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This study investigated the effects of carbon monoxide (CO) exposure on cardiac function during exercise. Subjects had their blood COHb level raised to 5%, 10%, 15%, and 20% COHb by inhaling air and CO mixtures from Douglas bags and by breathing air and CO chamber mixtures to maintain COHb level during exercise. All subjects performed both multistage treadmill (to 10 METS) and hand-crank (to 5 METS) exercise at each CO exposure level. Sixteen subjects ranging from 21 to 29 years of age (mean of 24.6 years) completed the study. The results indicate that young, apparently healthy males can perform submaximal upper and lower-body exercise without adverse health effects after CO exposures attaining 20% COHb. The data also show that the cardiovascular system compensates for the reduced oxygen-carrying capacity of the blood by augmenting heart rate, cardiac contractility, and cardiac output for both types of exercise. The enhanced response begins to fail at higher levels of CO exposure and exercise, and although not tested in this study, must ultimately result in reduced maximal exercise capacity.

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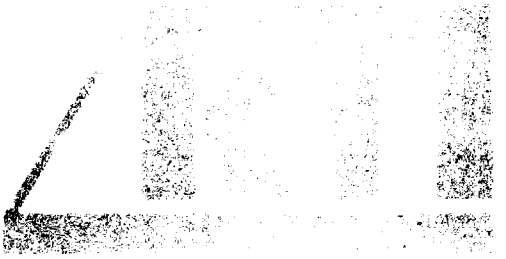

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Noninvasive Ambulatory Assessment of Cardiac Function and Myocardial Ischemia in Healthy Subjects Exposed to Carbon Monoxide

FINAL REPORT
DAMD17-91-C-1007

by

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SYMBOLS AND DEFINITIONS

α	Error of rejecting an hypothesis when it is actually true (Type I error)
μ	Population mean
μ_D	Population mean of paired-difference values
ρ	Resistivity of blood (ohm-cm)
Ω	Ohms, unit of electrical resistance
ACCEL	ICG acceleration (cardiac contractility) (Ω/s^2)
ACSM	American College of Sports Medicine
AECG	Ambulatory electrocardiogram
ANOVA	Analysis of variance
BFMS	Biomedical Field Monitoring System
BSA	Body surface area
CAD	Coronary artery disease
CFK	Coburn-Foster-Kane
CO	Carbon monoxide
C.O.	Cardiac output
COHb	Carboxyhemoglobin
CV	Coefficient of variation
dZ/dt	ICG first derivative
dZ/dt_{peak}	Peak systolic amplitude of dZ/dt (Ω/s)
ECG	Electrocardiogram
ft^3/min	Cubic feet per minute
HEGA	High efficiency gas filters
HEPA	High efficiency particle filters
Hz	Hertz
ICG	Impedance cardiogram
IL	Instrumentation Laboratories
L	Distance between ICG electrodes
l/min	Liters per minute
LA	Left arm
LL	Left leg
LSD	Least Significant Difference
M*	Carbon monoxide-oxygen affinity
METS	Metabolic equivalent units
mm	Millimeters (of ST segment depression)

SYMBOLS AND DEFINITIONS (continued)

mV	Millivolts
N	Number of Subjects
NDIR	Non-dispersive infrared
PAC	Premature atrial contraction
pO_2	Oxygen partial pressure in blood
ppm	Parts per million
r_{mean}	Average correlation coefficient
RA	Right arm
RATE	heart rate (beats/min)
RL	Right leg
RTI	Research Triangle Institute
SD	Standard deviation
ST	Segment of ECG wave
S.V.	Stroke volume
TEI	Thoracic Electrical Impedance
TZavo	Time from ECG Q-wave to aortic valve opening (ms)
TZpeak	Time from ECG Q wave to dZ/dt_{peak} (ms)
TZx	Time from ECG Q-wave to aortic valve closing (ms)
UNC	University of North Carolina (Center for Environmental Medicine and Lung Biology)
V_5	Placement of chest electrode at precordial lead 5
VEB	Ventricular ectopic beat
WRAIR	Walter Reed Army Institute of Research
Y	Output measure for RATE, S.V., C.O., ACCEL, and TZPEAK
ΔY	Difference in output measure from rest condition
$\Delta_{AE}Y$	Difference in output measure from air exposures segment
ΔZ	Cardiac bioimpedance signal
Zo	Mean thoracic electrical impedance

1.0 INTRODUCTION

1.1 Nature of the Problem

Maintenance of a high level of military capability requires that neither man nor machine be unnecessarily compromised during combat. Unfortunately, in weapons systems with closed crew compartments there are sources of risk to the human component which are only incidental to combat and are present during routine training exercises as well. These are the gaseous combustion products produced by armament propellants which enter the crew environment.

Carbon monoxide (CO) is one of the toxic materials known to be produced. Although the effects on behavior and cardiopulmonary function at high CO exposure levels are fairly well documented, the effects on individuals in uncontrolled and changing exposures, such as military training and combat, are nearly impossible to predict. The transient nature of weapons firing, the spatial distribution of CO concentration, and differences in individual physiology will cause the CO dose to vary significantly among crew members. Furthermore, CO is only one species within the complex and dynamic chemical mixture. Continuous and noninvasive ambulatory monitoring of cardiopulmonary measurements *in situ* may provide an understanding of the effects of CO exposure in the field environment.

The military training environment imposes measurement difficulties which are not encountered in the typical civilian or clinical setting. Bulky protective clothing, breathing apparatus, cramped quarters, and a wide variety of postures, physical activity, and ambient conditions place severe restrictions on systems for gathering reliable cardiopulmonary information. Consequently, noninvasive measurements such as echocardiography, Doppler ultrasound, radionuclide angiography, and gas rebreathing, which serve admirably in the laboratory settings, are incompatible with field environments.

Electrocardiography (ECG) and impedance cardiography (ICG) are electrode-based techniques that could be used to assess electrical and mechanical cardiac function (Kizakevich, et al., 1993a). Both offer minimal subject intrusion and are adaptable to continuous measurement in the field using wearable, ambulatory instrumentation (Kizakevich, et al., 1993b).

This project evaluates the utility of combined ECG and ICG estimators of cardiac function during exercise in air and with exposure to CO. If the results of this project demonstrate that these noninvasive measurements reliably detect effects of CO exposure on cardiac performance in exercise, then the foundation for ambulatory monitoring in the field will be set.

1.2 Background of Previous Work

Carbon monoxide has been long recognized as a potentially life-threatening toxic gas and remains a common cause of mortality among poisoning victims (Sokol, 1985). The effects of carbon monoxide on respiration are considered to be threefold (Haab, 1990). The first factor is the relative carbon monoxide-oxygen affinity (M*) of various oxygen-carrying proteins including hemoglobin (M=220), myoglobin (M=23), and cytochrome oxidases (M=0.5). Although carbon monoxide competes with oxygen for sites on myoglobin and cytochrome oxidases, the relatively larger affinity for hemoglobin means that carboxyhemoglobin (COHb) is often used as the primary marker of carbon monoxide exposure. In addition to reducing the number of heme sites available for oxygen, carbon monoxide augments the oxygen affinity of the oxygen-occupied sites resulting in a leftward shift in the oxygen saturation curve. This reduces the blood oxygen partial pressure (pO_2) and decreases the driving force for oxygen diffusion to peripheral tissues. Finally, recent evidence indicates that reduction in

maximum oxygen consumption by exercising muscles with carbon monoxide may be linked to a decrease in the blood-to-mitochondria oxygen conductance (Haab, 1990). This is because carbon monoxide in blood may affect the off-rate kinetics of oxyhemoglobin and the carrier function of myoglobin in oxygen transport.

Several investigators have reported on the effects of carbon monoxide on submaximal and maximal exercise, and related factors such as onset of anaerobic metabolism. These papers indicate that heart rate in the presence of carbon monoxide as compared to air exposure may or may not increase at rest, generally is higher at a given work load for submaximal exercise, and is equivalent to air exposure at maximum aerobic capacity (Vogel, 1972). Oxygen consumption, on the other hand, is generally decreased during submaximal exercise and maximal oxygen consumption is decreased compared to air exposure in proportion to the COHb concentration (Ekblom, 1972; Horvath, 1975). There is no conclusive information of the effects of carbon monoxide on stroke volume and cardiac contractility at rest or exercise, however, one could surmise that stroke volume will increase at rest to increase cardiac output when heart rate remains the same (Stewart, 1973).

The effects of carbon monoxide exposure on anaerobic threshold were reported in several studies. In normal subjects, both the time to onset of anaerobic threshold (Hirsh, 1985) and the level of oxygen consumption at which anaerobic threshold is reached were reduced. In several case studies of patients with carbon monoxide poisoning, lactate dehydrogenase was substantially elevated in those patients as compared with controls, and the amount of elevation was proportional to the duration of exposure (Sokal, 1985).

In patients with coronary artery disease (CAD), carbon monoxide exposure achieving 2-4% carboxyhemoglobin reduces time to angina in exercise, reduces time to significant ST segment depression, and in some cases, increases ST segment depression at end of exercise (Aronow, 1981; Allred, 1989 & 1991; Kleinman, 1989). Limited information also shows that CAD patients may experience a reduction in cardiac function during exercise (Adams, 1988). With CO exposures yielding a COHb of 6.0%, CAD patients increase the rate of single and multiple ventricular premature depolarizations (Sheps, 1990).

With regard to the current project, the reviewed literature brings out several important points. First, a study population of young, healthy subjects can be expected to safely exercise to maximum aerobic capacity with COHb levels under 20%. In addition, it is unlikely that these subjects will experience CO-induced arrhythmias or significant myocardial ischemia (ST segment depression greater than 0.1 mV). This is not to say, however, that sub-clinical myocardial ischemia may not arise in a slightly older, healthy population (30-40 years of age). Finally, our unique ability to noninvasively assess myocardial contractility using indices of impedance cardiography may yield new information on the exercise response of healthy subjects exposed to carbon monoxide.

1.3 Purpose of the Present Work

The goal of Study I was to demonstrate whether or not CO plus exercise can elicit measurable changes in the impedance cardiogram (ICG) in a pilot experiment. Study I incorporated both lower and upper body exercise and a wide range of CO exposure levels. Treadmill exercise was performed for comparison with the existing body of data on exercise performance in asymptomatic patients and the body of data which reflects performance decrements with exercise and CO in normals. Upper body exercise was performed to determine whether this form of exercise places a greater strain on the cardiovascular system than lower body exercise, both with and without CO exposure.

The following hypotheses were examined:

1) Cardiac contractility (i.e., ICG acceleration) exhibits a dose-response relationship to CO exposure during exercise.

2) Cardiac output exhibits a dose-response relationship to CO exposure during exercise.

3) Short-term CO exposure resulting in 5-20% COHb does not induce pathological changes in ECG rhythm or waveshape in normal subjects;

The specific objectives for Study I were:

1) To determine the effects of CO exposure on the electrocardiogram rhythm, waveshape, and ST segment level during exercise.

2) To determine the effects of CO exposure on cardiac contractility during exercise as measured by the ICG-derived aortic blood acceleration.

3) To compare certain ICG measurements of cardiac function to the more traditional measures of cardiac output, stroke volume, and oxygen consumption during exercise and CO exposure.

4) To evaluate ICG estimates of cardiac function and contractility during episodes of ECG dysrhythmia or ST segment change.

1.4 Technical Approach

To meet the goals and objectives of this project, several major tasks were performed:

1) A comprehensive literature review on the effects of carbon monoxide exposure on the cardiac response to exercise was conducted.

2) An experiment protocol to conduct human studies was written, submitted to the RTI and U.S. Army human use review committees, and approved.

3) A detailed experiment plan and manual of operations was prepared.

4) A new human studies facility was constructed at Research Triangle Institute for study of the health effects of gaseous pollutants, including carbon monoxide.

5) All necessary laboratory instrumentation, data acquisition software, and analysis software was acquired, prepared, calibrated, and tested.

6) Human exposure studies were performed and the resultant data analyzed.

2.0 METHODS, RESULTS, AND DISCUSSION

2.1 Subjects

To minimize the variability of the subject population, a narrow distribution consisting of normal, apparently healthy, males within the age range of 18-30 years was defined. Females were not considered because the study population was intended to reflect the population of combat tank crews; currently female soldiers are not employed in that environment.

Eligibility criteria were established to help screen participants for enrollment. Inclusion criteria were established to help ensure optimal compliance with the study protocol and with quality control. Exclusion criteria were established to assure that the subjects would be likely to complete the study, and that meaningful and interpretable data would be collected. Special conditions for inclusion or exclusion by the recruitment coordinator, examining physician, or investigator were documented.

Inclusion Criteria

1) male
2) apparently healthy
3) within the age range of 18-30 years
4) willing and able to provide informed consent

Exclusion Criteria

1) history of smoking or substance abuse within 1 year or for any period > 5 years
2) judged unwilling or unable to cooperate with the study protocol
3) evidence of anemia, sickle cell anemia, or other blood abnormalities
4) evidence of valvular disease
5) cardiac conduction abnormalities
6) congenital cardiac defects
7) chronic cough, history of chronic pulmonary disease, significant (respiratory) allergies or asthma
8) past heart attack, stroke, or family history of coronary or other atherosclerotic disease in parents or siblings prior to age 50
9) acute illness within 1 month (e.g., upper respiratory tract infection)
10) diagnosed hypertension or blood pressure > 160/90
11) evidence or history of syncope
12) positive Bruce treadmill exercise tolerance test
13) total serum cholesterol > 200 mg/dl
14) diabetes mellitus or thyroid disorder
15) use of medication unless approved a priori by the attending physician
16) other cardiopulmonary disorders
17) obesity or substantially overweight so as to affect ECG and TEI recording quality
18) chamber exposure to pollutants within previous 4 weeks

Subject recruitment and qualification was conducted by the coinvestigators at the University of North Carolina School of Medicine (UNC). When a person responded for enrollment, the UNC recruitment coordinator informed the candidate of the overall objectives of the research study, his participation in the study, the procedures to be used in the study, and his incentive fee for completion of the study. The

candidate was also advised as to the enrollment procedure including qualification by medical history, physical examination, and exercise tolerance testing.

The recruitment coordinator or study co-investigator obtained written informed consent (Appendix 5.1) prior to initiating qualification procedures. The subject was informed of the nature of the experiment procedure, its risks, and its benefits, the purpose of the study, the information to be collected, and advised that the results from his experiment will be provided if requested. The experimental protocol and the consent form was approved by the RTI and UNC human subjects committees, and by the Army Human Use Review Office.

Subject qualification took several steps. A medical history was taken for review of prior illness and familiar illness patterns. Each subject then had a physical exam, including blood analysis, with particular emphasis on screening for cardiac, cardiovascular, and respiratory illness. Subjects passing the qualification history and physical performed an exercise tolerance test. A standard 12-lead electrocardiogram was taken and examined by a cardiologist. Subjects passing the exercise test were deemed fully qualified for the CO exposure study.

2.1 Experiment Protocol

The experiment protocol incorporated lower and upper body exercise and a wide range of CO exposure levels. Each exercise series (lower and upper body) comprised six replicate exercise segments (three segments per day) designed to achieve a range of blood COHb levels (Table 1). Exercise was specified in metabolic equivalent units (METS). There were a total of six AIR control exposures (0-2% COHb (endogenous or baseline level)) and eight AIR + CO exposures with targets of 5% COHb, 10% COHb, 15% COHb, and 20% COHb. Each subject served as his own control and experienced all levels of exposure with the exposures split into two experiment days with randomization of exposure day sequence. Detailed description of protocol activities are given in Appendix 5.2.

Table 1. Conditions of carbon monoxide exposure and exercise.

SESSION 1	SESSION 2	SESSION 3	SESSION 4	SESSION 5	SESSION 6
Training	**Training**	**Lower #1**	**Lower #2**	**Upper #1**	**Upper #2**
AIR		**AIR**	**AIR**	**AIR**	**AIR**
Rest, standing		Rest, standing	Rest, standing	Rest, sitting	Rest, sitting
4.6 METS		4.6 METS	4.6 METS	2.6 METS	2.6 METS
7.0 METS		7.0 METS	7.0 METS	3.6 METS	3.6 METS
10.2 METS		10.2 METS	10.2 METS	4.9 METS	4.9 METS
	AIR	**5% COHb**	**10% COHb**	**5% COHb**	**10% COHb**
	Rest, sitting	Rest, standing	Rest, standing	Rest, sitting	Rest, sitting
	2.6 METS	4.6 METS	4.6 METS	2.6 METS	2.6 METS
	3.6 METS	7.0 METS	7.0 METS	3.6 METS	3.6 METS
	4.9 METS	10.2 METS	10.2 METS	4.9 METS	4.9 METS
		15% COHb	**20% COHb**	**15% COHb**	**20% COHb**
		Rest, standing	Rest, standing	Rest, sitting	Rest, sitting
		4.6 METS	4.6 METS	2.6 METS	2.6 METS
		7.0 METS	7.0 METS	3.6 METS	3.6 METS
		10.2 METS	10.2 METS	4.9 METS	4.9 METS

Subjects were asked to eat a moderate breakfast (i.e., cereal, toast, and juice) and to refrain from consuming caffeinated beverages (coffee, tea, colas) on the morning of each visit to the laboratory. Subjects were also asked to refrain from using prescription or over-the-counter medications after 9 PM

on the evening prior to each visit to the laboratory. Each subject was picked up by courier at his place of residence and provided transportation to the laboratory on each of the CO exposure days.

On a day prior to the exposure days, each subject participated in a training study comprising one exercise series for both the lower and upper body exercise procedures. This was done to familiarize the subject with the experiment procedures, and to determine that he was able both to exercise as prescribed and to reliably perform sham bag exposure and other breathing maneuvers.

On each exposure day, the consulting physician and medical technologist inserted a catheter into a forearm vein for obtaining blood samples. On several occasions a reliable catheterization could not be performed, consequently venipunture was necessary for blood withdrawals. On training and exposure days, subjects were then instrumented with ECG electrodes, ICG electrodes, and a blood pressure cuff (Figure 1). Several subjects were also instrumented with a WRAIR Biomedical Field Monitoring System. After entry into the chamber, subjects sat at rest for at least 10 minutes to establish stable baseline signals and to insure the integrity of the venous catheter site. During this time, a check of signal quality was made for each transducer system and any problems resolved.

Two mechanism were used for CO exposure, bag breathing and chamber air. Subjects had their blood COHb level raised to each target level via short-term exposures (4-6 minute periods) while sitting at rest and inhaling precertified air and CO mixtures from Douglas bags and exhaling into the exposure chamber. After completing bag breathing, subjects breathed chamber air with a background level of CO set to maintain COHb level until the end of the experiment segment. At the end of each exposure day, subjects breathed 100% medical grade oxygen for sixty minutes or until the COHb level subsided to below 10%. Subjects were then provided transportation home.

2.3 Environmental, CO Exposure, and Exercise Conditions

2.3.1 Chamber Temperature, Humidity, and Ventilation

The environmental chamber had a single-pass air-flow design with regulation of temperature, humidity, and ventilation. Outside air was drawn in and passed through high efficiency gas contaminant (HEGA) and high efficiency particle (HEPA) filters to cleanse the incoming air. Prescribed ventilation (800 ft^3/min), temperature (72° F), and relative humidity (38%) were regulated using a closed-loop direct digital control system (Carrier Comfort Network). Environmental settings were made via a graphical software interface, visually monitored, and recorded throughout the experiment.

2.3.2 Mouthpiece Air and Carbon Monoxide Exposures

For each experiment segment, subjects had their blood COHb level raised to the specified target level while sitting at rest and inhaling precertified air and CO mixtures. A respiratory apparatus comprising a digital flowmeter, two Douglas bags (100 liter total capacity), a 4-way switching valve, a 2-way breathing valve, hoses, and a vacuum pump. An electronic controller was used for gas tank selection (air, 1500 ppm CO, 3000 ppm CO), and controlled bag filling, subject exposure, and bag emptying.

For air exposures, the volume of air introduced into the empty Douglas bags was set at 50 liters. For CO exposures, the volume of gas mixture required to raise a subject to the next prescribed COHb level was estimated using the Coburn-Forster-Kane (CFK) model of COHb formation (Coburn et al., 1965). Blood samples were taken at the beginning of each exposure segment to determine initial COHb and total hemoglobin. Using assumed CFK parameters (e.g., blood volume=3 liters, ventilation=10 l/min, etc.) and selected bag gas concentration, the volume of exposure gas was estimated and used to set

Figure 1. Subject instrumented with ECG spot electrodes, ICG band electrodes, and Biomedical Field Monitoring System prior to training day activities.

the electronic controller. To raise blood levels to 5% COHb, 1500 ppm CO in air was used, and to raise blood levels to 10%, 15%, and 20% COHb, 3000 ppm CO in air was used.

For each exposure episode, subjects sat at rest wearing nose clips and breathing chamber air via the respiratory apparatus mouthpiece (Figure 2). At a designated protocol time, the apparatus was switched to bag gas and the subject continued breathing until the bags were emptied. Subjects then removed the mouthpiece and nose clips, thereby breathing freely in the exposure chamber. The apparatus was then switched to the fill/purge position and any remaining gas withdrawn using a vacuum pump under electronic control. After a five minute post-exposure equilibration period, blood samples were taken and analyzed to record the actual COHb level.

