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Low-Level Carbon Monoxide Exposure and Work Capacity at 1600 Meters

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LOW-LEVEL CARBON MONOXIDE EXPOSURE AND WORK CAPACITY AT 1600 METERS

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

Results of two studies are discussed on the following pages. The initial study investigated nine, non-smoking, male subjects breathing either filtered air (FA) or 28 ppm CO in filtered air. The dose-response study exposed twelve subjects to FA or CO such that the end-exercise HbCO levels were 0.7, 3.5, 5.4, and 8.7 percent HbCO.

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ABSTRACT

At sea level, low-level carbon monoxide (CO) exposure impairs exercise performance. To determine if altitude residence at 1600 m augments this CO effect, two studies of graded treadmill work capacity were done. The Initial Study investigated nine, non-smoking, male subjects breathing either filtered air (FA) or 28 ppm CO in filtered air. End-exercise carboxyhemoglobin (HbCO) levels averaged 0.9 %HbCO breathing FA and 4.7. %HbCO breathing CO. Total work performance and aerobic work capacity were reduced. Work heart rate was elevated, and post-exercise left ventricular ejection time breathing CO did not shorten to the same degree as with FA exposure. CO exposure resulted in a lower anaerobic threshold, and a greater minute ventilation occurred at work rates heavier than the anaerobic threshold due to an increased blood lactate level. The Dose-Response Study exposed twelve subjects to FA or CO such that the end-exercise HbCO levels were 0.7, 3.5, 5.4 and 8.7 %HbCO. Exercise performance and aerobic work capacity were impaired in proportion to the CO exposure. In both studies, maximal cardiopulmonary responses were not different, but submaximal exercise changes were elevated breathing CO. Thus, in healthy young men residing near 1600 m, an increase in low-level CO exposure produced a linear decrement in maximal aerobic performance similar to that reported at sea level.

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SECTION I

INTRODUCTION

Ambient Air Quality Standards (AAQS) have been established to protect, with a reasonable margin of safety, susceptible segments of the population as well as healthy individuals from the harmful effects of air pollution. The present AAQS for carbon monoxide (CO) is 9 ppm averaged over an eight hour period and 35 ppm averaged over a one hour period. These levels of CO and exposure times are sufficient to increase the blood carboxyhemoglobin concentration (HbCO) about 1.5%. The AAQS have been established, however, from data acquired from sea-level studies. Information necessary to adequately evaluate any additional risk factors for sojourners or residents during CO exposure at altitude does not exist.

Acute exposure to CO impairs exercise performance as measured by maximal aerobic power ($\dot{V}O_2$ max) at sea level (2,8,12,14,18,19). The threshold for a statistically significant decrease in $\dot{V}O_2$ max appears to be at a HbCO level of 4.0% (2,12). Above this level, the decrease in $\dot{V}O_2$ max is proportional to the HbCO level (2,17).

Hypobaric hypoxia that occurs at altitude also impairs maximal aerobic power. The threshold for an altitude-induced decrease in $\dot{V}O_2$ max is at an elevation of 1600 m. Above this altitude, the loss of $\dot{V}O_2$ max is proportional to the decrease in inspired oxygen tension (5,10).

The purpose of this study was to determine if the effects of low-level CO exposure upon aerobic work capacity would be augmented in healthy young men who reside at an altitude of 160m (Denver). Their aerobic work capacity was measured using graded treadmill tests with and without CO exposure. Also, the electrocardiogram and systolic time intervals were investigated also to determine if decrements in cardiac function occurred. In the initial research research study, 9 healthy young males had their maximum oxygen consumption measured four times: twice while breathing filtered air, and twice while breathing ambient air which contained

sufficient CO to maintain a blood concentration of 5% HbCO after a quick CO loading. In a subsequent dose-response study, 12 healthy young males performed maximal exercise tests at each of four different levels of HbCO. Each subject was exposed randomly to filtered air, nearly free of CO, and to sufficient CO in the other three experiments to maintain venous COHb levels of approximately 4, 6, and 9% HbCO after quick CO loading. The results of these tests were analyzed to determine the effects of low-level CO concentrations on exercise performance and cardiac function in healthy young males acclimated to residence at 1610m.

SECTION II
CONCLUSIONS

1. At an altitude of 1610m (Denver, Colorado), a proportional reduction of total exercise time, total vertical work done, and final work rate was found when the HbCO level was increased from 1% to 9% HbCO.
2. Maximal aerobic work capacity, measured as $\dot{V}_{O_2}$ max, decreased linearly with the level of CO exposure.
3. Although work capacity during CO exposure was reduced, maximal heart rates, maximal minute ventilations, peak venous lactates, and oxygen debts were not significantly different suggesting that CO exposure provoked a greater cardio-respiratory adaptation at a given submaximal workload.
4. At 3-4 minutes post-exercise, left ventricular ejection time was not shorted as much during CO exposure as it was during FA breathing. This finding has also been reported for patients reporting chest pain during exercise.
5. The changes found in exercise performance and cardiac function during CO exposure were comparable to those reported in sea level studies.

