ppm as reported in the Penney studies.
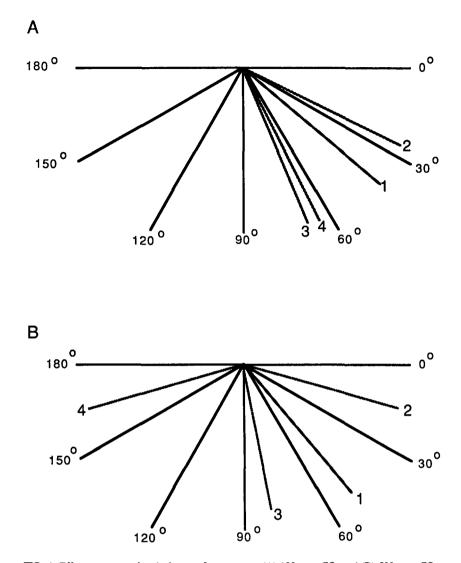
A

B

FIG. 4. Effects on mean electrical axes of exposure to (A) 100 ppm CO, and (B) 500 ppm CO at 15,000 feet. Labeled lines: 1—Ambient, 2—Ambient + CO, 3—Altitude, 4—Altitude + CO.

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