2.3.3 Chamber Air and Carbon Monoxide Exposures

The chamber air dosing system was designed to allow chamber CO concentrations which range from 0 to approximately 2000 ppm. Chamber concentration is measured by a non-dispersive infrared (NDIR) spectrometer (Rosemount 80 and controls the flow of pure CO through a pair of mass flowmeters which are in a software-mediated feedback loop. To assure that the Rosemount monitor was working properly, calibrations were made by attaching a 155 ppm CO gas calibration tank to the air sample inlet and checking the Rosemount panel meter.

Chamber CO concentrations were set to maintain the COHb levels attained by bag breathing for each protocol exercise segment. Therefore, chamber CO settings were specified which would move the subject toward COHb equilibration at the specified protocol levels. Chamber levels were raised to the next desired level during periods while subjects were performing bag-breathing. This assured that a stable background level would have been achieved whenever the subject came off of the mouthpiece. Chamber CO concentrations for target COHb equilibrations were as follows:

Table 2. Chamber carbon monoxide exposure levels for COHb maintenence.

Protocol Condition	Chamber Exposure Level
TRAINING	0 ppm
AIR	0 ppm
5% COHb	27 ppm
10% COHb	55 ppm
15% COHb	83 ppm
20% COHb	100 ppm

During normal chamber operation, the desired CO concentration was continuously compared with the ratio of CO flow to chamber air flow. The computer software held this ratio within approximately 10% of the target concentration. If the measured ratio exceeded the nominal value by some preset value (e.g., 1.5), then there would have been a problem with the control loop or with the gas distribution in the chamber, and the system would have been automatically be shut down. If the ratio exceeded the nominal value by a smaller amount (e.g., 1.25), for an extended period, then the system would also have been shut down.

Numerous additional safety features reduced the likelihood of injury to subjects or operating personnel. For example, chamber concentration was continuously measured by the NDIR instrument and by an auxiliary monitor which uses an electrochemical sensing element. Furthermore, the control software contained a "watchdog" timer to ensure that the mass flow controllers were always receiving a "live" signal, and that the computer which controls the feedback loop could not simply crash and leave the exposure system running. In case of any emergency, manually-operated stop switches were provided inside and outside of the chamber to immediately halt exposure and flush the chamber air.

Figure 2. Subject receiving air exposure while breathing on bag exposure system.

2.3.4 Exercise Conditions and Control

Subjects performed lower-body exercise using a treadmill (Marquette Series 1900) located inside the exposure chamber (Figure 3). Treadmill work load was controlled using a Marquette Model MTC1 treadmill controller located outside the chamber. For subject safety, emergency stop switches were located on the treadmill handlebar and on the external chamber instrumentation rack. Conversion of treadmill speed and elevation to METS was done using a standard formula (see Guidelines for Exercise Testing and Prescription, American College of Sports Medicine (ACSM), 1991). Treadmill speed and elevation were set according to a modified Bruce protocol as follows:

Table 3. Subject activities and exercise conditions during lower-body exercise.

STAGE	ACTIVITY	POWER (METS)	SPEED (mph)	ELEVATION (% grade)
1	Rest, standing	1.0	0	0
2	Walking, level 1	4.6	1.7	10
3	Walking, level 2	7.0	2.5	12
4	Walking, level 3	10.2	3.4	14
	Cool-down	1.5	0.7	0
5	Rest, sitting, 5' post			
6	Rest, sitting, 10' post			

Subjects performed upper-body exercise using a hand-crank ergometer (modified Collins "Pedalmate") located inside the exposure chamber (Figure 4). Ergometer work load was controlled using a Collins Total Work Integrator ergometer controller located outside the chamber. Since accurate maintenance of the intended work load required subject participation, a meter was provided inside the chamber for visual feedback to the subject. The subject was asked to crank the ergometer at a rate sufficient to keep the meter indicator within the "green band" on the meter scale. A second meter was located outside the chamber for observation be the study investigator. Conversion of ergometer work load to METS was done using a standard formula (see Guidelines for Exercise Testing and Prescription, ACSM, 1991). Ergometer work load was set as follows:

Table 4. Subject activities and exercise conditions during upper-body exercise.

STAGE	ACTIVITY	POWER (METS)	WORK LOAD (watts)
1	Rest, sitting	1.0	0
2	Cycling, level 1	2.6	25
3	Cycling, level 2	3.6	40
4	Cycling, level 3	4.9	60
	Cool-down	1.0	0
5	Rest, sitting, 5' post		
6	Rest, sitting, 10' post		

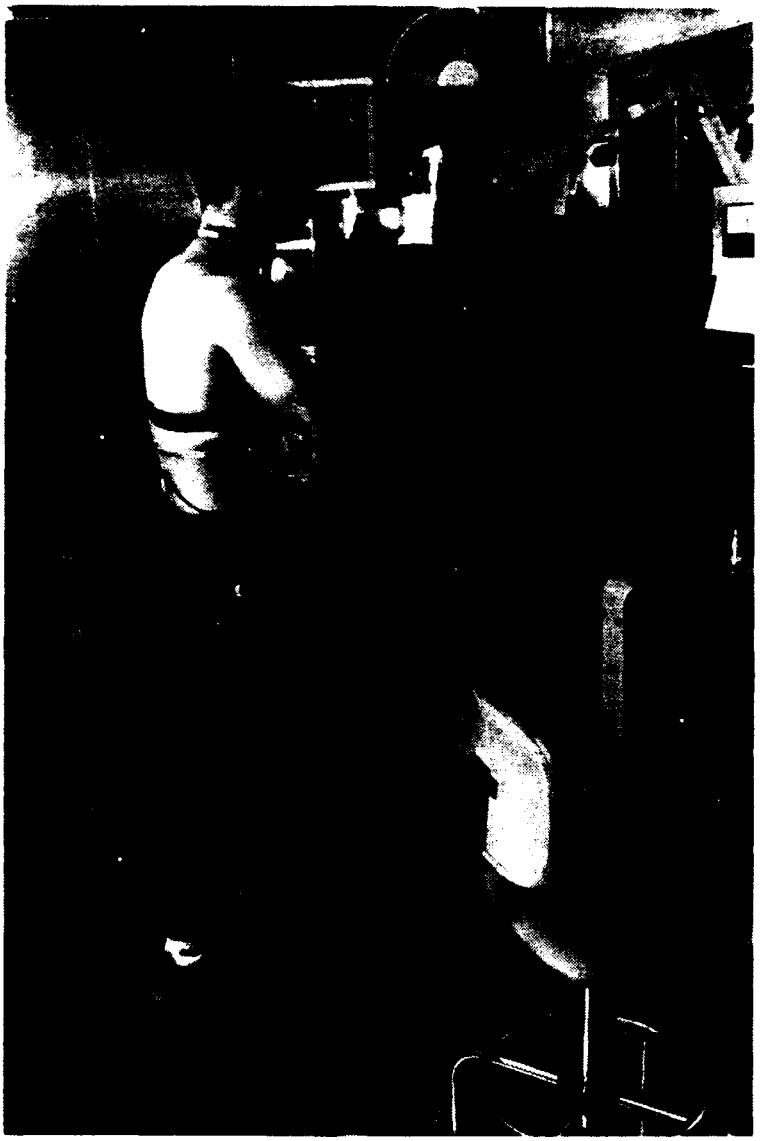


Figure 3. Subject performing lower-body exercise using treadmill.

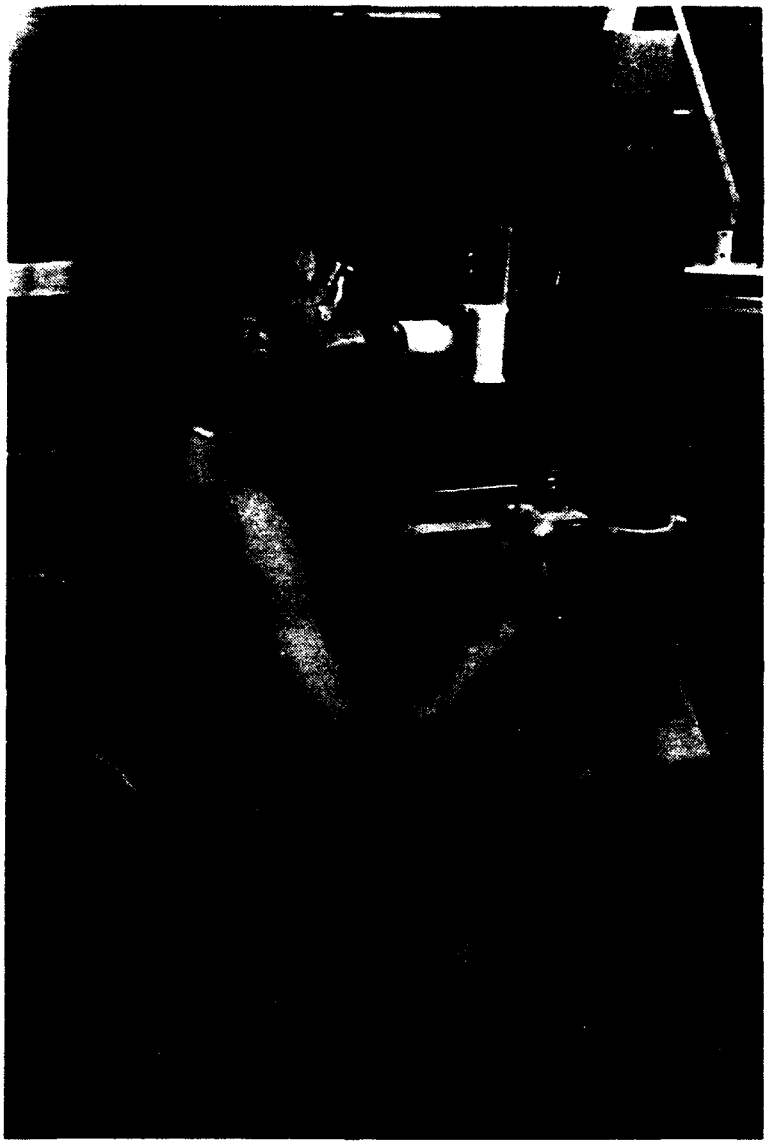


Figure 4. Subject performing upper-body exercise using hand crank ergometer.

2.4 Data Acquisition, Reduction, Integration, and Analysis

2.4.1 Blood Measurements

Venous blood samples were obtained at predetermined times during the experiment. Percent carboxyhemoglobin, oxyhemoglobin, methemoglobin and total hemoglobin was measured using a CO-Oximeter (Instrumentation Laboratories IL-282). The hematoctrit was determined using a Clay-Adams Microhematocrit II Centrifuge and reader. The well-mixed heparinized samples were analyzed immediately and a reserved sample refrigerated in case of any analysis difficulties. CO-Oximeter analyses were made in triplicate and hematoctrit analyses were made in duplicate. Calibration of the CO-Oximeter was performed weekly and controls were run daily using standards provided by the manufacturer.

2.4.2 Cardiac Function Measurements

For noninvasive cardiac function measurements, ECG leads V_5, II, and aVf, the cardiac bioimpedance signal (ΔZ) or impedance cardiogram (ICG), the ICG first derivative (dZ/dt) and the mean thoracic electrical impedance (Zo) were monitored continuously throughout each experiment, sampled at 400 Hz per channel, and stored on computer disk. The acquired cardiac signals were analyzed off-line using RTI's WVSHELL software according to methods previously described (Kizakevich et al., 1989; Kizakevich et al., 1993a). At thirty-second intervals throughout the acquired datasets, an ensemble average of the ECG, ΔZ, dZ/dt, and Z_0 signals was initiated. During ensemble averaging, successive cardiac cycles were extracted, displayed, and automatically accepted or rejected according to qualification template parameters (e.g., R-R interval, QRS width, peak-to-peak dZ/dt amplitude) to enhance signal quality. After thirty-two (32) qualified cycles were averaged, the six ensemble-averaged waveforms were automatically analyzed for specific waveform features, i.e. ECG ST-segment level, systolic time intervals (Sheps, 1982), peak-systolic dZ/dt amplitude and mean-systolic ICG acceleration. The primary ECG and ICG variables were:

RATE	heart rate (beats/min)
dZ/dt_{peak}	peak systolic amplitude of dZ/dt (Ω/s)
TZavo	time from ECG Q-wave to aortic valve opening [dZ/dt_{up}] (ms)
TZpeak	time from ECG Q wave to dZ/dt_{peak} (ms)
TZx	time from ECG Q-wave to aortic valve closing [dZ/dt_X] (ms)
ACCEL	ICG acceleration (cardiac contractility) (Ω/s^2)

Stroke volume and cardiac output were calculated using an empirical model relating TEI measurements to changes in thoracic blood flow (Kubicek et al., 1966; Sherwood et al., 1993; Everson et al, 1991):

$$S.V. = \rho \cdot (L/Z_0)^2 \cdot dZ/dt_{peak} \cdot (TZx - TZavo) \quad \text{cc}$$

$$C.O. = RATE \cdot (SV / 1000) \quad \text{L/min}$$

where the thoracic electrical impedance electrode separation, L, was measured for each subject and the blood resistivity, ρ, was assumed to be 135 Ω-cm (Kubicek et al., 1966). Measured and calculated variables (a data record) were stored to disk, while selected variables were appended to time-series trend waveforms. A composite of the analyzed ensemble-averaged signals and trend variables was then displayed and a printed copy made for the experiment archive (Figure 5).

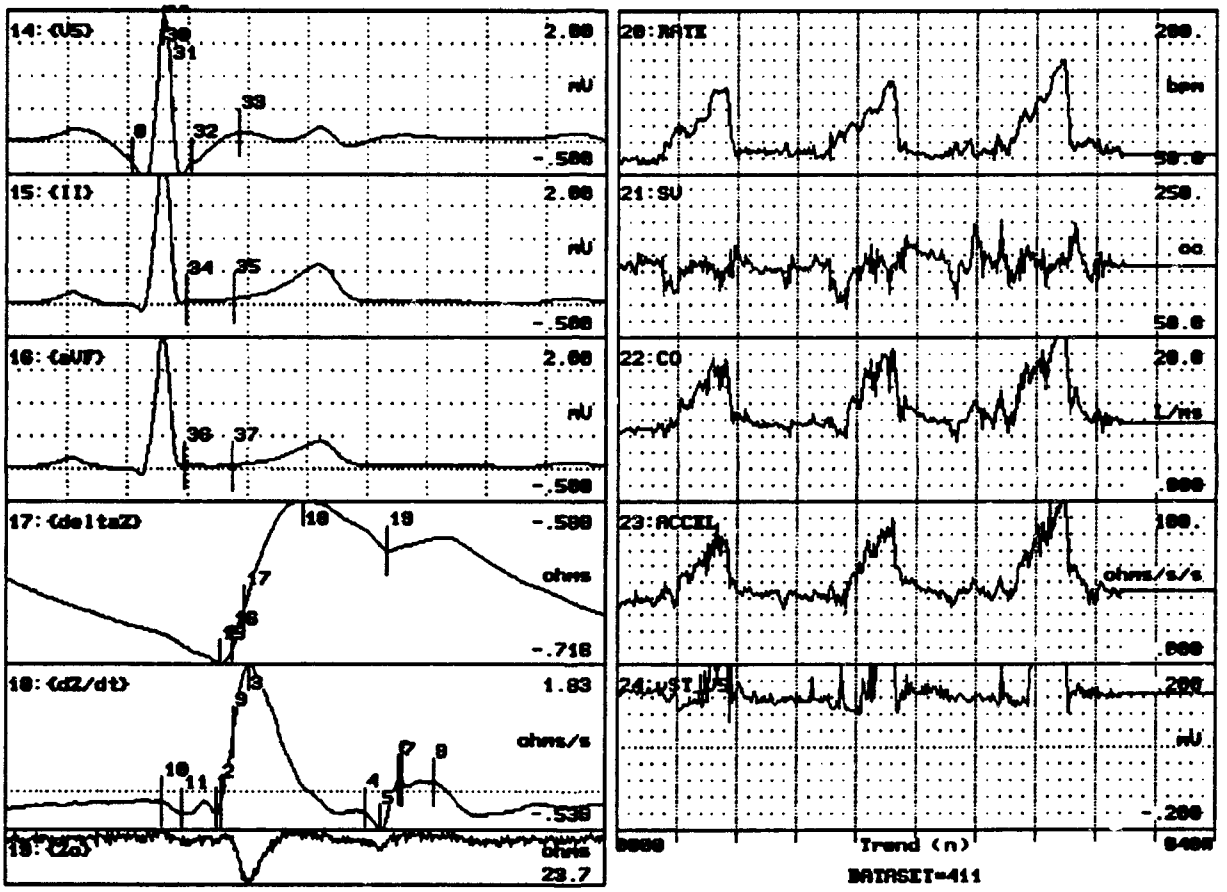


Figure 5. Analysis of cardiac function data. The physiological waveforms (LEFT) are the ECG leads V_5, II, and aVF, the cardiac bioimpedance signal (ΔZ) or impedance cardiogram (ICG), the ICG first derivative (dZ/dt) and the mean thoracic electrical impedance (Zo). The trend display waveforms (RIGHT) are heart rate (RATE), stroke volume (SV), cardiac output (CO), ICG acceleration (ACCEL), and ECG lead V_5 ST segment level (vST_V5).

The resultant data set was extensive. Over 200 records were stored for each training session (2 segments/session) and 300 records stored for each of four exposure sessions (3 segments/session) resulting in over 1400 data records per subject. Several processes were performed to assure data quality and prepare a more tractable data set for statistical analysis. The graphic trend of each key variable was reviewed to identify trend outliers, measurement errors, missing data records, experiment procedure problems, and other easily observable inconsistencies in the raw acquired data (Figure 6). As a result of this review, several data sets were completely reanalyzed, other data sets had missing data series repaired, and a few data sets were deemed unrepairable and discarded (see section 2.6.1). Qualified data sets were then converted to a data base format (Foxpro/dBase) for archival storage and further analysis.

Additional data adjustments were made after converting the cardiac variables to data base format. Remaining episodes of missing data, occurring within a continuous trend of qualified data, were repaired by substituting estimated data values by assuming a linear transition between pre- and post-missing data records. If the missing data series exceeded two samples, the data were left as missing.

Time-series data for each variables were smoothed (Figure 4) using a weighted filter as follows:

$$
\begin{aligned}
Y_1 &= X_1 \\
Y_2 &= X_2 \\
Y_i &= 0.1 \bullet X_{i-2} + 0.2 \bullet X_{i-1} + 0.4 \bullet X_i + 0.2 \bullet X_{i-1} + 0.1 \bullet X_{i-2} \\
Y_{n-1} &= X_{n-1} \\
Y_n &= X_n
\end{aligned}
$$

where

n = number of records

i = 3 to n-2

In spite of careful adherence to the experiment protocol, execution of multiple exercise segments in phase with the prescribed work-level transitions were affected somewhat by variable factors including investigator vigilance, equipment response, and subject compliance. Therefore, to align data trends across subjects, sessions, and exposure segments, graphic trends of smoothed heart rate were analyzed for each data series and the end of the third exercise stage (maximal) within each exposure segment was identified. The data set record number corresponding to the end of maximal exercise was used as a fiducial index to extract six records (exercise stage) relative to the fiducial index: the end of the pre-exercise rest period, the end of each exercise periods, five minutes post exercise, and ten minutes post exercise. Thus, the 300 data records of cardiac data comprising each exposure day were reduced to 18 records (3 SEGMENTS of 6 STAGES each). Since the experiment design did not call for post-exercise data, post-exercise data were used for exploratory charting only and were excluded from the statistical analyses.

2.4.3 Cardiac Electrophysiology Measurements

For noninvasive cardiac electrophysiology measurements, ECG leads V_5, II, and aVf were recorded using an ambulatory recorder (Spacelabs Model 90208). Five electrodes, corresponding to right arm (RA), left arm (LA), right leg (RL), left leg (LL), and chest (V) were applied as for stress test monitoring, (i.e., the electrodes are applied to the torso rather than to the limbs). Standard, disposable, and pre-gelled exercise stress-test electrodes were used (3M Red Dot).

On each experiment day, the subject number, test date, and time were noted on the designated cassette tape, and the tape placed in the recorder. As soon as the subject entered the chamber, the AECG

recording procedure was initiated. A calibration signal was automatically recorded for the first 12.8 minutes of operation before ECG signals were recorded. ECG rhythm and ST segment analysis was conducted off-line using an semi-automated ambulatory ECG analyzer (SpaceLabs FT1000) with interactive analysis verification. Each analysis produced a summary report including rhythm analysis, significant ECG strips, ST segment trends, etc. (Appendix 5.4). Reports were reviewed by a cardiologist at UNC for validation of signal quality, rhythm assessment, and ST segment analysis.