SECTION III
RECOMMENDATIONS

1. Since it is believed that the rate of CO uptake is increased as the partial oxygen pressure level decreases, i.e., the higher the altitude, then a test of this hypothesis should be made in Denver residents before any affirmation or modification of the current AAQS for 1600m is made.
2. Since Denver's elevation is at the threshold for altitude-induced aerobic work capacity decrement, then both the exercise performance and cardiac function of residents at a higher elevation, e.g., Leadville (3100m), and sojourners from Denver altitude to that higher altitude should be studied.
3. Since the oxygen supply to the heart tissue, especially in heart patients, is crucial to work performance, the effect of CO on angina-limited exercise in patients living at Denver altitude should be studied.
4. Since patients with chronic obstructive pulmonary disease living in Los Angeles show a remarkable loss of work capacity when exposed to low CO level, patients with lung disease who reside in Denver should be studied to determine if altitude aggravates exercise-induced breathlessness.
5. Since the blood supply to the brain is crucial, the effects of CO exposure on judgment should be studied in asymptomatic 50-to-60 year old individuals who live in Denver.

SECTION IV
EXPERIMENTAL DESIGN AND METHODS

1. Initial Study

We studied nine healthy, male volunteers with a mean (±SEM) age of 24.7 ± 1.4 years, height of 178 ± 2 cm, and weight of 76.6 ± 3.1 kg. Analysis of variance showed no significant change in the subjects' weights during the study. All subjects were non-smokers. Informed consent was obtained from all the subjects. Before participating actively in the study, each subject was given a preliminary physical examination which included a resting 12-lead electrocardiogram (ECG), pulmonary function evaluation, blood analysis, preliminary exercise ECG, and graded stress test to V_{O_2} max.

In the study itself, each subject exercised four times, twice breathing filtered air (FA) and twice breathing air containing CO. These four sessions were divided into two pairs, with each pair consisting of one FA and one CO experiment. The order of FA and CO experiments in each pair was assigned in a double-blind fashion.

In each experimental session, the same protocol was used. Following resting 12-lead ECG and systolic time interval (STI) measurements, a forearm venous blood sample was taken and analyzed for HbCO. The initial HbCO estimate was always made on a CO-Oximeter (Instrumentation Laboratory) with the more accurate HbCO measurement made later using a gas-chromatograph technique which was modified for use with a flame-ionization detector (Baseline Industries). The desired blood HbCO concentration was obtained quickly in the CO experiments by having the subject rebreath from a closed-circuit system to which a bolus of 100% CO had been added (7). The volume CO required to increase the subject's HbCO level to 5% was calculated from a preliminary estimate of total body hemoglobin. About 90% of the calculated CO volume was added to a 4.2 liter rebreathing circuit over a 1-3 minute period. After 8 minutes of rebreathing, another

venous blood sample was taken, and the HbCO level measured. Additional CO was administered at that time if needed to achieve the 5 %HbCO level. The total volume of 100% CO administered ranged from 37 to 53 ml (STPD). A third blood sample was taken at the end of the 20 minute rebreathing period to determine the final pre-exercise HbCO level. For the remainder of the experiment, the subject breathed from an open-circuit system. This system provided the inspired CO level that was required to maintain the desired HbCO for that experiment. Throughout the experiment, the inspired and expired CO levels were monitored by a long-path infrared analyzer (Beckman, Model 315B).

Maximal oxygen consumption ($\dot{V}_{O_2}$ max) was measured using a modified incremental treadmill test (4). The work test was preceded by a 9 minute resting period with the subject in the supine position. The subject began the test by walking for 4 minutes at 2.0 mph on a 0% grade. The treadmill speed was then increased at 2 minute intervals, to 3.0 and 3.75 mph. At 3.75 mph, the grade was increased 2% every 2 minutes until the subject could no longer continue or until the treadmill had reached its maximum grade of 20%. If the subject could still exercise at a 20% grade, then the speed was increased every 2 minutes to 4.5, 5.0, and 5.5 mph until the subject's maximal performance was reached. Following exercise, the subject walked slowly in place for 1-2 minutes and then rested in the supine position for the remainder of the 60 minute recovery period.

During the exercise tests, minute ventilation ($\dot{V}_E$, BTPS), the expired air fractions of oxygen (F_EO_2) and carbon dioxide (F_{ECO_2}), and heart rate (HR) were measured. These data were processed by an on-line digital computer (Health Garde), which calculated oxygen consumption and other parameters. During the 9 minute pre exericse rest period, computer data sampling was done over the last two minutes of each three minute interval. For work rates producing a HR of less than 180 bpm, the second minute of each 2-minute period was sampled. For heavy work producing a HR above 180 bpm, sampling was done over the last twenty seconds of each work minute. For the first six minutes following exercise sampling was done over the last 20 seconds of each minute. Thereafter during the

recovery period, the sampling intervals were progressively lengthened. A blood sample was taken every fourth minute during exercise and at the fourth minute of recovery.