2.4.4 Respiratory Measurements

Breath-by-breath ventilation and gas concentration measurements were taken over a 1.5 minute period beginning at 2 minutes into each protocol activity stage. While performing their protocol activities, subjects put on nose clips and breathed via an apparatus comprising a mouthpiece, gas sample port, and flowmeter (Figures 3 and 4). A gas exchange analysis system comprising a mass spectrometer (Marquette MGA1100), pneumotachograph (Fleish 3700), carrier demodulator (Validyne), and computer software (First Breath, Inc.) was used. The software included modules for flow and gas calibration, data management, data acquisition and display, and ventilation and gas exchange analysis. Each measurement series (e.g., set of breaths within an activity stage) was inspected for data quality and consistency; then were averaged to obtain a single estimate for the exercise stage. Since the system was not available until midway in data collection, respiratory measurements were only made on 10 subjects. Furthermore, complete respiratory data sets were only available on 7 of these 10 subjects for data analysis. The respiratory data were integrated with blood variables, cardiac variables, and other data into the unified CO Study data base and indexed by SUBJECT, experiment SESSION, exposure SEGMENT, and exercise STAGE.

2.5 Results

2.5.1 Subjects

Twenty-one (21) subjects were entered into the study. Each gave informed consent, completed a medical history and physical examination, and passed a maximal exercise tolerance test (Bruce treadmill protocol) before participating in any experiment procedures. Of the original 21 subjects (Figure 6), three were withdrawn after completing training: one because of schedule conflicts (#1), one who failed to show up for the experiments (#8), and one who was discovered to be a smoker (#6). Eighteen (18) subjects participated in carbon monoxide exposure studies. Of these subjects, one (#3) could not be analyzed because of data file corruption (disk errors) and a second (#2) was excluded from data analysis because the attained COHb levels were off target. A third subject (#13) was excluded from treadmill data analysis only because of disk errors on one treadmill experiment day. Therefore, sixteen (16) subjects were included in the hand crank data analysis and fifteen (15) subjects were included in the treadmill data analysis.

Anthropometric characteristics of subjects included in hand crank and treadmill data analyses are presented in Table 5. The primary subject-dependent recruitment criteria was to include individuals ranging from 18 to 30 years of age. The final study population ranged from 21 to 29 years of age with a mean of 24.6 years, closely meeting the desired range. Furthermore, the subjects were substantially equivalent with respect to body build with only a 7.8% variation in weight, 3.3% variation in height, and 4.3% variation in estimated body surface area (BSA).

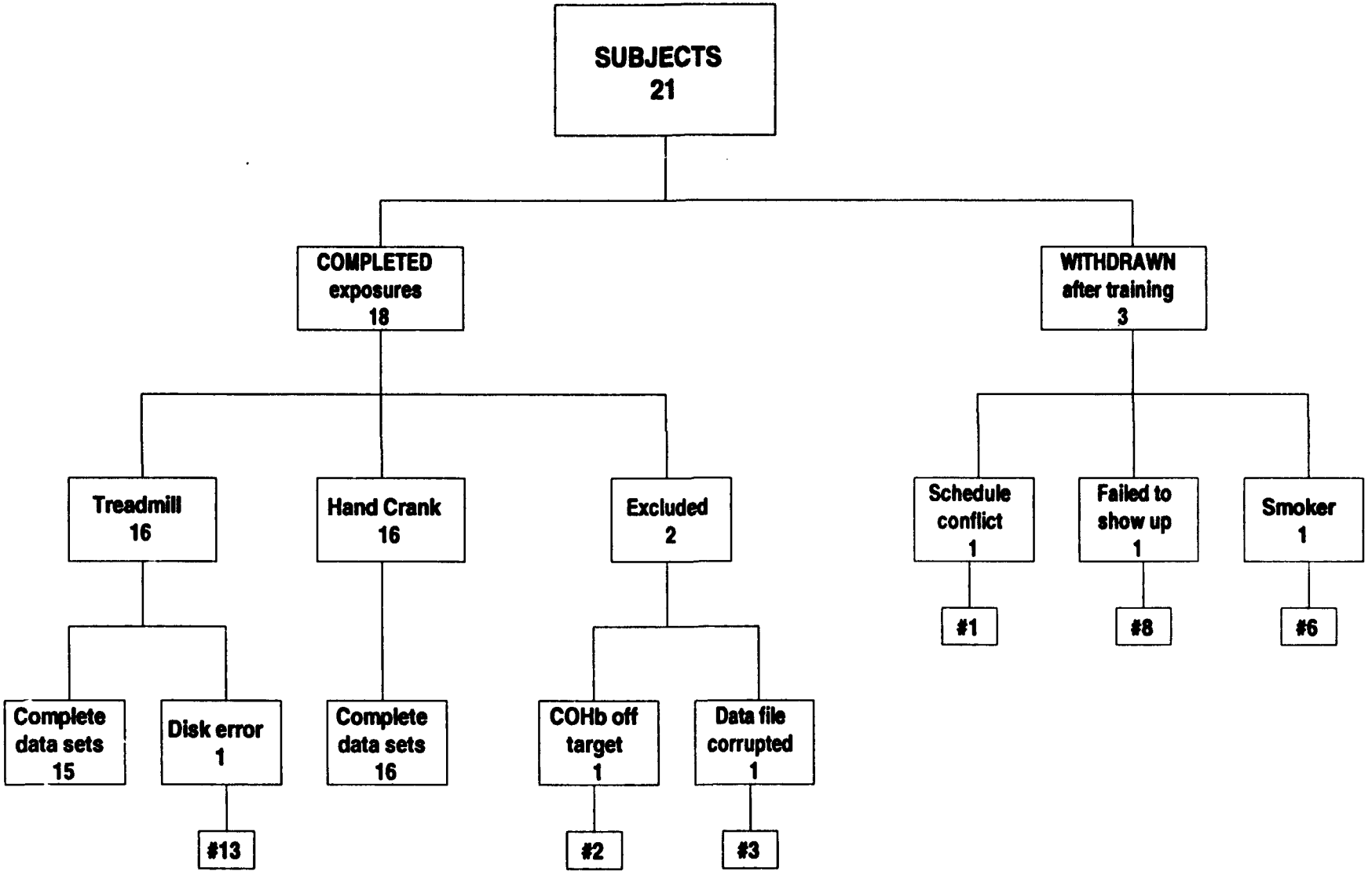


Figure 6. Distribution of subject participation and data status among completed and excluded experiment groups.

Table 5. Distribution of anthropometric data for study population.

Subject (#)	Age (yrs)	Weight (kg)	Height (cm)	Length (cm)	Neck (cm)	Thorax (cm)	BSA (cm^2)
4	23	72.7	181.6	31.0	38.0	87.0	1.93
5	28	80.9	181.6	33.5	37.0	94.0	2.02
7	23	75.9	175.3	30.5	38.5	92.0	1.91
9	25	84.1	177.8	37.0	41.0	93.0	2.02
10	27	88.2	172.7	29.0	42.5	95.0	2.02
11	21	84.1	195.6	33.0	22.0	72.0	2.16
12	21	72.7	176.5	30.0	39.0	86.0	1.89
*13	23	78.6	180.3	31.0	36.0	83.0	1.98
14	23	90.0	177.8	33.0	41.5	92.0	2.08
15	24	86.4	185.4	34.0	39.0	93.0	2.11
16	26	81.8	182.9	31.5	37.0	89.0	2.04
17	27	76.4	185.4	30.0	39.0	88.5	2.00
18	24	84.1	185.4	33.0	40.0	93.5	2.08
19	22	69.5	180.3	31.0	37.0	80.0	1.88
20	29	74.1	175.3	34.0	38.5	89.0	1.89
21	28	79.5	188.0	37.0	38.5	91.0	2.05
All Subjects							
MIN	21.0	69.5	172.7	29.0	22.0	72.0	1.9
MAX	29.0	90.0	195.6	37.0	42.5	95.0	2.2
Hand Crank Subjects							
MEAN	24.6	79.9	181.4	32.4	37.8	88.6	2.0
SD	2.6	6.0	5.8	2.4	4.6	6.1	0.1
CV	10.5%	7.5%	3.2%	7.3%	12.1%	6.8%	4.2%
Treadmill Subjects							
MEAN	24.7	80.0	181.4	32.5	37.9	89.0	2.0
SD	2.6	6.2	6.0	2.4	4.7	6.1	0.1
CV	10.6%	7.8%	3.3%	7.4%	12.4%	6.8%	4.3%

* Subject 13 excluded from treadmill analysis

2.5.2 Reproducibility of Cardiac Variables in Exercise

According to the experiment study design, effects CO exposure on cardiac exercise response were investigated using multiple experiment sessions and experiment days. Furthermore, each subject participated in all experimental conditions so that changes in individual exercise responses might be identified. Therefore, it was necessary to verify that equivalent exercise response data could be acquired independent of a subject's recording session. If reproducible data could not be acquired, then differences in exercise response due to CO exposure could not be differentiated from within-subject variability of measurements or exercise response.

The within-subject reproducibility of ICG measurements was examined across three air-exposure data segments for each exercise type and included rest, exercise, and exercise recovery data. For lower-body exercise, experiment sessions 1, 3, and 4 were compared. For upper-body exercise, experiment sessions 2, 5, and 6 were compared. Variables were analyzed by repeated measures analysis of variance (ANOVA) and tested for a significant effect using an α of 0.05. Variables were also analyzed by correlation of paired subject data (days 1-2, 1-3, and 2-3) and the average correlation coefficient (r_{mean}) computed.

Cardiac measurements were substantially equivalent across experiment session (Tables 6 and 7). For treadmill exercise a significant effect was found for heart rate ($p<0.01$) and aortic valve closing time ($p<0.01$), a heart rate related parameter. For hand crank exercise a significant effect was also found for heart rate ($p<0.02$), but not for aortic valve closing time. An effect was also found for Zo ($p<0.01$), however the effect on Zo did not carry into the ICG-based calculation of stroke volume. In spite of the significant heart rate effect, cardiac output was equivalent across experiment sessions for both types of exercise. Plots of mean ICG acceleration measurements taken at rest, during exercise, and post-exercise for the three upper-body and the three lower-body experiment sessions are shown in Figure 7. Similar plots for the remaining variables are presented in Appendix 5.5.

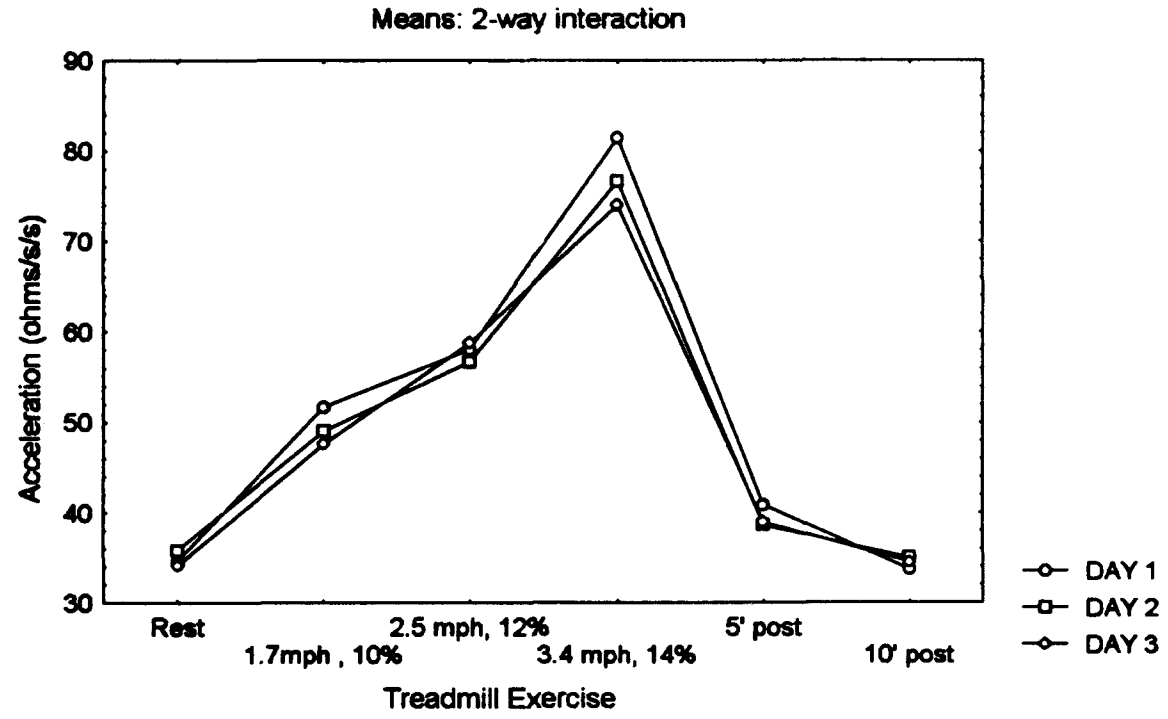
Since heart rate is closely linked to exercise level, it was not surprising that heart rate was best correlated variable across experiment sessions. Correlation of measured and derived ICG variables was generally better for treadmill exercise than for hand-crank exercise, particularly for the timing variables and estimated cardiac output. Of the timing variables, TZavo had a lower correlation than TZpeak and TZx, indicating the difficulty in automatically determining the onset of the rapid dZ/dt systolic pulse. The ICG amplitude variables (dZ/dt_{peak}, Zo, and ACCEL) had a better correlation for hand-crank than treadmill exercise. Finally, although the calculated SV estimate had only slightly better correlation in treadmill exercise, the CO correlation was much better for treadmill than hand-crank exercise.

Reproducibility of ICG variables may have been affected by several factors: ability to reproduce exercise conditions (i.e., hand-crank exercise), variability of physiological exercise response, variability in ICG representation of the physiological response, effects of ICG signal processing, and accuracy of automatic ICG waveforms analysis. Considering these factors, the results demonstrate that automated impedance cardiography is effective in noninvasive serial assessment of cardiac function. Specifically, serial assessment is proved reliable for grouped repeated-measures studies where each subject is assessed before and after some intervention.

Table 6. Reproducibility of primary cardiac measurements before, during, and after lower-body (N=15) and upper-body (N=13) exercise across three experiment days by repeated measures analysis of variance. Tests for significant differences were made using α=0.05.

Measured and Derived Cardiac Variables	Treadmill Exercise		Hand-Crank Exercise	
	ANOVA	r_{mean}	ANOVA	r_{mean}
Heart rate	0.01	0.93	0.02	0.89
Time-to-aortic valve opening	ns	0.86	ns	0.71
Time-to-peak ejection	ns	0.92	ns	0.89
Time-to-aortic valve closing	0.01	0.92	ns	0.86
Peak dZ/dt amplitude	ns	0.85	ns	0.89
Mean thoracic impedance	ns	0.64	0.01	0.75
Acceleration	ns	0.78	ns	0.86
Stroke volume	ns	0.71	ns	0.68
Cardiac output	ns	0.77	ns	0.67

PANEL A



PANEL B

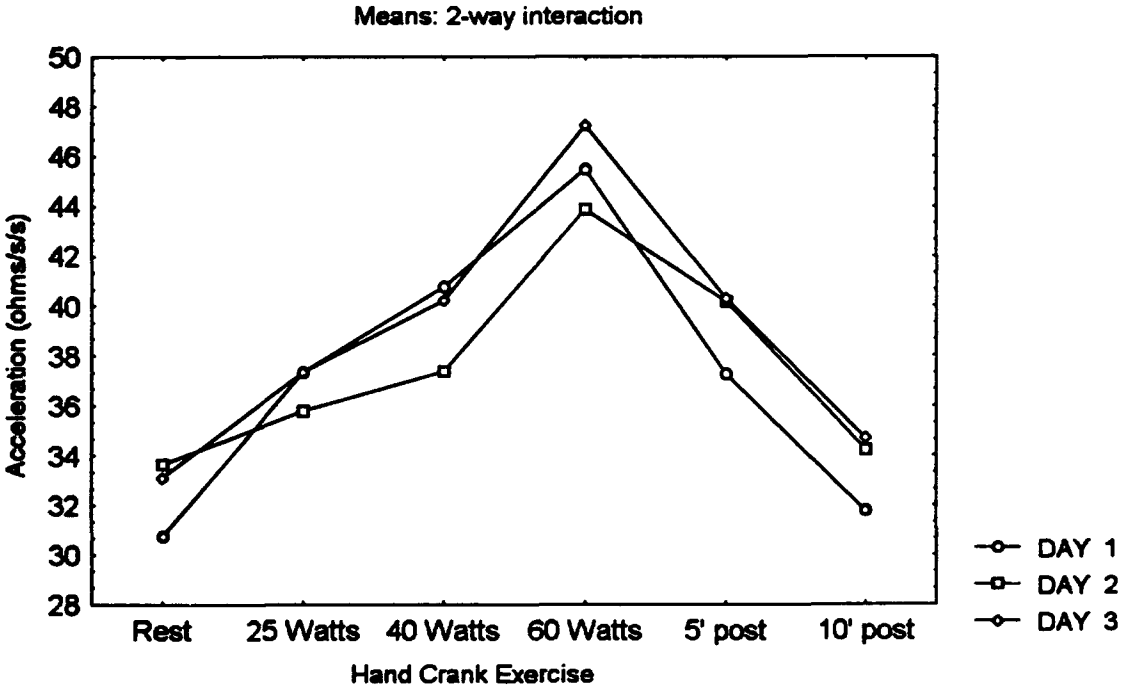


Figure 7. Mean ICG acceleration response during treadmill (Panel A) hand crank (Panel B) exercise.

2.5.3 Effects of CO Exposure on Lower-Body Exercise Response

Overall effects of CO exposure and treadmill exercise

The effects of carbon monoxide exposure on the cardiac and respiratory responses to lower-body treadmill exercise were evaluated by several means. As a first step, CO exposure, treadmill exercise, and CO x treadmill exercise interaction were evaluated by repeated-measures analysis-of-variance (ANOVA) for five cardiac variables and four respiratory variables using raw unadjusted measurements (Actual Data, Table 7), pre-exercise adjusted measurements (Change from Rest, Table 8), and air-exposure adjusted measurements (Delta Air Exposure, Table 9). Air-exposure adjusted measurements (paired-difference) were calculated for each activity and exposure level by subtracting the paired value for each activity level after air exposure to account for variation in exercise response across subjects.

For Actual Data, significant CO effects were found for heart rate, acceleration, and time-to-peak ejection ($p<0.0001$). For the Change-from-Rest and Delta Air Exposure adjusted data sets, significant CO effects were found for heart rate and acceleration only ($p<0.0001$). Effects of CO x treadmill exercise interaction were significant for heart rate ($p<0.0001$), acceleration ($p<0.004$), and time-to-peak ejection ($p<0.032$) for Actual Data, but not for the Change-from-Rest data set. For Delta Air Exposure data, the effects of CO x treadmill exercise interaction were significant for heart rate ($p<0.0001$) and acceleration ($p<0.004$) only. No significant effects of CO exposure on respiratory variables were observed (Tables 7, 8, and 9).

Table 7. Effects of carbon monoxide exposure and lower-body treadmill exercise on Actual Data by repeated measures analysis of variance. Tests for significant differences were made using $\alpha=0.05$.

Actual Data	CO	Treadmill	CO x Treadmill	N
Heart Rate	0.0001	0.0001	0.0001	15
Stroke Volume	ns	0.0001	ns	15
Cardiac Output	ns	0.0001	ns	15
Acceleration	0.0001	0.0001	0.004	15
Time-to-peak Ejection	0.0001	0.0001	0.032	15
O_2 Consumption	ns	0.0001	ns	7
CO_2 Production	ns	0.0001	ns	7
Ventilation	ns	0.0001	ns	7
Resp. Exchange Ratio	ns	0.0001	ns	7

Table 8. Effects of carbon monoxide exposure and lower-body treadmill exercise on Change-from-Rest Data by repeated measures analysis of variance. Tests for significant differences were made using α=0.05.

Change from Rest	CO	Treadmill	CO x Treadmill	N
Heart Rate	0.0001	0.0001	ns	15
Stroke Volume	ns	0.001	ns	15
Cardiac Output	ns	0.0001	ns	15
Acceleration	0.0001	0.0001	ns	15
Time-to-peak Ejection	ns	0.0001	ns	15
O_2 Consumption	ns	0.0001	ns	7
CO_2 Production	ns	0.0001	ns	7
Ventilation	ns	0.0001	ns	7
Resp. Exchange Ratio	ns	0.0001	ns	7

COHb: 1.8%, 5.0%, 9.8%, 14.8%, 19.2%

Exercise: Rest standing, 1.7 mph, 10%; 2.5 mph, 12%; 3.4 mph, 14%

Table 9. Effects of carbon monoxide exposure and lower-body treadmill exercise on Delta Air Exposure Data by repeated measures analysis of variance. Tests for significant differences were made using α=0.05.