Minute ventilation was measured in a 120 liter gasometer (Tissot, Collins), and respiratory rate was obtained by monitoring inspiratory flow with a Fleisch pneumotachygraph (Instrumentation Associates) that was connected to a differential strain gauge (PM197, Statham). Expired gas was analyzed for F_{ECO_2} and F_EO_2 by a mass spectrometer (Model 1100, Perkin Elmer) which sampled expired gas from the outlet of a 9 liter mixing chamber. Heart rate was obtained from the ECG recordings. Venous blood samples were analyzed for pH (Radiometer), lactate (Sigma), 2,3-diphosphoglycerate (Sigma), hemoglobin by the cyanmethemoglobin method, and hematocrit by the microhematocrit method.

During the twelve minutes which preceded the sub-maximal exercise, resting, baseline measurement were made. Ventilation was measured over the last two minutes of successive three-minute intervals and a blood sample was drawn during the last minute of the rest period. Submaximal exercise followed the rest with each subject walking continuously for 12 minutes at 5.3 kilometers per hour. The submaximal work intensity (treadmill grade) was adjusted for each subject to produce a heart rate between 100 and 120 bpm at the end of a FA test. The submaximal work was set at the same intensity for each of the four exercise tests for a given subject. Ventilation was measured the last minute of successive two-minute intervals and blood was drawn at the end of the fifth and twelth minutes of the submaximal test. The treadmill and monitoring were then stopped for four minutes while the equipment was recalibrated. The subject came off the mouthpiece for the first minute of the recalibration period. After recalibration, maximal oxygen consumption was measured using a modified incremental treadmill test (11). The subject ran at a constant rate of 10.5 kph (6.5 MPH) and the initial treadmill grade was the same as that during the submaximal walking test. The grade was increased by 2.5% every two minutes until the subject became exhausted and could no longer continue to exercise at such a rate. Data was collected over the last 27 seconds of each minute period. No blood

samples were taken during the maximal test. The subject remained on the breathing system for a sixteen minute recovery period after the maximal test. The first part of recovery consisted of four, one-minute periods, with 27 second collections. This was followed by six, two-minute periods, with 60 seconds collections over the second minte. Blood samples were drawn and measurements for STI calculations were made at the 2nd, 4th, 8th, and 15th minutes of recovery.

The following parameters were monitored on-line using a digital computer (Health Garde): minute ventilation by gasometer (Tissot, Collins); respiratory rate with a Fleisch pneumotachygraph (Instrumentaton Associates) in series with a differential strain gauge (Statham Model 515); and mixed expired oxygen and carbon dioxide concentrations sampled from a 9 liter chamber by a mass spectrometer (Perkin Elmer, Model 1100). Using these signals, the computer calculated values for oxygen consumption.

3. Statistical Analysis

The data were analyzed using a one-way analysis of variance with repeated measures across all exposure conditions (FA vs 5% CO for the initial study; FA, 3%, 6%, vs 9% for the dose-response study). When the F-value was significant at the 5% level, an orthogonal comparison between the individual means was made (20, pp. 171-175). For these analyses, the selected variables included all physiological variables measured at $\dot{V}_{O_2}$ max and the venous blood variables measured immediately following the exercise test.

SECTION V
RESULTS

A. Initial Study

Changes in HbCO during the experiments are shown in table 1. The CO bolus increased HbCO from about 1.0% to about 5.1% HbCO. Maximal exercise during FA breathing significantly decreased HbCO by approximately 0.1% Hb. During exposure to 28 ppm CO, light exercise significantly decreased HbCO by about 0.2% Hb and maximal exercise decreased HbCO by an additional 0.4% Hb.

Exercise performance was decreased by CO exposure (Table 2). Total exercise time was significantly decreased by 3.8% from an average of 27.0 minutes for the two FA experiments to an average of 26.0 minutes for the CO experiments. Total vertical work done during uphill walking or running (i.e., at a work rate of 3.75 mph, 2% grade or greater) was significantly decreased by 10.0% from an average of 1.40×10^4 kpm for the FA experiments to 1.26×10^4 kpm for the CO experiments. These changes in work done were also associated with a significant 3.5% decrease in $\dot{V}O_2$ max.

Although both the total vertical work done and $\dot{V}O_2$ max were reduced during CO exposure, other physiological variables measured at the end of the work capacity tests were not significantly changed (Table 3). Both the maximal heart rate and maximal minute ventilation during CO exposure were not different from the FA values. Maximal end-exercise ventilatory equivalent ($\dot{V}_E/\dot{V}O_2$), as well as the respiratory exchange ratio (R), were not significantly different between the two conditions.