Delta Air Exposure	CO	Treadmill	CO x Treadmill	N
Heart Rate	0.0001	0.005	0.0001	15
Stroke Volume	ns	ns	ns	15
Cardiac Output	ns	ns	ns	15
Acceleration	0.0001	0.005	0.004	15
Time-to-peak Ejection	ns	0.005	ns	15
O_2 Consumption	ns	0.005	ns	7
CO_2 Production	ns	0.001	ns	7
Ventilation	ns	ns	ns	7
Resp. Exchange Ratio	ns	ns	ns	7

COHb: 1.8%, 5.0%, 9.8%, 14.8%, 19.2%

Exercise: Rest standing, 1.7 mph, 10%; 2.5 mph, 12%; 3.4 mph, 14%

Effects of increasing CO exposure

Three post-hoc analyses were conducted to explore effects of increasing CO exposure. Two analyses used Actual Data (raw unadjusted measurements) to compare mean measurements across subjects and exercise levels by blood COHb level (μ_{CO} versus μ_{air}) after repeated-measures ANOVA. First, the Least Significant Difference method (LSD) was employed for sensitive detection of CO effects on Actual Data. Since five levels of CO exposure were considered, multiple comparison errors were reduced by testing for significant differences using an adjusted α of 0.01 (0.05/5). For comparison, Scheffé's procedure was also employed for a more conservative analysis of Actual Data. Tests for significant differences were made with an α of 0.05. Delta Air Exposure data (paired air-exposure adjusted measurements) were then tested for $\mu_D=0$. P-values are reported for $\alpha<0.05$; however tests for significant differences were made with an α of 0.01. Change-from-Rest data were not employed in the post-hoc analyses. Results are presented in Tables 10 through 15.

Means and standard deviations of cardiac and respiratory measurements were computed across subjects by attained COHb levels and prescribed exercise activity levels for Actual Data, Delta Air Exposure Data, and percent change in Delta Air Exposure Data. Results are summarized in Table 16 by mean and standard deviation. Mean data per exposure level are also illustrated as functions exercise level (in METS) in Figures 8 through 16.

Mean COHb levels for air and CO exposures were 1.8%, 5.0%, 9.8%, 14.8%, and 19.2%. COHb levels attained after mouthpiece exposure and just before standing at rest (5.2%, 9.9%, 15.0%, and 19.6%) were very close to the experiment target levels of (5%, 10%, 15%, and 20% COHb). Although COHb tended to decrease during exercise, the chamber CO exposure during exercise limited the decrement to less than 1% COHb (Table 16). All of these results are well within the specifications of the IL-282 CO-Oximeter which has a combined measurement and display accuracy of ±1.1% COHb.

Actual Data (raw unadjusted measurements)

The effects of CO exposure on the overall cardiac exercise response of Actual Data were similar using both the LSD and Scheffé analyses (Tables 10 and 11). No significant overall effects of CO exposure on respiratory variables were observed using either analysis (Tables 13 and 14).

Heart rate and acceleration were significantly increased for COHb≥14.8% as compared to COHb=1.8% (air exposure). Likewise, time-to-peak ejection velocity was significantly decreased for COHb≥14.8%. Using the more sensitive LSD analysis, heart rate also showed a significant difference at 5.0% COHb and acceleration showed a significant difference at 9.8% COHb.

Neither stroke volume nor cardiac output had a significantly different overall exercise response after CO exposure rather than after air exposure (Tables 10 and 11). Stroke volume increased substantially from rest to initial exercise, held steady for the second level, and fell off at the highest level of exercise (Figure 9-A). This stroke volume response was consistent across all CO exposures. Cardiac output showed no difference at 5.0% COHb, followed by a small progressive increase in the mean exercise response for COHb≥9.8% (Figure 10-A). Apparently a large intersubject variability prevented the attainment of significant effects for either variable.

Delta Air Exposure data (paired air-exposure adjusted measurements)

The Delta Air Exposure analysis provided increased sensitivity for effects of CO exposure for both cardiac and respiratory variables (Tables 12 and 15). Significant differences in overall exercise response were found for heart rate at each level of CO exposure ($p<0.0001$) with increases of about 5% for COHb≤9.8% and 13% for COHb≥14.8% relative to air exposure responses.

Stroke volume was decreased significantly at rest and during early exercise at 5.0% COHb relative to air exposure ($p<0.01$), but remained only slightly decreased at higher levels of COHb (Figure 9-B).

Cardiac output began to show an increased exercise response at 9.8% COHb ($p=0.05$) and was significantly enhanced for COHb≥14.8% (Figure 10-B) attaining a peak difference of 19% for the first exercise level and a 14.9% overall increase at 19.2% COHb. The enhanced response was somewhat diminished for increasing exercise at 9.8% and 14.8% COHb, and was substantially reduced at the highest exercise level (3.4 mph, 14% grade) for 19.2% COHb.

Acceleration showed a dramatic and progressive response using Delta Air Exposure data. Enhanced exercise responses were observed at each level of CO exposure (Figure 11-B) with overall increases of 4.9%, 10.4%, 16.5%, and 25.9% for the four CO exposures (Table 16). Very significant responses were observed for COHb≥9.8% with a 38.4% peak difference achieved during exercise at 19.2% COHb (Table 16). Although the acceleration response was significantly enhanced, the progressive increases at the lower exercise levels could not be maintained throughout exercise. This indicates that CO exposure may adversely limit cardiac contractility in exercise.

Mean time-to-peak ejection velocity was decreased at each level of CO exposure (Table 16), becoming significantly decreased for COHb≥14.8% (Table 12, Figure 13-B). At these higher levels of exposure, the exercise response was enhanced by about 5%.

The respiratory variables demonstrated only minor effects of CO exposure after Delta Air Exposure adjustment and had substantial intersubject variance (Table 16). Mean oxygen consumption and carbon dioxide production were consistently decreased relative to air exposure, especially at the higher levels of exercise (Figures 13-B and 14-B), but these differences were not significant. Ventilation demonstrated no significant effect until COHb achieved 19.2% ($p>0.006$). At this level, overall ventilation after CO exposure was increased by about 6% over air exposure, as evident in Figure 15-B. No significant effect was observed for respiratory exchange ratio.

Table 10. Comparative effects of carbon monoxide exposure relative to air exposure for each cardiac variable during lower-body exercise using the Least Significant Difference method (LSD) for testing comparisons. To reduce multiple-comparison errors, tests for significant differences were made using α=0.01.

Overall Response - Actual Data (LSD)				
COHb Level	**5.0%**	**9.8%**	**14.8%**	**19.2%**
Rate	0.01	ns	0.0001	0.0001
Stroke Volume	ns	ns	ns	ns
Cardiac Output	ns	ns	ns	ns
Acceleration	ns	0.01	0.001	0.0001
Time-to-peak Ejection	ns	ns	0.01	0.001

Table 11. Comparative effects of carbon monoxide exposure relative to air exposure for each cardiac variable during lower-body exercise using Scheffé's conservative method for testing comparisons. Tests for significant differences were made using α=0.05.

Overall Response - Actual Data (Scheffé)				
COHb Level	**5.0%**	**9.8%**	**14.8%**	**19.2%**
Rate	ns	ns	0.0001	0.0001
Stroke Volume	ns	ns	ns	ns
Cardiac Output	ns	ns	ns	ns
Acceleration	ns	ns	0.01	0.0001
Time-to-peak Ejection	ns	ns	0.05	0.05

Table 12. Comparative effects of carbon monoxide exposure relative to air exposure for each cardiac variable during lower-body exercise. Paired-difference variables were calculated for measurements at each activity level by subtracting the paired value for air exposure and tested for μ=0. Tests for significant differences were made using α=0.01.

Overall Treadmill Response - Delta Air Exposure				
COHb Level	**5.0%**	**9.8%**	**14.8%**	**19.2%**
Rate	0.0001	0.0001	0.0001	0.0001
Stroke Volume	0.01	ns	ns	ns
Cardiac Output	ns	(0.05)	0.01	0.0001
Acceleration	(0.04)	0.0001	0.0001	0.0001
Time-to-peak Ejection	ns	ns	0.0001	0.0001

Table 13. Comparative effects of carbon monoxide exposure relative to air exposure for each respiratory variable during lower-body exercise using the Least Significant Difference method (LSD) for testing comparisons. To reduce multiple-comparison errors, tests for significant differences were made using α=0.01.

Overall Response - Actual Data (LSD)				
COHb Level	**5.0%**	**9.8%**	**14.8%**	**19.2%**
O_2 Consumption	ns	ns	ns	ns
CO_2 Production	ns	ns	ns	ns
Ventilation	ns	ns	ns	ns
Resp. Exchange Ratio	ns	ns	ns	ns

Table 14. Comparative effects of carbon monoxide exposure relative to air exposure for each respiratory variable during lower-body exercise using Scheffé's conservative method for testing comparisons. Tests for significant differences were made using α=0.05.

Overall Response - Actual Data (Scheffé)				
COHb Level	**5.0%**	**9.8%**	**14.8%**	**19.2%**
O_2 Consumption	ns	ns	ns	ns
CO_2 Production	ns	ns	ns	ns
Ventilation	ns	ns	ns	ns
Resp. Exchange Ratio	ns	ns	ns	ns

Table 15. Comparative effects of carbon monoxide exposure relative to air exposure for each respiratory variable during lower-body exercise. Paired-difference variables were calculated for measurements at each activity level by subtracting the paired value for air exposure and tested for μ=0. Tests for significant differences were made using α=0.01.

Overall Treadmill Response - Delta Air Exposure				
COHb Level	**5.0%**	**9.8%**	**14.8%**	**19.2%**
O_2 Consumption	ns	(0.02)	ns	(0.02)
CO_2 Production	ns	(0.02)	ns	(0.05)
Ventilation	ns	ns	ns	0.006
Resp. Exchange Ratio	ns	(0.04)	ns	ns

Table 16. Combined effects of carbon monoxide exposure and lower-body treadmill exercise. Means and standard deviations are presented across subjects for each level of CO exposure and treadmill exercise. Actual data, subject-paired difference from air-exposure data, and subject-paired percent difference from air-exposure data are listed.

COHb (%)	1.8% COHb	5.0% COHb	9.8% COHb	14.8% COHb	19.2% COHb
Rest	1.8 ± 0.32	5.2 ± 0.72	9.9 ± 1.12	15.0 ± 1.28	19.6 ± 0.92
1.7 mph, 10%	1.8 ± 0.32	4.6 ± 0.21	9.8 ± 1.06	14.9 ± 1.28	19.3 ± 0.89
2.5 mph, 12%	1.8 ± 0.32	4.9 ± 0.44	9.7 ± 1.05	14.7 ± 1.28	19.0 ± .90
3.4 mph, 14%	1.8 ± 0.34	5.1 ± 0.64	9.6 ± 1.02	14.5 ± 1.33	18.7 ± 0.95

Heart Rate (beats/min)	1.8%	5.0%	9.8%	14.8%	19.2%
Rest	80.7 ± 11.0	86.6 ± 13.5	85.4 ± 14.6	91.4 ± 17.9	88.5 ± 16.4
1.7 mph, 10%	93.9 ± 11.1	101.1 ± 16.3	99.4 ± 15.6	108.9 ± 18.5	109.4 ± 17.5
2.5 mph, 12%	111.1 ± 13.4	116.9 ± 18.4	115.5 ± 15.5	126.5 ± 21.0	128.6 ± 20.1
3.4 mph, 14%	135.0 ± 19.2	140.1 ± 21.9	140.7 ± 18.5	150.0 ± 23.5	153.1 ± 20.3
Rest, Δ AIR	0.0 ± 0.0	5.9 ± 5.2	4.7 ± 7.1	10.7 ± 8.7	7.7 ± 8.8
1.7 mph, 10%, Δ AIR	0.0 ± 0.0	7.1 ± 5.8	5.5 ± 8.0	14.9 ± 9.2	15.5 ± 9.5
2.5 mph, 12%, Δ AIR	0.0 ± 0.0	5.9 ± 6.2	4.4 ± 8.2	15.4 ± 9.7	17.5 ± 10.1
3.4 mph, 14%, Δ AIR	0.0 ± 0.0	5.1 ± 5.9	5.7 ± 10.8	15.0 ± 8.9	18.1 ± 10.2
Overall, Δ AIR	*0.0 ± 0.0*	*6.0 ± 5.7*	*5.1 ± 8.4*	*14.0 ± 9.1*	*14.7 ± 10.3*
Rest, %Δ AIR	0.0 ± 0.0	7.1 ± 6.5	5.6 ± 8.4	12.5 ± 10.2	9.2 ± 10.4
1.7 mph, 10%, %Δ AIR	0.0 ± 0.0	7.1 ± 5.8	5.6 ± 7.9	15.4 ± 8.8	16.2 ± 9.0
2.5 mph, 12%, %Δ AIR	0.0 ± 0.0	4.9 ± 5.5	4.0 ± 6.9	13.4 ± 7.7	15.5 ± 8.3
3.4 mph, 14%, %Δ AIR	0.0 ± 0.0	3.5 ± 4.3	4.6 ± 7.7	10.9 ± 6.1	13.8 ± 8.2
Overall, %Δ AIR	*0.0 ± 0.0*	*5.6 ± 5.7*	*4.9 ± 7.6*	*13.0 ± 8.3*	*13.7 ± 9.2*

Table 16 (continued). Combined effects of carbon monoxide exposure and lower-body treadmill exercise.

Stroke Volume (cc)	1.8% COHb	5.0% COHb	9.8% COHb	14.8% COHb	19.2% COHb
Rest	110.3 ± 28.8	102.6 ± 35.3	115.2 ± 26.3	110.6 ± 41.6	111.8 ± 27.3
1.7 mph, 10%	149.6 ± 44.9	137.2 ± 50.4	149.1 ± 46.4	144.1 ± 56.5	150.1 ± 39.8
2.5 mph, 12%	149.7 ± 44.3	143.0 ± 50.2	149.4 ± 42.4	143.5 ± 54.7	147.5 ± 36.2
3.4 mph, 14%	135.7 ± 42.7	129.6 ± 53.2	132.1 ± 38.9	127.8 ± 51.7	128.5 ± 35.2
Rest, Δ AIR	0.0 ± 0.0	-7.6 ± 17.9	4.92 ± 17.2	0.37 ± 19.2	1.52 ± 16.0
1.7 mph, 10%, Δ AIR	0.0 ± 0.0	-12.4 ± 17.2	-0.54 ± 25.3	-5.52 ± 21.5	0.49 ± 20.0
2.5 mph, 12%, Δ AIR	0.0 ± 0.0	-6.8 ± 19.4	-0.27 ± 25.0	-6.18 ± 25.7	-2.19 ± 21.6
3.4 mph, 14%, Δ AIR	0.0 ± 0.0	-6.2 ± 22.3	-3.67 ± 15.6	-7.95 ± 21.0	-7.25 ± 18.1
Overall, Δ AIR	*0.0 ± 0.0*	*-8.3 ± 19.0*	*0.11 ± 20.9*	*-4.82 ± 21.6*	*-1.86 ± 18.9*
Rest, %Δ AIR	0.0 ± 0.0	-8.4 ± 20.5	7.0 ± 19.1	-2.3 ± 19.7	3.2 ± 17.9
1.7 mph, 10%, %Δ AIR	0.0 ± 0.0	-10.1 ± 16.7	1.2 ± 21.6	-6.1 ± 20.3	2.4 ± 16.8
2.5 mph, 12%, %Δ AIR	0.0 ± 0.0	-6.1 ± 19.3	2.1 ± 21.4	-5.9 ± 22.6	1.3 ± 19.6
3.4 mph, 14%, %Δ AIR	0.0 ± 0.0	-7.2 ± 22.0	-0.6 ± 17.9	-8.1 ± 20.8	-2.5 ± 18.9
Overall, %Δ AIR	*0.0 ± 0.0*	*-8.0 ± 19.3*	*2.4 ± 19.7*	*-5.6 ± 20.5*	*1.1 ± 18.0*

Cardiac Output (l/min)	1.8%	5.0%	9.8%	14.8%	19.2%
Rest	8.7 ± 2.1	8.9 ± 3.4	9.7 ± 1.8	9.9 ± 3.9	9.6 ± 2.0
1.7 mph, 10%	13.7 ± 3.2	13.4 ± 4.2	14.4 ± 3.4	15.2 ± 5.1	16.0 ± 3.0
2.5 mph, 12%	16.3 ± 3.9	16.3 ± 4.9	16.9 ± 3.5	17.6 ± 5.7	18.6 ± 3.5
3.4 mph, 14%	17.9 ± 4.4	17.7 ± 6.1	18.1 ± 3.5	18.6 ± 6.2	19.2 ± 3.5
Rest, Δ AIR	0.0 ± 0.0	0.13 ± 1.8	0.92 ± 1.4	1.19 ± 2.3	0.86 ± 1.5
1.7 mph, 10%, Δ AIR	0.0 ± 0.0	-0.24 ± 2.0	0.75 ± 2.5	1.47 ± 2.8	2.30 ± 1.8
2.5 mph, 12%, Δ AIR	0.0 ± 0.0	-0.01 ± 2.4	0.60 ± 3.0	1.29 ± 3.4	2.35 ± 2.1
3.4 mph, 14%, Δ AIR	0.0 ± 0.0	-0.21 ± 3.3	0.26 ± 2.6	0.73 ± 3.4	1.38 ± 2.4
Overall, Δ AIR	*0.0 ± 0.0*	*-0.08 ± 2.4*	*0.63 ± 2.4*	*1.17 ± 2.9*	*1.72 ± 2.0*
Rest, %Δ AIR	0.0 ± 0.0	-1.3 ± 22.8	13.5 ± 21.9	10.5 ± 25.6	12.6 ± 22.0
1.7 mph, 10%, %Δ AIR	0.0 ± 0.0	-3.3 ± 18.7	7.3 ± 23.5	8.6 ± 24.0	19.0 ± 19.3
2.5 mph, 12%, %Δ AIR	0.0 ± 0.0	-1.3 ± 20.7	6.5 ± 23.4	6.7 ± 25.2	16.9 ± 20.1
3.4 mph, 14%, %Δ AIR	0.0 ± 0.0	-3.4 ± 23.9	4.4 ± 21.6	2.2 ± 23.7	10.9 ± 21.8
Overall, %Δ AIR	*0.0 ± 0.0*	*-2.4 ± 21.1*	*7.9 ± 22.3*	*7.0 ± 24.2*	*14.9 ± 20.5*

Table 16 (continued). Combined effects of carbon monoxide exposure and lower-body treadmill exercise.

Acceleration (Ω/s/s)	1.8% COHb	5.0% COHb	9.8% COHb	14.8% COHb	19.2% COHb
Rest	35.1 ± 7.2	35.5 ± 8.3	38.4 ± 9.6	38.1 ± 9.4	39.7 ± 10.7
1.7 mph, 10%	48.1 ± 9.7	51.8 ± 11.9	53.6 ± 16.2	56.7 ± 12.1	62.7 ± 18.1
2.5 mph, 12%	59.4 ± 15.7	61.9 ± 15.2	66.5 ± 21.3	71.6 ± 18.8	81.0 ± 22.9
3.4 mph, 14%	77.2 ± 20.3	79.0 ± 17.5	85.1 ± 24.3	87.2 ± 22.6	93.6 ± 26.8
Rest, Δ AIR	0.0 ± 0.0	0.3 ± 4.1	3.3 ± 5.1	3.0 ± 5.9	4.6 ± 5.6
1.7 mph, 10%, Δ AIR	0.0 ± 0.0	3.6 ± 6.0	5.5 ± 9.7	8.5 ± 8.8	14.6 ± 12.6
2.5 mph, 12%, Δ AIR	0.0 ± 0.0	2.5 ± 8.9	7.1 ± 8.9	12.2 ± 11.0	21.5 ± 14.2
3.4 mph, 14%, Δ AIR	0.0 ± 0.0	1.8 ± 10.2	7.9 ± 11.1	10.0 ± 13.0	16.4 ± 18.0
Overall, Δ AIR	*0.0 ± 0.0*	*2.1 ± 7.6*	*5.9 ± 8.9*	*8.4 ± 10.3*	*14.3 ± 14.4*
Rest, %Δ AIR	0.0 ± 0.0	1.0 ± 10.7	9.3 ± 15.3	9.0 ± 16.1	12.3 ± 13.8
1.7 mph, 10%, %Δ AIR	0.0 ± 0.0	7.6 ± 12.8	10.5 ± 22.3	19.3 ± 19.3	30.4 ± 27.5
2.5 mph, 12%, %Δ AIR	0.0 ± 0.0	6.9 ± 21.6	11.4 ± 14.0	23.2 ± 23.5	38.4 ± 28.9
3.4 mph, 14%, %Δ AIR	0.0 ± 0.0	4.1 ± 14.4	10.3 ± 14.7	14.6 ± 18.5	22.3 ± 25.2
Overall, %Δ AIR	*0.0 ± 0.0*	*4.9 ± 15.3*	*10.4 ± 16.5*	*16.5 ± 19.8*	*25.9 ± 25.9*

Time-to-peak Ejection (ms)	1.8%	5.0%	9.8%	14.8%	19.2%
Rest	176.0 ± 9.0	177.2 ± 15.1	173.5 ± 15.3	170.2 ± 16.8	170.9 ± 12.1
1.7 mph, 10%	142.1 ± 7.9	141.6 ± 8.7	145.6 ± 20.0	136.2 ± 7.8	135.6 ± 10.8
2.5 mph, 12%	131.6 ± 11.6	129.6 ± 9.6	129.6 ± 10.1	124.1 ± 8.2	122.8 ± 11.6
3.4 mph, 14%	117.6 ± 9.3	118.3 ± 8.3	116.3 ± 10.2	111.7 ± 8.8	109.7 ± 10.3
Rest, Δ AIR	0.0 ± 0.0	1.26 ± 9.0	-2.44 ± 11.1	-5.8 ± 16.2	-5.0 ± 8.5
1.7 mph, 10%, Δ AIR	0.0 ± 0.0	-0.47 ± 4.9	3.48 ± 18.7	-5.6 ± 6.4	-6.6 ± 5.3
2.5 mph, 12%, Δ AIR	0.0 ± 0.0	-2.08 ± 7.9	-2.07 ± 7.5	-7.6 ± 7.5	-8.9 ± 6.2
3.4 mph, 14%, Δ AIR	0.0 ± 0.0	-1.35 ± 5.1	-1.33 ± 8.6	-5.9 ± 5.5	-8.0 ± 4.7
Overall, Δ AIR	*0.0 ± 0.0*	*-0.66 ± 6.9*	*-0.59 ± 12.2*	*-6.2 ± 9.6*	*-7.1 ± 6.3*
Rest, %Δ AIR	0.0 ± 0.0	0.6 ± 5.1	-1.4 ± 6.6	-3.2 ± 9.1	-2.9 ± 4.9
1.7 mph, 10%, %Δ AIR	0.0 ± 0.0	-0.3 ± 3.5	2.5 ± 13.4	-3.8 ± 4.4	-4.7 ± 3.8
2.5 mph, 12%, %Δ AIR	0.0 ± 0.0	-1.4 ± 5.3	-1.4 ± 5.9	-5.5 ± 4.7	-6.7 ± 4.2
3.4 mph, 14%, %Δ AIR	0.0 ± 0.0	-1.0 ± 4.3	-0.9 ± 8.1	-4.9 ± 4.5	-6.8 ± 4.1
Overall, %Δ AIR	*0.0 ± 0.0*	*-0.5 ± 4.6*	*-0.3 ± 8.9*	*-4.4 ± 5.9*	*-5.3 ± 4.5*

Table 16 (continued). Combined effects of carbon monoxide exposure and lower-body treadmill exercise.

O2 Consumption (ml/min)	1.8% COHb	5.0% COHb	9.8% COHb	14.8% COHb	19.2% COHb
Rest	242.3 ± 70.5	245.3 ± 75.9	223.0 ± 78.6	281.7 ± 96.1	263.2 ± 68.4
1.7 mph, 10%	648.1 ±266.9	684.4 ±285.0	553.2 ±202.7	646.8 ±326.2	617.1 ±223.4
2.5 mph, 12%	880.2 ±351.6	864.1 ±437.3	723.5 ±268.9	842.9 ±474.1	759.7 ±302.5
3.4 mph, 14%	1196.8 ±429.5	1188.1 ±560.4	1000.6 ±375.3	1168.4 ±555.9	1009.5 ±379.9
Rest, Δ AIR	0.0 ± 0.0	0.6 ±104.4	-15.5 ±124.8	34.8 ± 78.2	-2.7 ± 74.2
1.7 mph, 10%, Δ AIR	0.0 ± 0.0	-11.7 ±114.6	-98.4 ±129.9	-44.2 ±138.9	-25.3 ±166.9
2.5 mph, 12%, Δ AIR	0.0 ± 0.0	-63.8 ±223.25	-93.4 ±219.8	-103.27 ±233.5	-129.9 ±184.8
3.4 mph, 14%, Δ AIR	0.0 ± 0.0	-54.0 ±241.1	-166.0 ±292.7	-66.4 ±245.8	-216.7 ±286.37
Overall, Δ AIR	*0.0 ± 0.0*	*-32.2 ±173.5*	*-93.3 ±199.8*	*-44.8 ±184.0*	*-93.6 ±202.1*
Rest, %Δ AIR	0.0 ± 0.0	4.9 ± 36.5	0.9 ± 39.8	16.1 ± 34.0	2.8 ± 26.1
1.7 mph, 10%, %Δ AIR	0.0 ± 0.0	-4.1 ± 20.0	-13.1 ± 11.9	-11.6 ± 21.8	-1.0 ± 21.7
2.5 mph, 12%, %Δ AIR	0.0 ± 0.0	-10.9 ± 26.3	-7.5 ± 22.6	-16.6 ± 27.2	-13.7 ± 18.6
3.4 mph, 14%, %Δ AIR	0.0 ± 0.0	-7.7 ± 17.3	-11.8 ± 18.2	-9.1 ± 19.6	-16.1 ± 19.4
Overall, %Δ AIR	*0.0 ± 0.0*	*-4.4 ± 25.3*	*-7.9 ± 24.5*	*-5.3 ± 27.9*	*-7.0 ± 22.0*

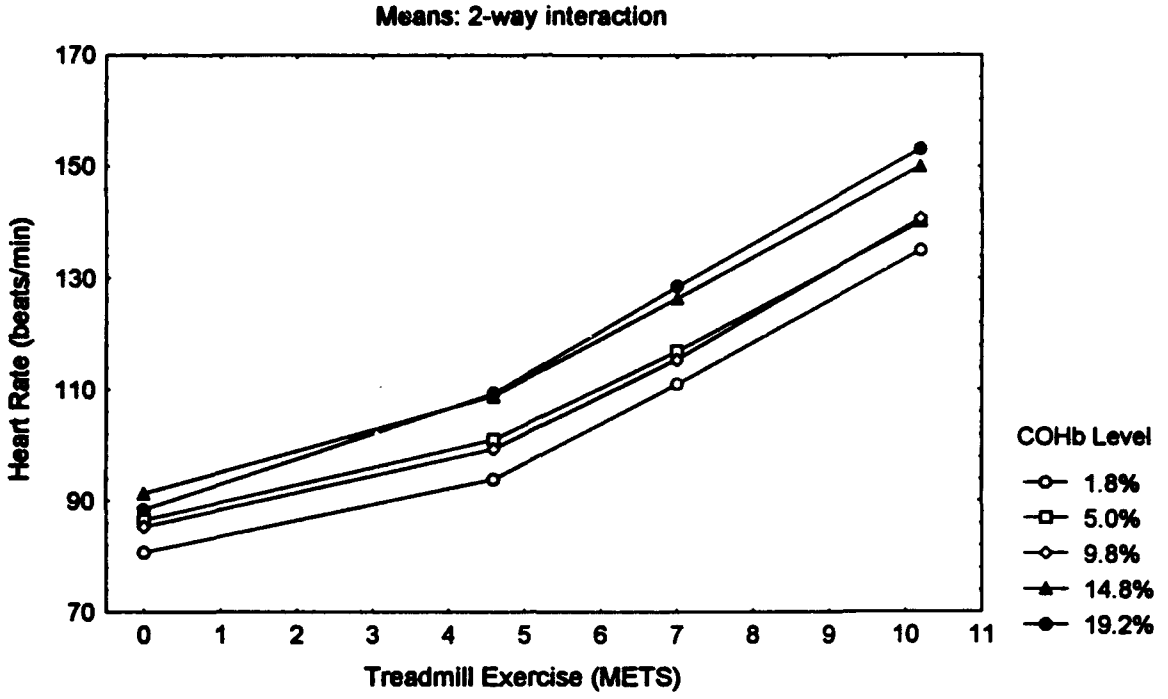
CO2 Production (ml/min)	1.8%	5.0%	9.8%	14.8%	19.2%
Rest	204.7 ± 52.0	212.3 ± 61.6	186.6 ± 63.4	241.4 ± 67.9	226.2 ± 59.5
1.7 mph, 10%	482.4 ±213.1	515.9 ±235.1	404.5 ±163.2	481.2 ±255.6	463.4 ±178.6
2.5 mph, 12%	732.7 ±309.7	716.6 ±399.0	597.3 ±248.9	687.5 ±409.9	632.4 ±274.5
3.4 mph, 14%	1087.3 ±435.8	1043.7 ±555.7	891.5 ±377.6	1057.3 ±574.4	926.5 ±398.3
Rest, Δ AIR	0.0 ± 0.0	7.0 ± 79.5	-14.9 ±102.0	37.4 ± 62.8	6.0 ± 54.5
1.7 mph, 10%, Δ AIR	0.0 ± 0.0	1.6 ± 97.8	-80.2 ± 94.7	-33.6 ±110.1	-20.0 ±128.1
2.5 mph, 12%, Δ AIR	0.0 ± 0.0	-50.8 ±206.1	-86.4 ±200.7	-90.5 ±202.9	-112.7 ±184.4
3.4 mph, 14%, Δ AIR	0.0 ± 0.0	-84.4 ±225.4	-173.2 ±311.4	-61.9 ±239.89	-197.3 ±316.9
Overall, Δ AIR	*0.0 ± 0.0*	*-31.6 ±160.5*	*-88.7 ±195.2*	*-37.1 ±166.9*	*-81.0 ±202.2*
Rest, %Δ AIR	0.0 ± 0.0	7.3 ± 38.7	-1.0 ± 38.7	20.6 ± 34.2	4.8 ± 27.2
1.7 mph, 10%, %Δ AIR	0.0 ± 0.0	-2.6 ± 20.5	-14.2 ± 10.8	-11.7 ± 22.6	-0.7 ± 23.1
2.5 mph, 12%, %Δ AIR	0.0 ± 0.0	-11.3 ± 28.2	-7.8 ± 24.7	-17.6 ± 68.2	-13.4 ± 22.4
3.4 mph, 14%, %Δ AIR	0.0 ± 0.0	-11.3 ± 18.2	-13.0 ± 20.1	-10.1 ± 20.9	-15.2 ± 23.3
Overall, %Δ AIR	*0.0 ± 0.0*	*-4.5 ± 27.2*	*-9.0 ± 24.7*	*-4.7 ± 29.7*	*-6.1 ± 24.3*

Table 16 (continued). Combined effects of carbon monoxide exposure and lower-body treadmill exercise.

Ventilation (l/min)	1.8% COHb	5.0% COHb	9.8% COHb	14.8% COHb	19.2% COHb
Rest	17.7 ± 3.7	17.6 ± 3.7	16.5 ± 3.8	17.5 ± 2.5	18.2 ± 3.3
1.7 mph, 10%	32.7 ± 3.1	31.8 ± 3.9	31.0 ± 3.9	33.7 ± 4.1	34.0 ± 3.7
2.5 mph, 12%	43.3 ± 5.6	43.6 ± 7.2	42.3 ± 5.9	44.2 ± 7.4	45.4 ± 6.9
3.4 mph, 14%	59.9 ± 11.2	58.8 ± 13.7	57.2 ± 9.7	60.9 ± 15.9	63.9 ± 12.1
Rest, Δ AIR	0.0 ± 0.0	0.62 ± 1.8	-0.92 ± 2.1	0.36 ± 1.2	0.8 ± 3.1
1.7 mph, 10%, Δ AIR	0.0 ± 0.0	-0.85 ± 2.7	-0.77 ± 2.5	0.34 ± 2.0	1.7 ± 3.5
2.5 mph, 12%, Δ AIR	0.0 ± 0.0	-0.07 ± 1.7	0.26 ± 1.9	0.49 ± 3.7	2.1 ± 4.1
3.4 mph, 14%, Δ AIR	0.0 ± 0.0	-1.82 ± 2.9	0.14 ± 5.1	-0.21 ± 6.9	3.9 ± 4.2
Overall, Δ AIR	*0.0 ± 0.0*	*-0.53 ± 2.4*	*-0.32 ± 3.0*	*0.25 ± 3.8*	*2.1 ± 3.7*
Rest, %Δ AIR	0.0 ± 0.0	3.0 ± 9.3	-5.8 ± 12.0	2.2 ± 6.7	6.8 ± 19.0
1.7 mph, 10%, %Δ AIR	0.0 ± 0.0	-2.5 ± 9.2	-2.4 ± 8.6	1.5 ± 6.8	5.5 ± 11.0
2.5 mph, 12%, %Δ AIR	0.0 ± 0.0	-0.2 ± 4.3	0.4 ± 4.7	1.4 ± 8.7	4.9 ± 9.9
3.4 mph, 14%, %Δ AIR	0.0 ± 0.0	-3.0 ± 4.7	0.4 ± 8.9	0.0 ± 11.1	7.0 ± 7.3
Overall, %Δ AIR	*0.0 ± 0.0*	*-0.7 ± 7.3*	*1.3 ± 8.8*	*1.3 ± 8.1*	*6.0 ± 11.9*

Resp. Exchange Ratio	1.8%	5.0%	9.8%	14.8%	19.2%
Rest	0.88 ± 0.11	0.88 ± 0.08	0.84 ± 0.11	0.89 ± 0.13	0.87 ± 0.14
1.7 mph, 10%	0.74 ± 0.07	0.76 ± 0.08	0.73 ± 0.09	0.75 ± 0.06	0.77 ± 0.15
2.5 mph, 12%	0.83 ± 0.05	0.82 ± 0.07	0.81 ± 0.08	0.81 ± 0.07	0.83 ± 0.04
3.4 mph, 14%	0.90 ± 0.04	0.86 ± 0.05	0.88 ± 0.05	0.89 ± 0.06	0.91 ± 0.04
Rest, Δ AIR	0.0 ± 0.0	-0.01 ± 0.10	-0.08 ± 0.12	0.01 ± 0.11	0.00 ± 0.18
1.7 mph, 10%, Δ AIR	0.0 ± 0.0	0.01 ± 0.05	-0.01 ± 0.02	0.00 ± 0.02	0.03 ± 0.14
2.5 mph, 12%, Δ AIR	0.0 ± 0.0	-0.01 ± 0.06	0.00 ± 0.02	-0.01 ± 0.04	0.00 ± 0.06
3.4 mph, 14%, Δ AIR	0.0 ± 0.0	-0.04 ± 0.02	-0.02 ± 0.03	-0.01 ± 0.03	0.00 ± 0.04
Overall, Δ AIR	*0.0 ± 0.0*	*-0.01 ± 0.06*	*-0.03 ± 0.07*	*0.00 ± 0.06*	*0.01 ± 0.11*
Rest, %Δ AIR	0.0 ± 0.0	-0.2 ± 10.9	-7.7 ± 13.2	1.7 ± 11.6	0.6 ± 19.1
1.7 mph, 10%, %Δ AIR	0.0 ± 0.0	1.7 ± 6.2	-1.4 ± 3.2	-0.2 ± 3.0	4.6 ± 17.8
2.5 mph, 12%, %Δ AIR	0.0 ± 0.0	-1.6 ± 6.3	-0.2 ± 2.9	-1.6 ± 4.5	-0.1 ± 7.0
3.4 mph, 14%, %Δ AIR	0.0 ± 0.0	-4.3 ± 2.3	-2.3 ± 3.8	-1.3 ± 3.2	0.2 ± 4.0
Overall, %Δ AIR	*0.0 ± 0.0*	*-1.1 ± 7.1*	*-2.9 ± 7.4*	*-0.3 ± 6.4*	*1.3 ± 13.0*

PANEL A



PANEL B

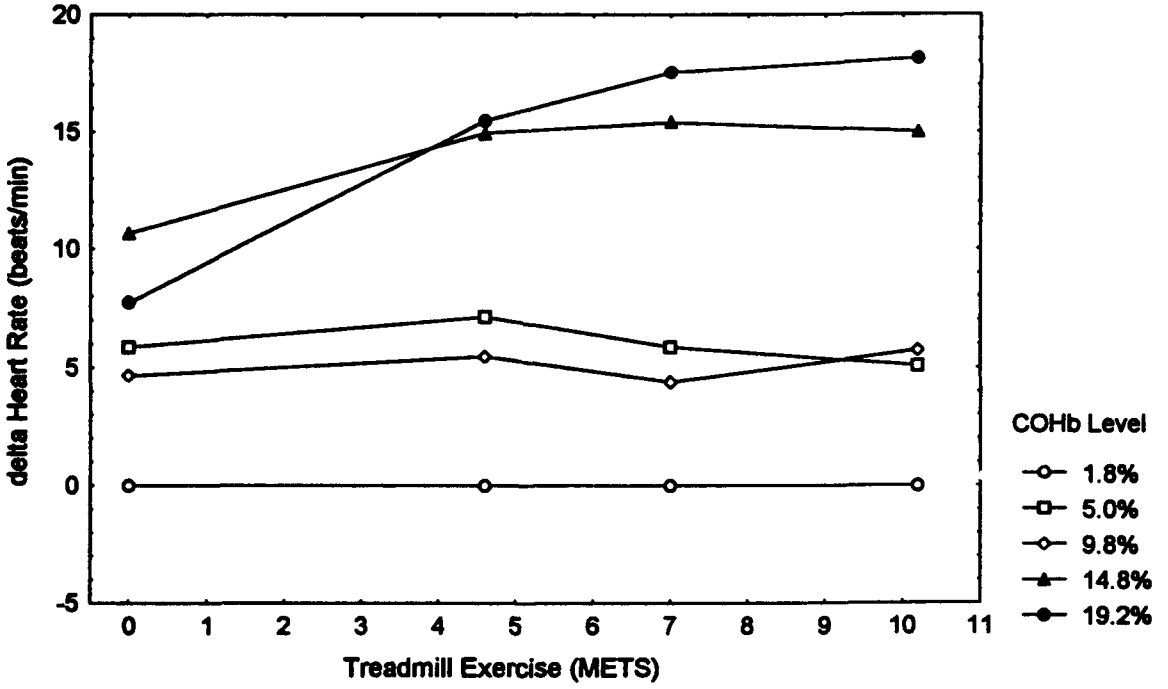
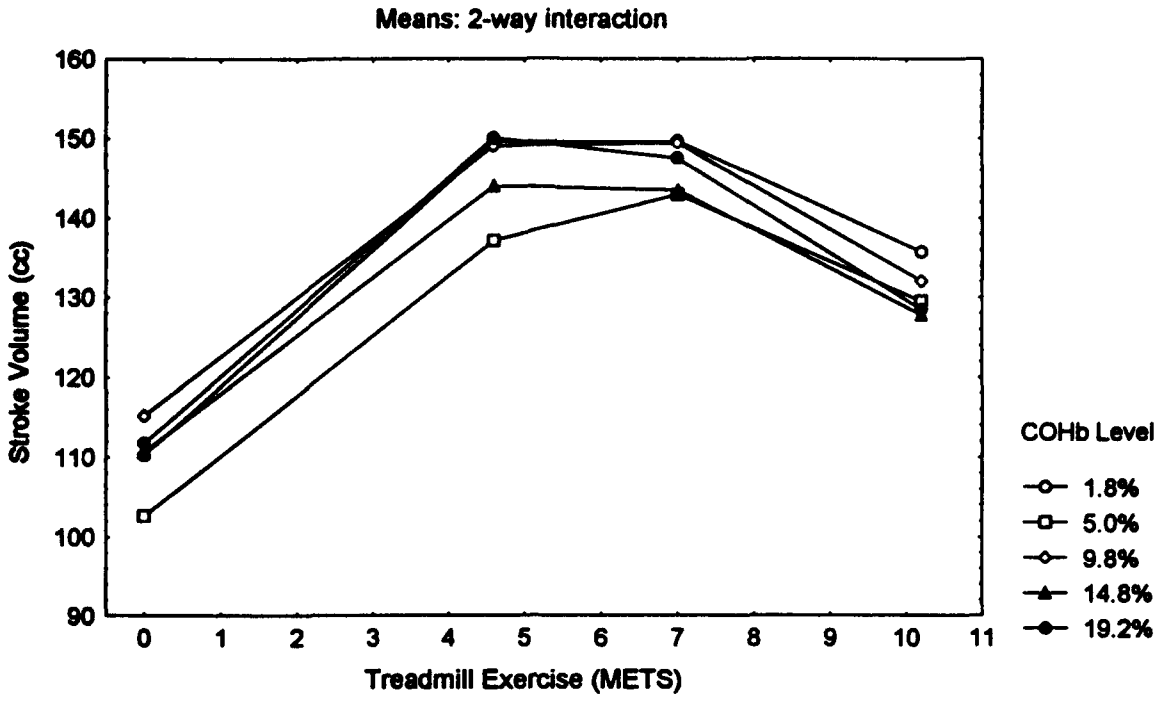


Figure 8. Mean heart rate response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