At a given submaximal work rate, a greater heart rate response occurred during CO exposure. To minimize individual differences in both maximal aerobic power and maximal heart rate, the data were reanalyzed, being expressed as a percent of both the highest achieved $\dot{V}O_2$ and highest heart rate in either the FA or CO condition. Exposure to CO increased the heart rate significantly at any work rate from rest to 75% $\dot{V}O_2$ max (Table 4).

At 89% $\dot{V}O_2$ max (highest common work rate for both the FA and CO conditions) and at $\dot{V}O_2$ max, no differences in heart rate between the FA and CO conditions were found.

Examination of the ECG records during exercise and recovery showed no occurrences of cardiac arrhythmias. No evidence of myocardial ischemia, including J-point depression, was found.

Cardiac function appeared to be altered by low-level CO exposure. Systolic time intervals were measured 3-4 minutes and 19-22 minutes after the exhaustive exercise test in six subjects and are shown in Table 5. Heart rates at these times were not statistically different between the FA and CO conditions. During both CO and FA exposures at 4 minutes post exercise, LVET was shortened relative to resting values. This LVET shortening was significantly greater during the FA exposure than for the CO conditon. Also, an impaired shortening of the electro-mechanical systole (QS_2) resulted, although no change in the pre-ejection period (PEP) or the PEP/LVET ratio was found. These changes were not present when STIs were measured at 20 minutes post-exercise.

Ventilatory responses to submaximal exercise during CO exposure were also altered. Minute ventilation was significantly greater at 75% and 89% $\dot{V}O_2$, max (table 4). Both respiratory rate and tidal volume were slightly but not significantly elevated during CO exposure. The anaerobic threshold (20) occurred at a lower work rate during CO exposure than during FA exposure, which resulted in the increased minute ventilation at heavy work rates. During FA exposure, the anaerobic threshold was 50.7 $\pm$ 2.6 $\dot{V}O_2$ max, whereas when breathing CO, the anaerobic threshold was reduced to 46.0 $\pm$ 2.2% $\dot{V}O_2$ max. At work rates above the anaerobic threshold, the venous lactate concentration was also increased significantly. Although lactate levels were significantly higher during heavy exercise, maximal post-exercise lactate levels were not significantly different between the two conditions.

Oxygen debt during 60 minutes of recovery was not significantly different between the FA and CO conditioning. Total oxygen consumed above baseline oxygen uptake was 7.2 $\pm$ 0.8 l after FA exercise and 7.2 $\pm$ 0.6 l after CO exercise.

Table 1. Initial Study--blood carboxyhemoglobin levels (% Sat)

Condition	FA_1	FA_2	Average FA	CO_1	CO_2	Average CO
Baseline	1.05 ±.05	1.08 ±.08	1.07[a] ±.05	1.03 ±.12	0.96 ±.05	0.99[a] ±.05
Resting after bolus	0.99 ±.06	1.11 ±.05	1.05[b] ±.04	5.08 ±.32	5.10 ±.19	5.09[c] ±.11
Light exercise (2mph,0% grade)	1.02 ±.05	1.10 ±.04	1.06[d] ±.03	4.80 ±.27	4.91 ±.16	4.85[e] ±.13
Maximal Exercise	0.87 ±.07	1.02 ±.05	0.94[f] ±.05	4.71 ±.25	4.66 ±.23	4.69[g] ±.16

[a] FA and CO baseline HbCO values not significantly different.

[b] FA resting and baseline HbCO values not significantly different.

[c] CO resting HbCO values greater than baseline value ($P<.001$).

[d] FA light exercise and resting HbCO values not significantly different.

[e] CO light exercise HbCO values less than resting value ($p<.01$).

[f] FA maximal exercise HbCO values less than resting or light exercise value ($p<.01$).

[g] CO maximal exercise HbCO values less than light exercise values ($p<.05$) and resting values ($p<.01$).

Table 2. Initial Study--changes in exercise performance for 9 subjects (mean ± SEM)

variable	FA_1	FA_2	Average FA	CO_1	CO_2	Average CO
Total Vertical Work ($kpm \times 10^4$)	1.42 ±.14	1.48 ±.15	1.45 ±.14	1.25 ±.12	1.36 ±.13	1.31[a] ±.12
Total Exercise Time (min)	26.7 ±1.1	27.2 ±1.1	27.0 ±1.1	25.6 ±1.0	26.4 ±1.0	26.0[a] ±1.0
Final Workrate ($kpm\ kg^{-1}$)	18.6 ±1.3	19.8 ±1.3	19.2 ±1.3	17.8 ±1.1	18.6 ±1.2	18.2[a] ±1.1
$\dot{V}_{O_2}$ max ($ml\ kg^{-1}\ min^{-1}$)	45.0 ±2.3	43.6 ±2.2	44.3 ±2.2	43.0 ±2.1	42.6 ±2.0	42.6[a] ±2.0

[a] Values for average CO performance less than FA performance ($p<.05$).