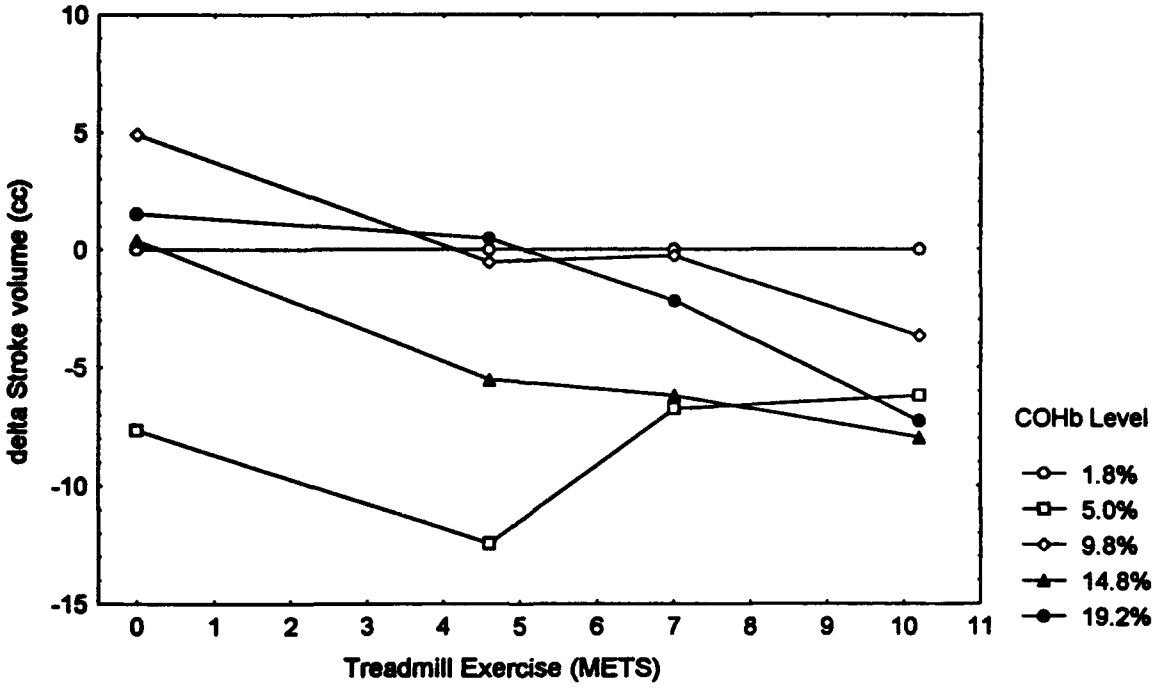
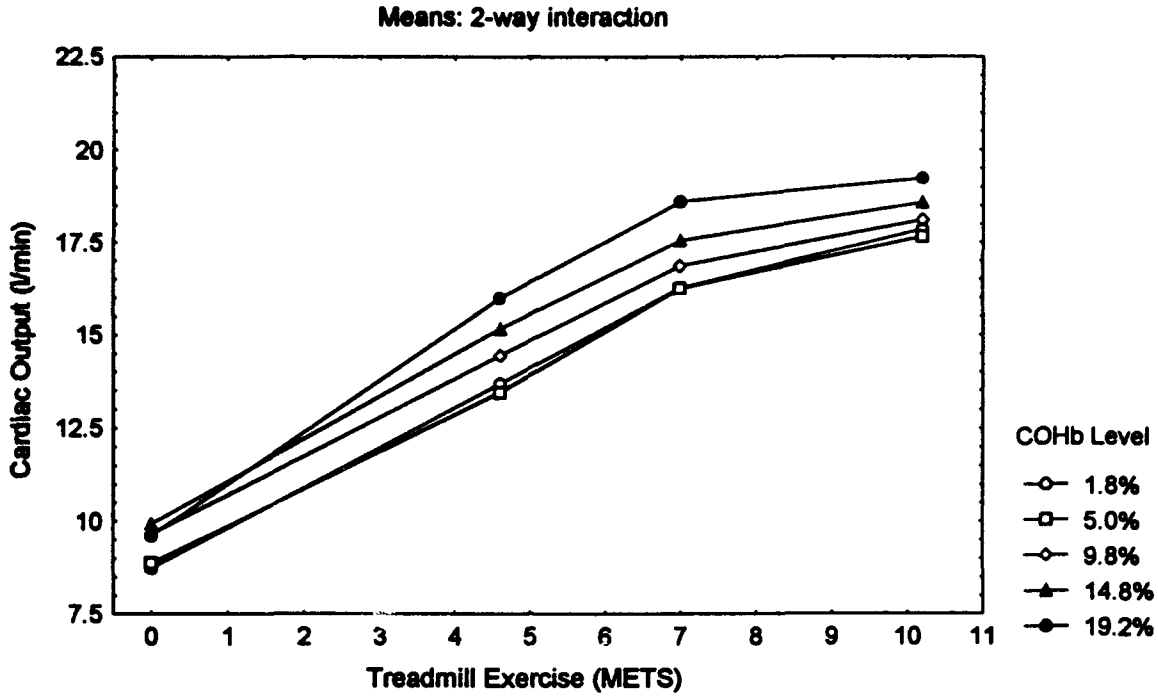


Figure 9. Mean stroke volume response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

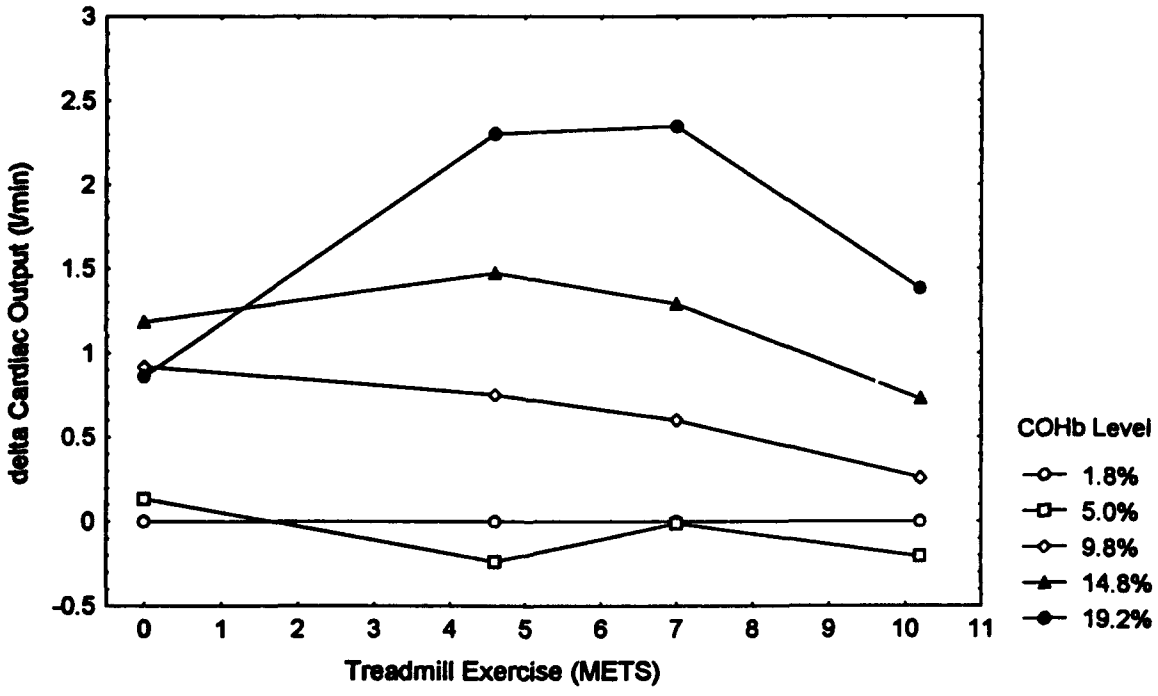
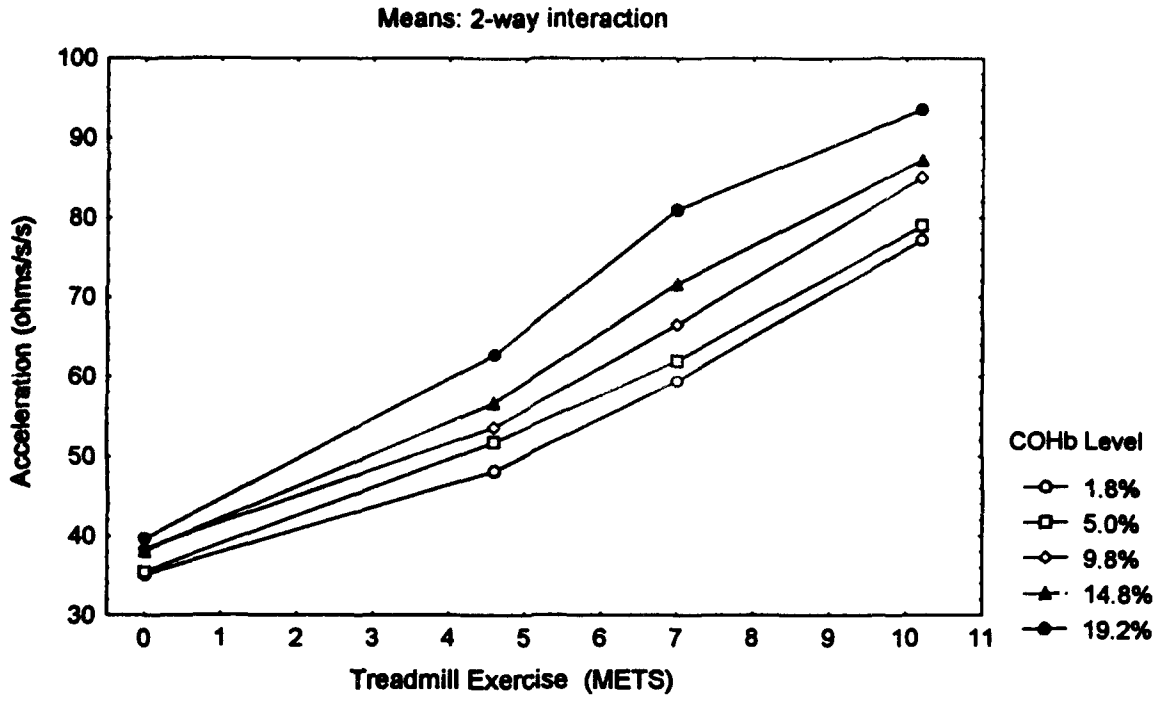


Figure 10. Mean cardiac output response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

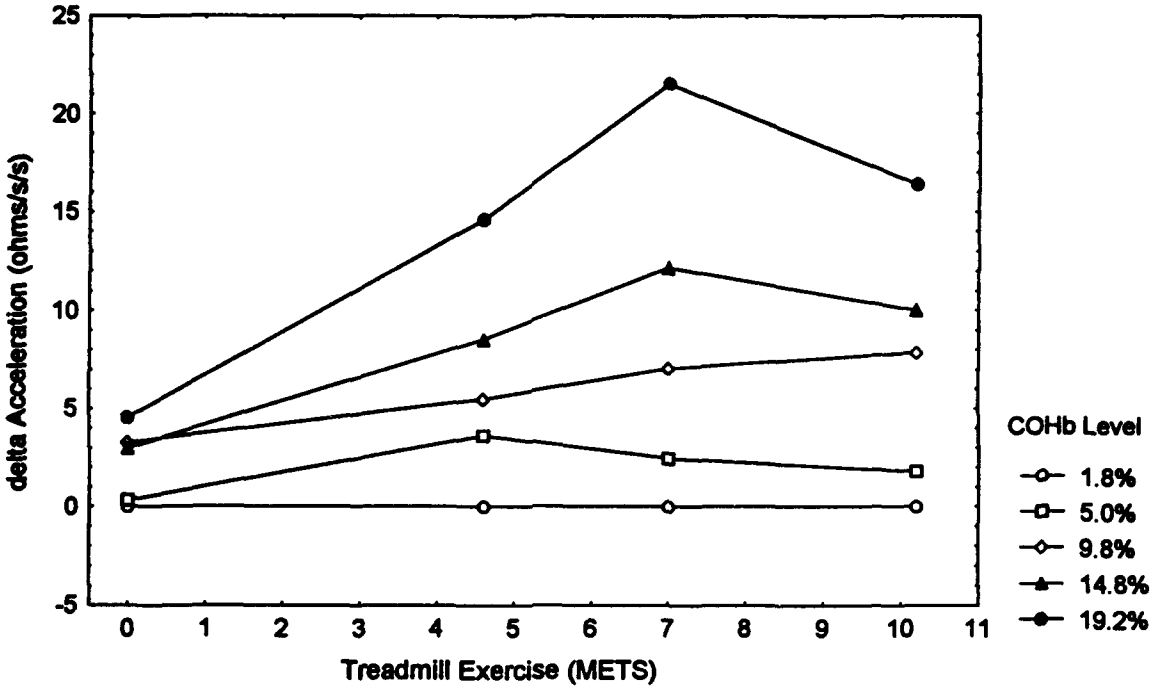
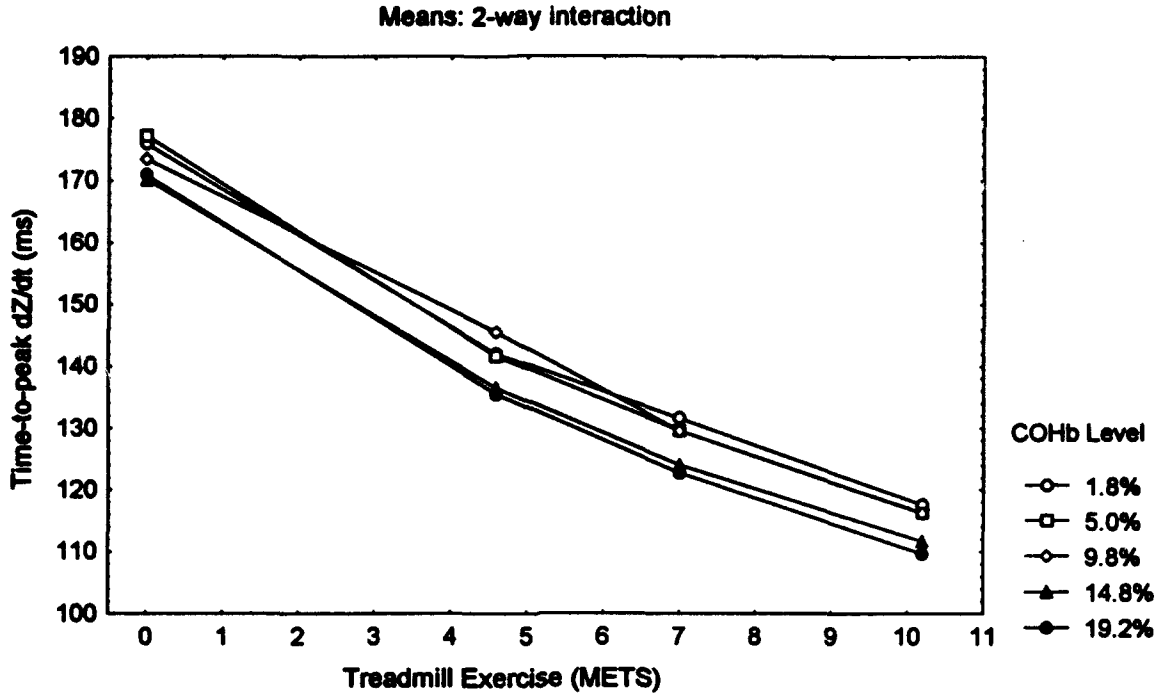


Figure 11. Mean ICG acceleration response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

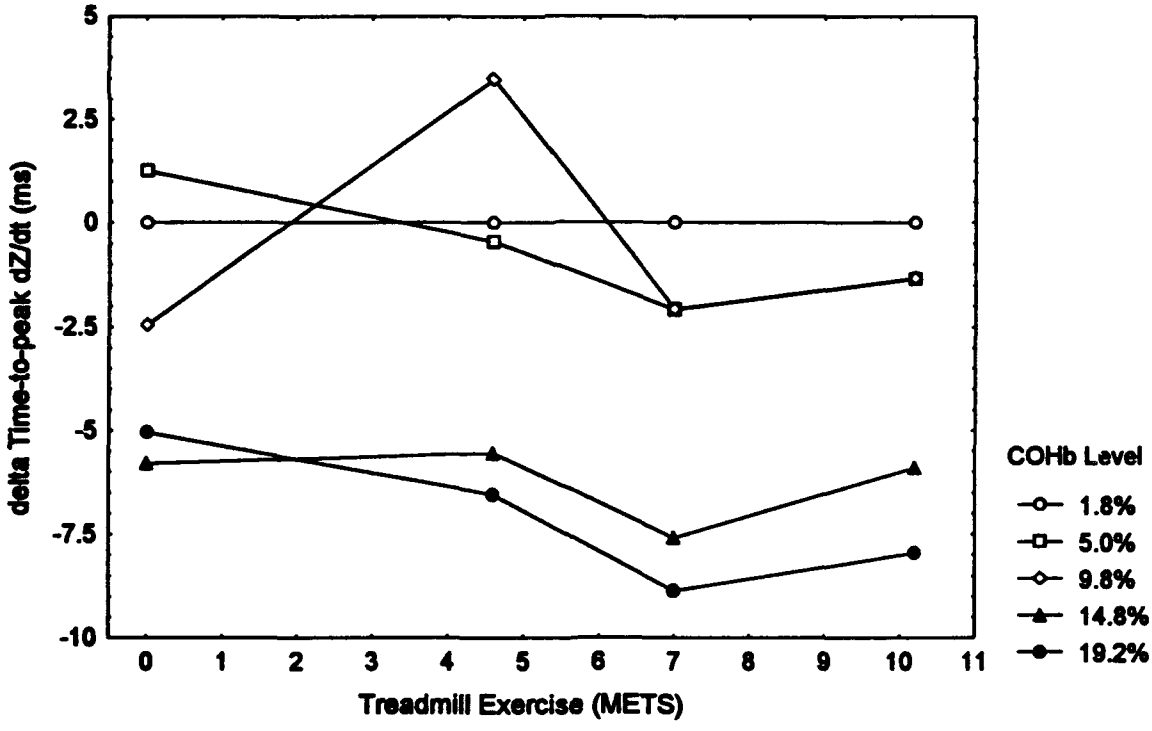
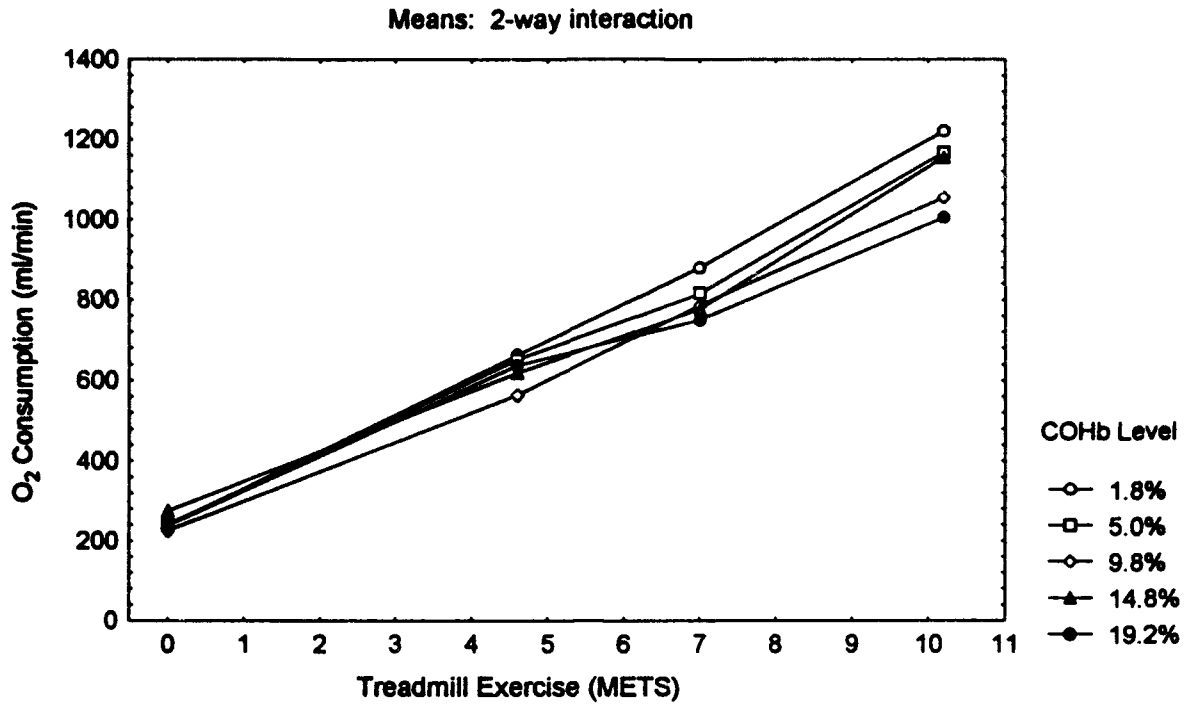


Figure 12. Mean time-to-peak velocity response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