Table 3. Initial Study--heart rate and ventilatory adaptations to maximal aerobic work

Variable	FA_1	FA_2	Average FA	CO_1	CO_2	Average CO
Heart Rate (bpm)	192 ±3	192 ±2	192 ±2	193 ±3	191 ±3	192 ±2
$\dot{V}_E$ (l/min)	165 ±10	158 ±10	161 ±9	158 ±8	153 ±10	155 ±8
V_T(l)	2.87 ±.14	2.85 ±.14	2.86 ±.14	2.92 ±.12	2.87 ±.12	2.90 ±.12
f_r(/min)	56.9 ±2.2	55.6 ±2.2	56.2 ±2.1	54.0 ±1.7	55.5 ±2.2	54.7 ±1.8
$\dot{V}_E/\dot{V}_{O_2}$	48.0 ±1.7	48.5 ±1.6	48.2 ±1.5	48.7 ±1.6	49.1 ±1.9	48.9 ±1.7
R	1.104 ±.010	1.114 ±.023	1.104 ±.012	1.081 ±.015	1.095 ±.019	1.089 ±.013

Table 4. Initial Study--effects of CO exposure during exercise (expressed as a percent of the highest $\dot{V}_{O_2}$ max) upon heart rate, ventilation, and blood lactate (LA) (expressed as a percent of the maximal value observed).

	WORK RATE							
	35%		50%		75%		89%	
	FA	CO	FA	CO	FA	CO	FA	CO
Heart Rate	52.4% ±1.0	53.2%[a] ±0.8	65.2% ±1.1	67.0%[a] ±1.1	87.2% ±0.9	89.3%[a] ±0.9	94.7% ±0.6	96.3%[a] ±0.5
$\dot{V}_E$	21.4% ±0.5	21.9% ±0.5	32.0% ±0.7	32.8% ±0.9	57.1% ±1.2	59.1%[b] ±1.1	79.0% ±1.7	83.9%[b] ±1.5
V_T	50.8% ±2.9	51.3% ±2.8	65.1% ±2.9	65.2% ±2.6	83.9% ±2.0	84.3% ±1.6	91.9% ±0.6	93.5% ±0.6
f_r	40.4% ±1.5	41.0%[a] ±1.5	46.9% ±1.7	48.0%[a] ±1.6	64.4% ±2.1	66.8%[a] ±1.9	79.1% ±2.1	82.9%[a] ±1.7
LA	8.8% ±0.7	9.0% ±0.6	11.6% ±0.7	12.7% ±0.8	25.5% ±1.5	29.5%[b] ±1.5	43.9% ±3.2	54.2%[b] ±2.0

[a]Main effect of CO greater than FA across all work rates ($p<.05$).

[b]CO values greater than FA for this work rate ($p<.05$).

Table 5. Initial Study--changes in electro-mechanical systole (QS_2), left ventricular ejection time (LVET), and the ratio of pre-ejection period (PEP) to LVET (9 measurements in 6 subjects).

	Heart Rate		QS_2 (msec)		LVET (msec)		PEP/LVET	
	FA	CO	FA	CO	FA	CO	FA	CO
Pre-Exercise	61.1 ±2.3	62.7 ±2.5	398 ±9	411 ±7	281 ±9	292 ±6	0.42 ±.03	0.41 ±.02
3-4 minutes Post-Exercise	118.2 ±3.0	120.2 ±3.2	277 ±12	309[a] ±6	193 ±9	220[a] ±5	0.43 ±.04	0.41 ±.03
19-20 minutes Post-Exercise	95.4 ±2.1	94.2 ±1.8	358 ±7	365 ±8	258 ±4	254 ±3	0.39 ±.01	0.44 ±.02

[a]CO values significantly greater than FA values ($p<.05$).

B. Dose-Response Study

HbCO changes during these experiments are shown in Table 6. The CO bolus established levels of about 4, 6, and 9% HbCO compared to the FA level of less than 1% HbCO. Maximal exercise reduced HbCO at 1-2 minutes post-exercise by about 0.1% Hb when breathing FA and from 0.4% to 0.9% Hb when exposed to CO.

Exercise performance progressively decreased as HbCO levels were increased (Table 7). At the final workrate achieved, HbCO decreased 8.5, 16.4, and 18.5% when the initial CO exposure was 4%, 6%, and 9% HbCO, respectively. Correspondingly, $\dot{V}_{O_2}$ max was decreased by 3.8, 8.3, and 11.1% at the levels of 4%, 6%, and 9% HbCO, respectively.

During maximal aerobic work that occurred at lower final workrates when breathing CO, maximal cardiac and ventilatory adaptations were about the same (Table 8). As in the initial study, maximal heart rate and maximal minute ventilation remained the same. No changes in end-exercise tidal volume and respiratory rate were found. Both end-exercise ventilatory equivalent ($\dot{V}_E/\dot{V}_{O_2}$) and respiratory exchange ratio (R) increased progressively as CO exposure increased.

As in the first study, examination of the ECG records during exercise and recovery revealed no occurrences of cardiac arrhythmias. Likewise, no evidence of myocardial ischemia was found. No differences in systolic time intervals were found before 4 min post maximal exercise in contrast to our initial study (Table 9).

After 15 minutes of recovery no differences were seen in O_2 debt among any of the exposure conditions. Net oxygen uptake above baseline oxygen uptake was 8.0 $\pm$ 0.2, 8.0 $\pm$ 0.3, 7.4 $\pm$ 0.4, and 7.6 $\pm$ 0.4 liters for the 1%, 4%, 6%, and 9% HbCO conditions, respectively.

Table 6. Dose-Response Study--blood carboxyhemoglobin levels (% Sat).

Condition	FA 1% HbCO	4% HbCO	CO 6% HbCO	9% HbCO
Baseline	0.85 ±.06	0.74[a] ±.03	0.76[a] ±.04	0.82[a] ±.05
Resting after bolus	0.76 ±.05	4.09[b] ±.17	6.28[b] ±.37	9.51[b] ±.22
End-Exercise	0.67[c] ±.05	3.51[c] ±.17	5.38[c] ±.28	8.71[c] ±.15

[a] Baseline HbCO values not different from FA HbCO values.

[b] Resting HbCO values greater than baseline values ($p<0.01$).

[c] End-Exercise HbCO values less than resting values after CO bolus ($p<0.01$).

Table 7. Dose-Response Study--changes in exercise performance for 12 subjects (Mean ± SEM).

Variable	FA 1% HbCO	4% HbCO	CO 6% HbCO	9% HbCO
Total Vertical Work (kpm x 10^3)	6.48 ±.87	5.61[a] ±.85	4.89[b] ±.72	4.63[c] ±.62
Total Exercise Time (min)	6.95 ±.42	6.35[a] ±.45	5.81[b] ±.41	5.67[c] ±.31
Final Workrate (kpm kg^{-1} min^{-1})	18.81 ±1.50	17.36[a] ±1.56	15.76[b] ±1.53	15.40[c] ±1.22
$\dot{V}_{O_2}$ max (ml $kg^{-1}min^{-1}$)	49.5 ±2.1	47.6[a] ±1.8	45.4[b] ±2.4	44.0[d] ±1.6

[a]Values for 4% HbCO less than 1% HbCO ($p<0.05$).

[b]Values for 6% HbCO less than 3% HbCO ($p<0.05$) and 1% HbCO ($p<0.01$).

[c]Values for 9% HbCO less than 3% HbCO ($p<0.05$) and 1% HbCO ($p<0.01$).

[d]Values for 9% HbCO less than 6% ($p<0.05$), 3% HbCO ($p<0.01$) and 1% HbCO ($p<0.01$).

Table 8. Dose-Response Study--heart and ventilatory adaptations to maximal aerobic work.

Condition	Filtered air	CO 4% HbCO	CO 6% HbCO	CO 9% HbCO
Heart Rate (bpm)	187 ±2	187 ±2	187 ±2	186 ±2
$\dot{V}_E$ (l/min)	161 ±5	160 ±5	154 ±6	157 ±4
V_T(l)	2.77 ±.12	2.78 ±.12	2.72 ±.10	2.76 ±.12
f_r (min)	59.0 ±1.8	58.2 ±2.0	57.0 ±2.4	57.8 ±2.4
$\dot{V}_E/\dot{V}_{O_2}$	43.0 ±1.3	44.6[a] ±1.2	45.0[a] ±1.6	47.5[b] ±1.6
R	1.073 ±.014	1.078 ±.018	1.106[c] ±.023	1.114[c] ±.019

[a] Value is greater than FA ($p=0.06$).

[b] Value is greater than FA, 4%, and 6% HbCO ($p<0.01$).

[c] Value is greater than FA and 4% HbCO ($p<0.05$).

Table 9. Dose-Response Study -- Changes in left ventricular ejection time (LVET), and the ratio of pre-ejection period (PEP) to LVET in 10 subjects (Means ± SEM).