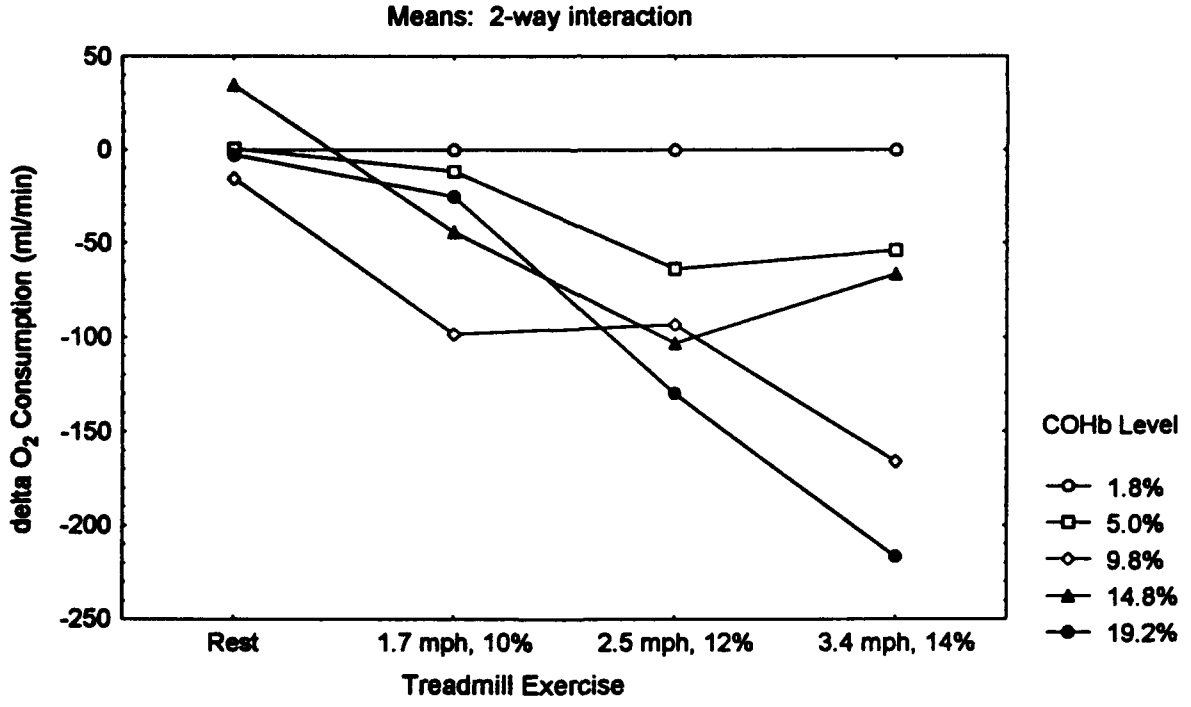
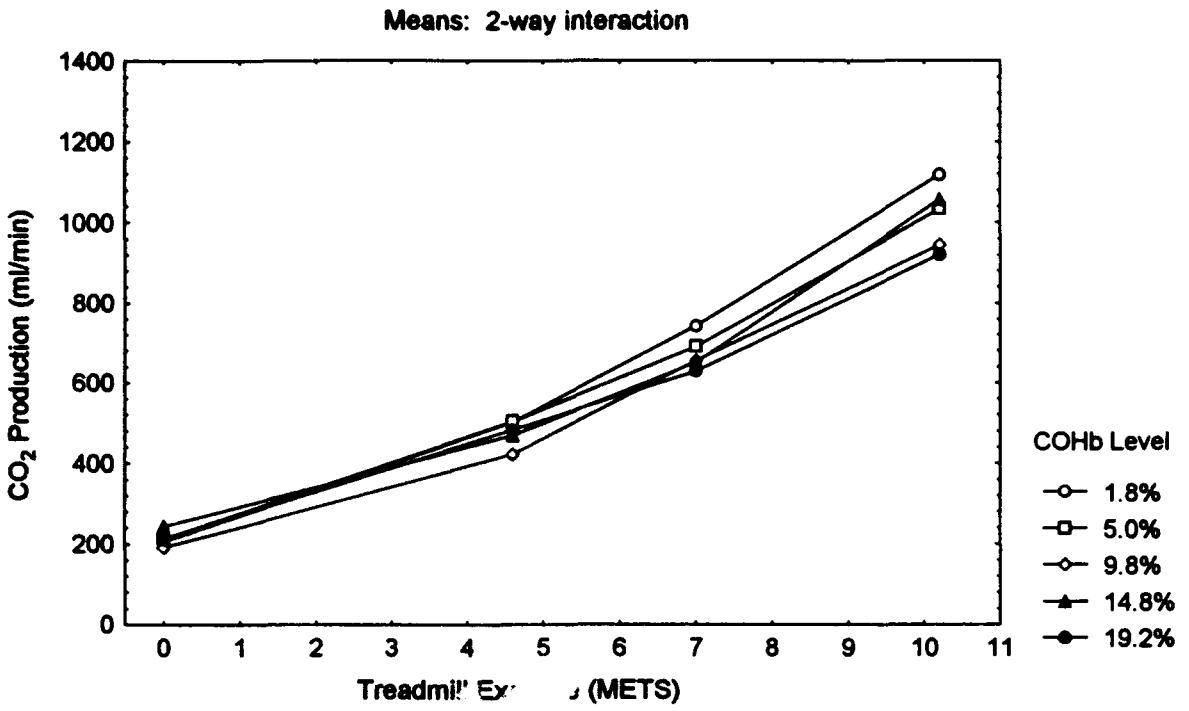


Figure 13. Mean oxygen consumption response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

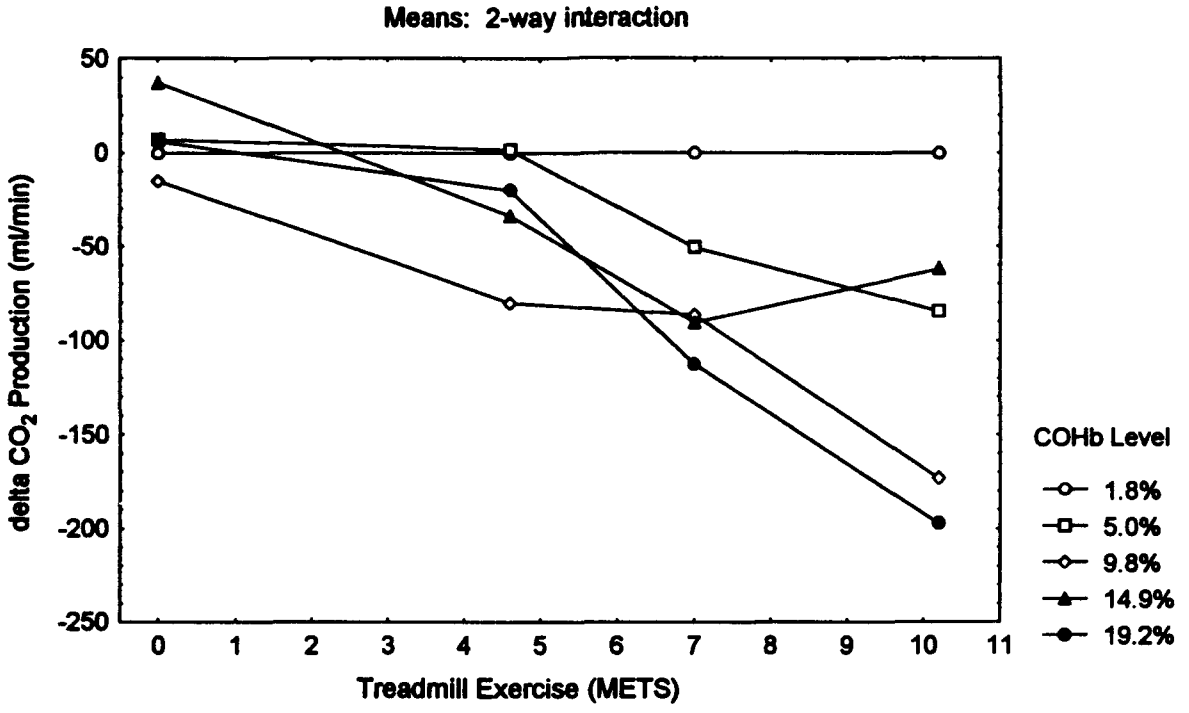
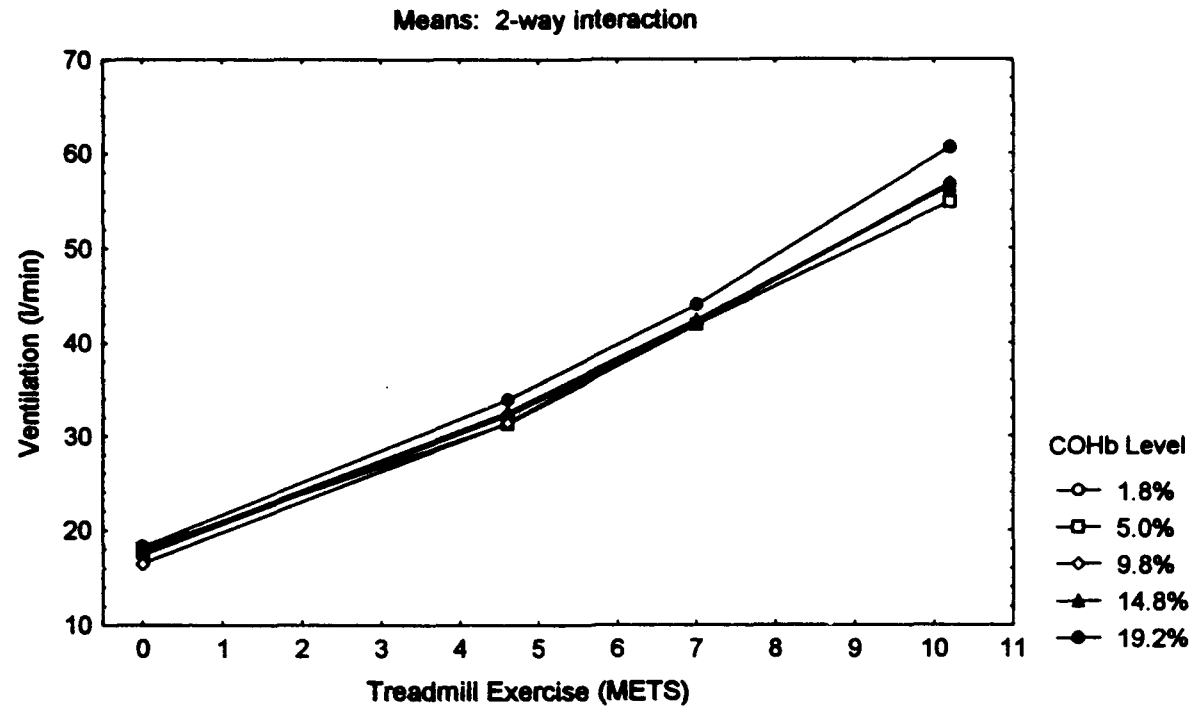


Figure 14. Mean carbon dioxide production response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

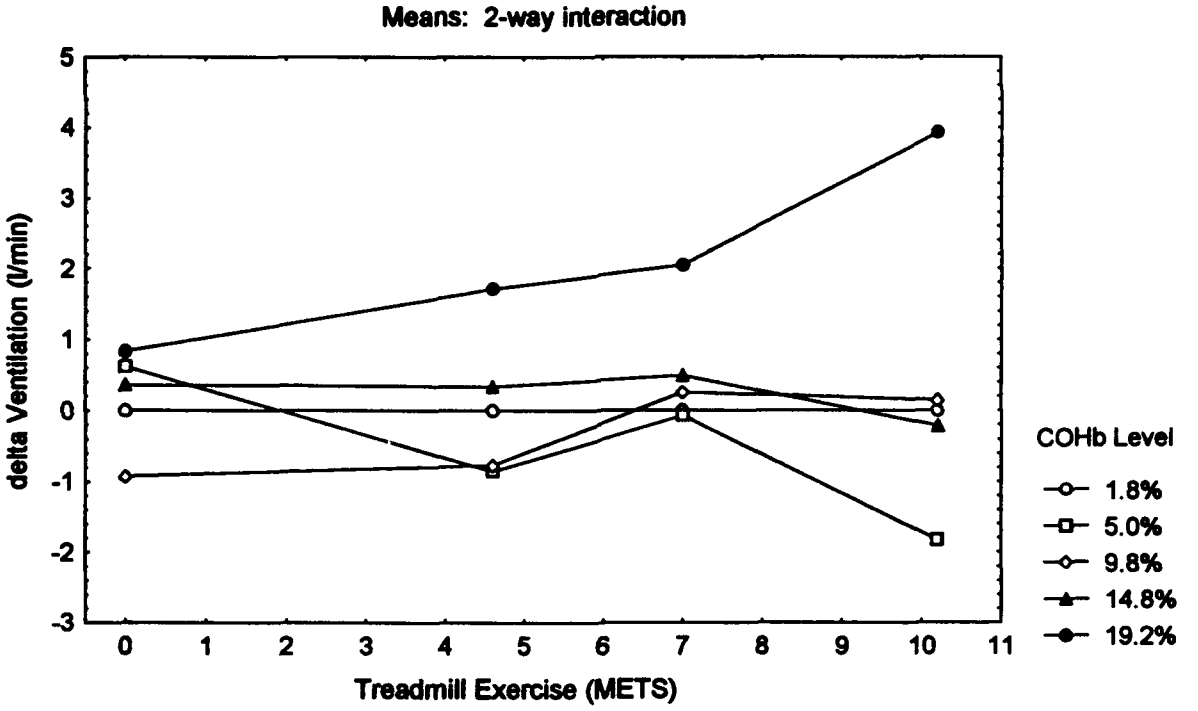
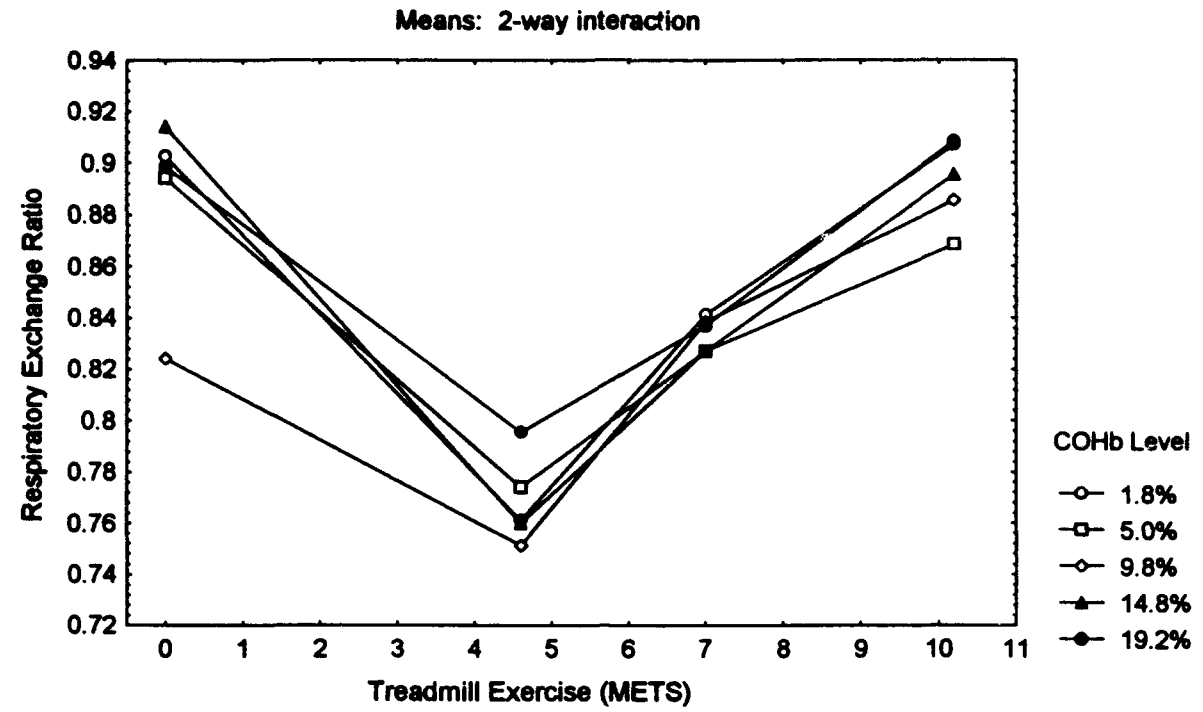


Figure 15. Mean ventilation response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

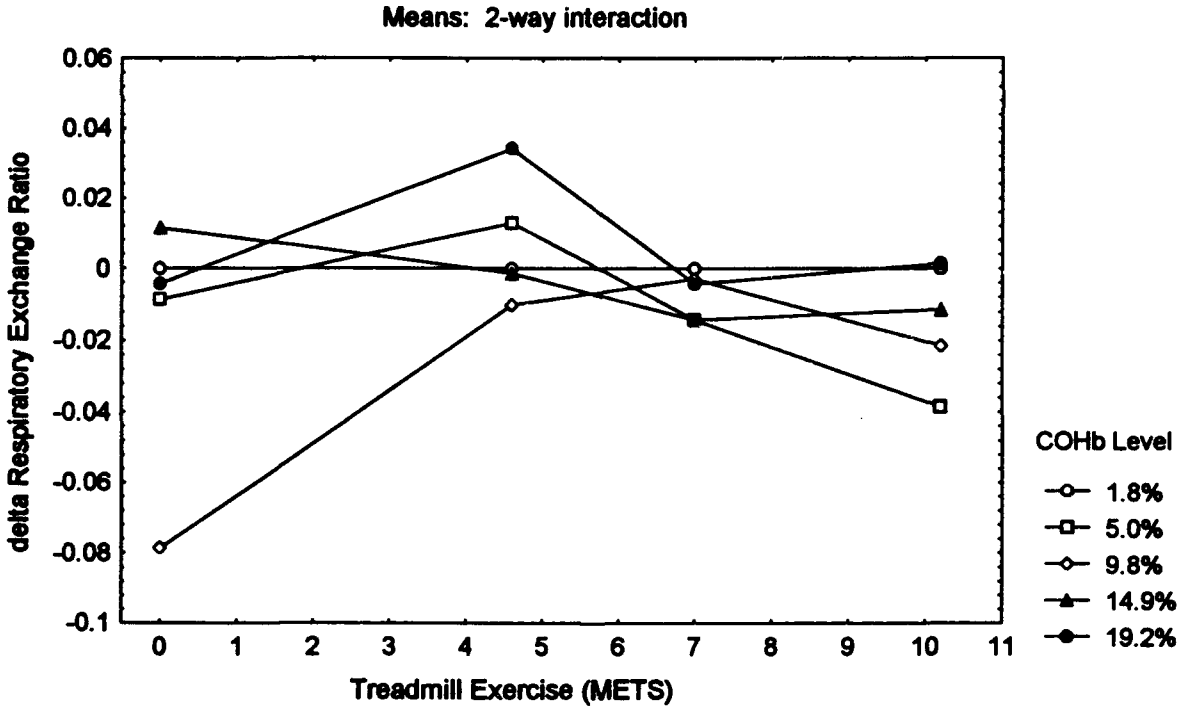


Figure 16. Mean respiratory exchange ratio response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

2.5.4 Effects of CO Exposure on Upper-Body Exercise Response

Overall effects of CO exposure and hand-crank exercise

Effects of CO exposure on the cardiac and respiratory responses to upper-body hand-crank exercise were evaluated by the same means applied to lower-body treadmill exercise. As a first step, CO exposure, hand-crank exercise, and CO x hand-crank exercise interaction were evaluated by repeated-measures ANOVA using raw unadjusted measurements (Actual Data, Table 17), pre-exercise adjusted measurements (Change from Rest, Table 18), and air-exposure adjusted measurements (Delta Air Exposure, Table 19). Air-exposure adjusted measurements were calculated for each activity and exposure level by subtracting the paired value for each activity level after air exposure.

Significant CO effects were found for all cardiac variables except stroke volume. Stronger effects were observed for cardiac output and time-to-peak ejection for Actual Data ($p<0.0001$) than for Change-from-Rest adjusted data. Stroke volume, however, showed a significant CO x hand-crank exercise interaction for Actual Data ($p<0.01$), Change-from-Rest ($p<0.002$), and Delta Air Exposure ($p<0.004$). Significant CO x hand-crank interactions were observed for cardiac output and time-to-peak ejection for Actual Data and Delta Air Exposure, but not for the Change-from-Rest data set. Of all the analyses of respiratory data, only CO_2 production after the Delta Air Exposure adjustment showed any significant effect ($p>0.039$) (Tables 17, 18, and 19).

Table 17. Effects of carbon monoxide exposure and upper-body hand-crank exercise by repeated measures analysis of variance (N=16). Tests for significant differences were made using $\alpha=0.05$.

Actual Data	CO	Hand Crank	CO x Hand Crank	N
Heart Rate	0.0001	0.0001	0.0001	16
Stroke Volume	ns	0.048	0.009	16
Cardiac Output	0.0008	0.0001	0.007	16
Acceleration	0.0001	0.0001	0.0001	16
Time-to-peak Ejection	0.0001	0.0001	0.032	16
O_2 Consumption	ns	0.0001	ns	7
CO_2 Production	ns	0.0001	ns	7
Ventilation	ns	0.0001	ns	7
Resp. Exchange Ratio	ns	0.0071	ns	7

Table 18. Effects of carbon monoxide exposure and upper-body hand-crank exercise by repeated measures analysis of variance (N=16). Tests for significant differences were made using α=0.05.