	Heart Rate				LVET				PEP/LVET			
	FA	4%	6%	9%	FA	4%	6%	9%	FA	4%	6%	9%
Pre-Exercise	63	68	73	70	279	276	269	292	.380	.369	.371	.362
	±4	±4	±4	±5	±8	±7	±7	±11	±.027	±.031	±.027	±.031
4/minutes	114	119	116	121	201	192	194	191	.270	.291	.287	.273
Post-Exercise	±4	±4	±3	±4	±6	±6	±6	±8	±.011	±.017	±.011	±.020
15/minutes	109	114	111	112	233	233	229	231	.379	.399	.402	.374
Post-Exercise	±3	±5	±3	±5	±7	±7	±7	±7	±.022	±.025	±.023	±.018

SECTION VI
COMMENTS

At an altitude of 1610 m (Denver, Colorado), performance was reduced as the HbCO level was increased. Compared to filtered air breathing resulting with less than 1% HbCO, exposure to 3-10 % HbCO produced a proportional decrease in total work done, total exercise time, and final work rate achieved. At sea level using a similar stress test, Aronow and Cassidy (3) found that raising the HbCO level from 1.07% to 3.95% in 45-55 year old asymptomatic subjects reduced the total exercise time by about the same amount (5.0%). Horvath et al. (12) studied the effects of increasing HbCO from 0.4% to 4.3% and found a decrease in the total exercise time of 8.1% for a graded stress test. Therefore, CO exposure at Denver's altitude resulted in a decrement in maximal exercise time similar to but no greater than that found at sea.

Maximal aerobic work capacity was decreased in proportion to the level of CO exposure. Figure 1 summarizes the decrement in $\dot{V}_{O_2}$ max found in our study and reported by others who used similar exercise testing during CO exposure from 3% to 21% HbCO (8,12,14,16,18,19). The decrement for $\dot{V}_{O_2}$ max (i.e., $\Delta\dot{V}_{O_2}$ max) is highly correlated ($p < .01$) to HbCO level ($\Delta\ \dot{V}_{O_2}$ max = 1.08 x HbCO + 0.35) with an intercept that is close to zero HbCO. The decrement in $\dot{V}_{O_2}$ max found at Denver altitude is similar to that found at sea level and is clearly not greater than that observed at sea level in normal subjects. Patients with chronic obstructive lung disease also show a greater decrement in work performance at sea level than normals (3), but any additional effect of altitude on work performance with these patients has not been studied. Hypobaric hypoxia produced by residing at altitudes higher than Denver does produce a significantly greater reduction in $\dot{V}_{O_2}$ max (5). Therefore, our observations do not exclude the possibility that at higher altitude than Denver's, low-level

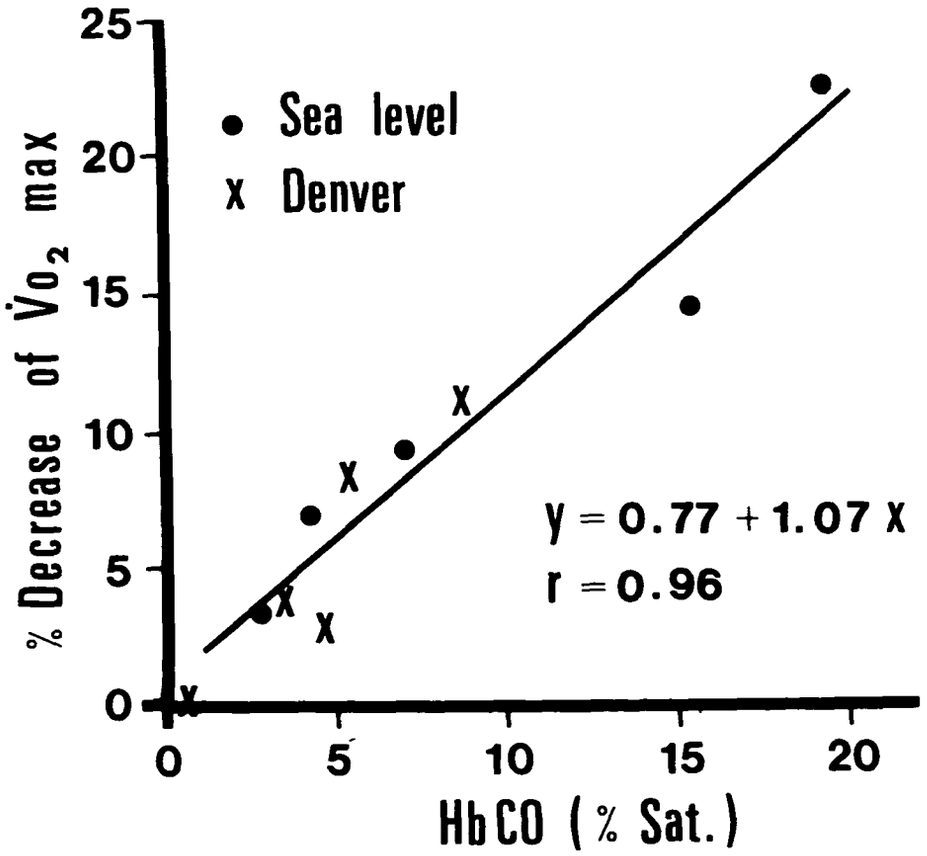

Figure 1. Effects of blood carboxyhemoglobin levels (HbCO) on physical work capacity ($\dot{V}_{O_2}$ max) in this altitude study (X) and in others reported in the literature but done at sea level.

CO exposure may have additional detrimental effects on maximal aerobic power compared to those found at 1600m altitude or below.

Although work capacity was reduced with CO exposure, certain physiological variables observed during VO_2 max work during the FA and CO experiments were not significantly different. Maximal heart rate was unaffected by CO in this study as has been reported in other studies done at sea level (3,8,12). However, with higher HbCO levels at sea level maximal heart rate was decreased (8,14,17,18,19). Maximal minute ventilation ($\dot{V}_E$) (BTPS) was significantly greater at Denver altitude than at sea level; however, $\dot{V}_E$ max during CO exposure was slightly but not significantly, lower than the FA $\dot{V}_E$ max. This small change was also found at sea level (8,12). Maximal ventilatory equivalent at 4-5 % HbCO was unchanged as previously observed (8,12), but at 6% and 9% HbCO, the maximal ventilatory equivalent and the respiratory exchange ratio increased suggest CO provoked overventilation. Oxygen debt was unchanged confirming an earlier report (12). Peak post-exercise venous lactates were the same in both conditons which is in agreement with the findings of Ekblom and Huot (8). Decreased post-exercise lactates have been reported by Horvath et al. (12), but this may be explained by differences in test procedures, subjects, or altitude conditions. These physiological adaptations to maximal exercise were similar regardless of the gas breathed; however, during CO breathing these adaptations to maximal work occurred at a significantly lower work rate than during FA breathing. This difference in maximal work rate suggests that CO exposure provokes a physiological compensation such that greater cardio-respiratory adaptations tube place at lower work rates during CO breathing.

Cardiac function appeared to be altered by low-level CO exposure. Systolic time intervals were measured 3-4 minutes and 19-22 minutes after the exhaustive exercise test. Heart rates at these times were not statistically different between the FA and CO conditions. During FA exposure in the inital study which used a long multistage exercise test, left ventricular ejection time (LVET) was shortened relative to LVET at rest, while the heart rate was elevated when measured in the supine position at 4 minutes post-exercise. At this time, during CO exposure, LVET was

significantly less shortened. A corresponding impaired shortening of the electro-mechanical systolic (QS_2) resulted, although no change in the pre-ejection period (PEP) or the PEP/LVET ratio was found. These changes were not present when STIs were measured at 20 minutes post-exercise. Also these changes were not found after the dose-response study when a shorter, supermaximal stress test was utilized, and measurements were taken in the sitting position.

Following maximal exercise in healthy young men at sea level, LVET was shortened to a similar extent whether subjects breathing CO or FA (1). In the present study, LVET was not shortened as much during CO breathing. A similar lack of LVET shortening at 4 min post-exercise has been reported in patients having chest pain upon exertion (9,11,13,15).

In summary, low-level CO exposure resulting in a blood HbCO level of 3-9% HB at an altitude of 1610 m impaired work capacity and performance. The impairments were of the same magnitude as those reported from sea level studies.

SECTION VII

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16. ABSTRACT

At sea level, low-level carbon monoxide (CO) exposure impairs exercise performance. To determine if altitude residence at 1600 m augments this CO effect, two studies of graded treadmill work capacity were done. The Initial Study investigated nine, non-smoking, male subjects breathing either filtered air (FA) or 28 ppm CO in filtered air. End-exercise carboxyhemoglobin (HbCO) levels averaged 0.9 %HbCO breathing FA and 4.7 %HbCO breathing CO. Total work performance and aerobic work capacity were reduced. Work heart rate was elevated, and post-exercise left ventricular ejection time breathing CO did not shorten to the same degree as with FA exposure. CO exposure resulted in a lower anaerobic threshold, and a greater minute ventilation occurred at work rates heavier than the anaerobic threshold due to an increased blood lactate level. The Dose-Response Study exposed twelve subjects to FA or CO such that the end-exercise HbCO levels were 0.7, 3.5, 5.4 and 8.7 %HbCO. Exercise performance and aerobic work capacity were impaired in proportion to the CO exposure. In both studies, maximal cardiopulmonary responses were not different, but submaximal exercise changes were elevated breathing CO. Thus, in healthy young men residing near 1600 m, an increase in low-level CO exposure produced a linear decrement in maximal aerobic performance similar to that reported at sea level.

17. KEY WORDS AND DOCUMENT ANALYSIS

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Air Pollution Carbon Monoxide Physiological Effects Exercise		06F

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