Change from Rest	CO	Hand Crank	CO x Hand Crank	N
Heart Rate	0.0001	0.0001	0.0001	16
Stroke Volume	ns	ns	0.002	16
Cardiac Output	0.014	0.0001	ns	16
Acceleration	0.0002	0.0001	0.0003	16
Time-to-peak Ejection	0.035	0.0001	ns	16
O_2 Consumption	ns	0.0001	ns	7
CO_2 Production	ns	0.0001	ns	7
Ventilation	ns	0.0001	ns	7
Resp. Exchange Ratio	ns	0.0001	ns	7

COHb: 1.8%, 5.1%, 9.8%, 14.9%, 19.2%

Exercise: Rest sitting, 25 Watts, 40 Watts, 60 Watts

Table 19. Effects of carbon monoxide exposure and upper-body hand-crank exercise by repeated measures analysis of variance. Tests for significant differences were made using α=0.05.

Delta Air Exposure	CO	Hand Crank	CO x Hand Crank	N
Heart Rate	0.0001	0.0001	0.0001	16
Stroke Volume	ns	0.018	0.004	16
Cardiac Output	0.0003	0.0003	0.0022	16
Acceleration	0.0001	0.0001	0.0001	16
Time-to-peak Ejection	0.0001	ns	0.0217	16
O_2 Consumption	ns	ns	ns	7
CO_2 Production	0.039	ns	ns	7
Ventilation	ns	ns	ns	7
Resp. Exchange Ratio	ns	ns	ns	7

COHb: 1.8%, 5.1%, 9.8%, 14.9%, 19.2%

Exercise: Rest sitting, 25 Watts, 40 Watts, 60 Watts

Effects of increasing CO exposure

As with lower-body exercise, three post-hoc analyses were conducted to explore effects of increasing CO exposure. Two analyses used Actual Data (raw unadjusted measurements) to compare mean measurements across subjects and exercise levels by blood COHb level (μ_{CO} versus μ_{air}) after repeated-measures ANOVA. First, the Least Significant Difference method (LSD) was employed for sensitive detection of CO effects on Actual Data. Since five levels of CO exposure were considered, multiple comparison errors were reduced by testing for significant differences using an adjusted α of 0.01 (0.05/5). For comparison, Scheffé's procedure was also employed for a more conservative analysis of Actual Data. Tests for significant differences were made with an α of 0.05. Delta Air Exposure data (paired air-exposure adjusted measurements) were then tested for $\mu_D=0$. P-values are reported for $\alpha<0.05$; however tests for significant differences were made with an α of 0.01. Change-for-Rest data were not employed in the post-hoc analyses. Results are presented in Tables 20 through 25.

Means and standard deviations of cardiac and respiratory variables were computed across subjects by attained COHb levels and prescribed exercise activity levels for Actual Data, Delta Air Exposure Data, and percent change in Delta Air Exposure Data. Results are summarized in Table 26 and illustrated in Figures 17 through 25.

Means and standard deviations of cardiac and respiratory measurements were computed across subjects by attained COHb levels and prescribed exercise activity levels for Actual Data, Delta Air Exposure Data, and percent change in Delta Air Exposure Data. Results are summarized in Table 26 by mean and standard deviation. Mean data per exposure level are also illustrated as functions exercise level (in METS) in Figures 17 through 25.

Mean COHb levels for air and CO exposures were 1.9%, 5.1%, 9.8%, 14.9%, and 19.2%. COHb levels attained after mouthpiece exposure and just before sitting at rest (5.2%, 10.0%, 15.3%, and 19.7%) were very close to the experiment target levels of (5%, 10%, 15%, and 20% COHb). Although COHb tended to decrease during exercise, the chamber CO exposure during exercise limited the decrement to less than 1% COHb (Table 26). All of these results are well within the specifications of the IL-282 CO-Oximeter which has a combined measurement and display accuracy of ±1.1% COHb.

Actual Data (raw unadjusted measurements)

The effects of CO exposure on the overall cardiac exercise response of Actual Data were similar using both the LSD and Scheffé analyses (Tables 20 and 21), with the LSD resulting in more sensitive results. No significant overall effects of CO exposure on respiratory variables were observed using either analysis (Tables 23 and 24).

The mean heart rate exercise response was increased after CO exposure (Figure 17-A) with significant differences found at 5.1% ($p<0.01$), 14.9% ($p<0.0001$), and 19.2% COHb ($p>0.0001$) (Table 20). For COHb≥14.8%, heart rate was increasingly elevated with increasing exercise after CO exposure, especially at the highest exercise level (Figure 17-A).

After CO exposure, mean stroke volume increased from rest to initial exercise, increased again at the second level, then decreased at the highest level of exercise (Figure 18-A). This response was consistent across all CO exposures, however these data were not significantly different than for air exposure (Table 20). In contrast, stroke volume after air exposure was fairly constant throughout exercise (Figure 18-A).

The mean cardiac output exercise response was increased after CO exposure relative to air exposure for COHb≥9.8% (Figure 19-A), but was not significantly increased until COHb reached 19.2% (Table 20). Intersubject variability most likely prevented the attainment of significant effects at lower levels of CO exposure.

The mean acceleration exercise response showed a consistent and progressive increase with increasing CO exposure (Figure 20-A). Significant differences were found for COHb≥9.8% by the LSD method (Table 20) and COHb≥14.9% by Scheffé's method (Table 21). Acceleration increased dramatically at the highest levels of exercise and CO exposure, demonstrating the strong interaction of CO x exercise (Table 17). Likewise, time-to-peak ejection velocity showed a progressive decrease with increasing CO exposure (Figure 21-A), however the response was not was significantly decreased until COHb≥14.9%. Both parameters indicate an enhanced cardiac contractile exercise response after CO exposure.

Delta Air Exposure data (paired air-exposure adjusted measurements)

The Delta Air Exposure analysis provided increased sensitivity for effects of CO exposure for both cardiac and respiratory variables (Tables 22 and 25). After adjustment for the air exposure data, strong significant differences in overall exercise response were found for heart rate at each level of CO exposure ($p<0.0001$). For COHb≤9.8%, the elevated resting heart rate remained fairly stable throughout exercise. For COHb≥14.9%, heart rate increased relative to air exposure throughout exercise with a maximum increase of 12.0% at 19.2% COHb and 4.9 METS (Table 26).

The adjusted stroke volume was significantly increased relative to air exposure for COHb≥14.9% ($p<0.01$) (Figure 18-B). For all CO exposures, the stroke volume response increased with initial exercise relative to air exposure, however this relative change decreased substantially as exercise continued.

Cardiac output showed an increased exercise response for exposures of COHb≥9.8% ($p<0.0004$), having mean increase of 17% over air exposure at 19.2% COHb and maximum increase of 23.8% at 19.2% COHb and 3.6 METS (Table 26, Figure 19-B). Mirroring the stroke volume exercise response, the elevated cardiac output response fell off dramatically at the highest level of exercise for each CO exposure.

Acceleration had a progressively increased exercise responses for each level of CO exposure (Figure 20-B) with overall increases of 3.3%, 9.4%, 12.8%, and 21.2% (Table 26). Very significant responses were observed for COHb≥9.8% ($p<0.0001$)(Table 22). In contrast to the treadmill exercise responses (Figure 11), acceleration in hand-crank exercise increased dramatically at the highest levels of CO exposure and exercise.

Time-to-peak ejection velocity was decreased at each level of CO exposure (Table 26), becoming significantly decreased for COHb≥9.8% (Table 22, Figure 21-B). At these higher levels of exposure, the exercise response was enhanced by a maximum of 2.5%, 5.6%, and 8.5%, however for COHb≥14.9%, the enhanced exercise response could not be maintained throughout exercise.

The respiratory variables showed moderate effects of CO exposure and, as with treadmill exercise, generally had large intersubject variance (Table 26). At 5.1% COHb, overall oxygen consumption was slightly decreased while carbon dioxide production was significantly decreased ($p<0.01$) relative to air exposure. For COHb≥9.8%, oxygen consumption and carbon dioxide production were consistently increased relative to air exposure (Figures 13-B and 14-B), becoming statistically

significant at COHb=19.2% (Table 25). At 19.2% COHb, overall oxygen consumption and carbon dioxide production after CO exposure was increased by about 10.6% and 8% over air exposure respectively.

In contrast, ventilation was consistently increased at each level of CO exposure relative to air exposure(Table 26), becoming significant for COHb≥14.8% ($p>0.008$). At 14.8% and 19.2% COHb, overall ventilation after CO exposure was increased by about 9% and 7% over air exposure. Respiratory exchange ratio was decreased at each level of CO exposure (Table 26), and was significantly reduced at COHb=9.8% ($p>0.002$) and COHb=19.2% ($p<0.007$).

Table 20. Comparative effects of carbon monoxide exposure relative to air exposure for each cardiac variable during upper-body exercise using the Least Significant Difference method (LSD) for testing comparisons. To reduce multiple-comparison errors, tests for significant differences were made using α=0.01.

Overall Response - Actual Data (LSD)				
COHb Level	**5.1%**	**9.8%**	**14.9%**	**19.2%**
Rate	0.01	ns	0.0001	0.0001
Stroke Volume	ns	ns	ns	ns
Cardiac Output	ns	ns	ns	0.001
Acceleration	ns	0.01	0.001	0.0001
Time-to-peak Ejection	ns	0.01	0.0001	0.0001

Table 21. Comparative effects of carbon monoxide exposure relative to air exposure for each cardiac variable during upper-body exercise using Scheffé's conservative method for testing comparisons. Tests for significant differences were made using α=0.05.

Overall Response - Actual Data (Scheffé)				
COHb Level	**5.1%**	**9.8%**	**14.9%**	**19.2%**
Rate	ns	ns	0.001	0.001
Stroke Volume	ns	ns	ns	ns
Cardiac Output	ns	ns	ns	0.01
Acceleration	ns	ns	0.01	0.0001
Time-to-peak Ejection	ns	ns	0.001	0.001

Table 22. Comparative effects of carbon monoxide exposure relative to air exposure for each cardiac variable during upper-body exercise. Paired-difference variables were calculated for measurements at each activity level by subtracting the paired value for air exposure and tested for μ=0. Tests for significant differences were made using α=0.01.

Overall Hand Crank Response - Delta Air Exposure				
COHb Level	**5.1%**	**9.8%**	**14.9%**	**19.2%**
Rate	0.0001	0.0001	0.0001	0.0001
Stroke Volume	ns	ns	ns	0.01
Cardiac Output	ns	0.0004	0.002	0.0001
Acceleration	ns	0.0001	0.0001	0.0001
Time-to-peak Ejection	ns	0.0004	0.0001	0.0001

Table 23. Comparative effects of carbon monoxide exposure relative to air exposure for each respiratory variable during upper-body exercise using the Least Significant Difference method (LSD) for testing comparisons. To reduce multiple-comparison errors, tests for significant differences were made using α=0.01.

Overall Response - Actual Data (LSD)				
COHb Level	**5.1%**	**9.8%**	**14.9%**	**19.2%**
O_2 Consumption	ns	ns	ns	ns
CO_2 Production	ns	ns	ns	ns
Ventilation	ns	ns	ns	ns
Resp. Exchange Ratio	ns	ns	ns	ns

Table 24. Comparative effects of carbon monoxide exposure relative to air exposure for each respiratory variable during upper-body exercise using Scheffé's conservative method for testing comparisons. Tests for significant differences were made using α=0.05.

Overall Response - Actual Data (Scheffé)				
COHb Level	**5.1%**	**9.8%**	**14.9%**	**19.2%**
O_2 Consumption	ns	ns	ns	ns
CO_2 Production	ns	ns	ns	ns
Ventilation	ns	ns	ns	ns
Resp. Exchange Ratio	ns	ns	ns	ns

Table 25. Comparative effects of carbon monoxide exposure relative to air exposure for each respiratory variable during upper-body exercise. Paired-difference variables were calculated for measurements at each activity level by subtracting the paired value for air exposure and tested for μ=0. Tests for significant differences were made using α=0.01.

Overall Hand Crank Response - Delta Air Exposure				
COHb Level	**5.1%**	**9.8%**	**14.9%**	**19.2%**
O_2 Consumption	ns	(0.04)	ns	0.0003
CO_2 Production	0.01	ns	ns	0.007
Ventilation	ns	ns	0.008	0.007
Resp. Exchange Ratio	ns	0.002	ns	0.007

Table 26. Combined effects of carbon monoxide exposure and upper-body hand-crank exercise. Means and standard deviations are presented across subjects for each level of CO exposure and hand-crank exercise. Actual data, subject-paired difference from air-exposure data, and subject-paired percent difference from air-exposure data are listed.

COHb (%)	1.9% COHb	5.1% COHb	9.8% COHb	14.9% COHb	19.2% COHb
Rest	1.9 ± 0.43	5.2 ± 0.51	10.0 ± 1.06	15.3 ± 1.17	19.7 ± 0.68
25 Watts	1.9 ± 0.41	5.1 ± 0.49	9.8 ± 1.02	15.0 ± 1.10	19.4 ± 0.78
40 Watts	1.9 ± 0.38	5.1 ± 0.48	9.7 ± 0.99	14.8 ± 1.06	19.0 ± 0.93
60 Watts	1.9 ± 0.38	5.1 ± 0.49	9.5 ± 0.97	14.5 ± 1.04	18.7 ± 1.12

Heart Rate (beats/min)	1.9%	5.1%	9.8%	14.9%	19.2%
Rest	73.5 ± 9.4	78.3 ± 11.7	74.4 ± 10.4	75.5 ± 11.5	78.1 ± 10.7
25 Watts	85.8 ± 8.6	90.4 ± 10.3	89.3 ± 9.6	92.6 ± 11.6	94.3 ± 12.1
40 Watts	94.7 ± 9.6	98.9 ± 12.6	97.4 ± 11.3	103.6 ± 14.1	104.7 ± 13.0
60 Watts	112.2 ± 13.4	112.9 ± 17.3	115.6 ± 15.3	124.3 ± 19.7	125.9 ± 17.9
Rest, Δ AIR	0.0 ± 0.0	4.8 ± 7.5	0.9 ± 6.4	2.0 ± 8.1	4.6 ± 7.5
25 Watts, Δ AIR	0.0 ± 0.0	4.7 ± 5.2	3.5 ± 4.1	6.8 ± 6.4	8.5 ± 6.4
40 Watts, Δ AIR	0.0 ± 0.0	4.3 ± 5.8	2.7 ± 4.3	8.9 ± 7.4	10.0 ± 6.7
60 Watts, Δ AIR	0.0 ± 0.0	0.8 ± 7.5	3.4 ± 4.6	12.1 ± 9.2	13.7 ± 6.4
Overall, Δ AIR	*0.0 ± 0.0*	*3.6 ± 6.7*	*2.6 ± 4.9*	*7.5 ± 8.5*	*9.2 ± 7.2*
Rest, %Δ AIR	0.0 ± 0.0	6.6 ± 10.7	1.5 ± 8.3	2.9 ± 11.5	6.5 ± 10.4
25 Watts, %Δ AIR	0.0 ± 0.0	5.5 ± 6.2	4.1 ± 4.7	7.9 ± 7.5	9.8 ± 7.2
40 Watts, %Δ AIR	0.0 ± 0.0	4.4 ± 6.1	2.8 ± 4.4	9.2 ± 7.6	10.5 ± 6.0
60 Watts, %Δ AIR	0.0 ± 0.0	0.5 ± 6.7	3.0 ± 4.0	10.5 ± 8.1	12.0 ± 5.0
Overall, %Δ AIR	*0.0 ± 0.0*	*4.2 ± 7.8*	*2.8 ± 5.6*	*7.6 ± 9.1*	*9.7 ± 7.5*

Table 26 (continued). Combined effects of carbon monoxide exposure and upper-body hand-crank exercise.

Stroke Volume (cc)	1.9% COHb	5.1% COHb	9.8% COHb	14.9% COHb	19.2% COHb
Rest	125.1 ± 33.0	115.6 ± 30.8	126.9 ± 38.7	121.3 ± 28.4	131.3 ± 29.1
25 Watts	125.6 ± 35.6	121.3 ± 24.3	132.7 ± 36.6	129.2 ± 29.6	136.3 ± 35.1
40 Watts	129.8 ± 33.9	127.9 ± 30.3	137.8 ± 40.3	131.5 ± 31.7	138.6 ± 38.9
60 Watts	129.8 ± 33.1	124.1 ± 34.4	131.7 ± 42.1	120.1 ± 35.4	128.1 ± 37.4
Rest, Δ AIR	0.0 ± 0.0	-9.5 ± 17.9	1.8 ± 19.3	-3.8 ± 20.0	6.2 ± 17.7
25 Watts, Δ AIR	0.0 ± 0.0	-4.3 ± 21.9	7.1 ± 21.3	3.6 ± 15.0	10.7 ± 21.5
40 Watts, Δ AIR	0.0 ± 0.0	-2.0 ± 18.4	7.9 ± 16.8	1.7 ± 17.8	8.8 ± 16.1
60 Watts, Δ AIR	0.0 ± 0.0	-5.7 ± 13.6	1.9 ± 15.5	-9.8 ± 20.6	-1.8 ± 14.8
Overall, Δ AIR	*0.0 ± 0.0*	*-5.4 ± 17.9*	*4.9 ± 18.1*	*-2.1 ± 18.8*	*6.0 ± 18.0*
Rest, %Δ AIR	0.0 ± 0.0	-6.7 ± 14.5	1.6 ± 14.3	-1.2 ± 15.0	6.7 ± 14.6
25 Watts, %Δ AIR	0.0 ± 0.0	0.1 ± 19.0	8.7 ± 26.9	4.9 ± 12.7	12.0 ± 27.8
40 Watts, %Δ AIR	0.0 ± 0.0	-0.3 ± 14.7	6.1 ± 13.5	2.4 ± 13.4	6.8 ± 12.5
60 Watts, %Δ AIR	0.0 ± 0.0	-4.4 ± 10.2	0.5 ± 11.7	-7.2 ± 15.3	-1.7 ± 11.4
Overall, %Δ AIR	*0.0 ± 0.0*	*-2.8 ± 14.8*	*4.2 ± 17.6*	*-0.3 ± 14.5*	*6.0 ± 18.1*

Cardiac Output (l/min)	1.9%	5.1%	9.8%	14.9%	19.2%
Rest	8.9 ± 1.6	8.8 ± 1.8	9.2 ± 2.1	8.9 ± 1.3	10.1 ± 1.8
25 Watts	10.6 ± 2.6	10.8 ± 1.7	11.6 ± 2.5	11.8 ± 2.2	12.6 ± 2.5
40 Watts	12.1 ± 2.7	12.4 ± 2.2	13.2 ± 3.1	13.3 ± 2.2	14.3 ± 3.3
60 Watts	14.2 ± 2.8	13.6 ± 2.5	14.9 ± 3.8	14.4 ± 2.5	15.7 ± 3.5
Rest, Δ AIR	0.0 ± 0.0	-0.01 ± 1.1	0.28 ± 1.2	0.02 ± 1.3	1.2 ± 1.6
25 Watts, Δ AIR	0.0 ± 0.0	0.22 ± 1.7	1.04 ± 1.9	1.21 ± 1.3	2.0 ± 2.0
40 Watts, Δ AIR	0.0 ± 0.0	0.34 ± 1.7	1.06 ± 1.5	1.24 ± 1.5	2.2 ± 2.0
60 Watts, Δ AIR	0.0 ± 0.0	-0.61 ± 1.3	0.63 ± 1.7	0.18 ± 1.9	1.5 ± 2.1
Overall, Δ AIR	*0.0 ± 0.0*	*-0.03 ± 1.5*	*0.75 ± 1.6*	*0.70 ± 1.6*	*1.7 ± 1.9*
Rest, %Δ AIR	0.0 ± 0.0	-0.5 ± 13.7	3.2 ± 13.7	1.7 ± 13.1	14.7 ± 18.5
25 Watts, %Δ AIR	0.0 ± 0.0	5.6 ± 18.3	14.0 ± 30.7	13.5 ± 13.1	23.8 ± 33.2
40 Watts, %Δ AIR	0.0 ± 0.0	4.4 ± 14.5	9.5 ± 14.2	11.7 ± 12.4	18.9 ± 17.1
60 Watts, %Δ AIR	0.0 ± 0.0	-3.8 ± 8.2	3.9 ± 11.7	2.2 ± 12.8	10.7 ± 14.3
Overall, %Δ AIR	*0.0 ± 0.0*	*[illegible] ± 14.3*	*7.7 ± 19.2*	*7.3 ± 13.7*	*17.0 ± 22.1*

Table 26 (continued). Combined effects of carbon monoxide exposure and upper-body hand-crank exercise.

Acceleration (Ω/s/s)	1.9% COHb	5.1% COHb	9.8% COHb	14.9% COHb	19.2% COHb
Rest	34.0 ± 8.0	34.8 ± 9.2	35.5 ± 10.2	35.4 ± 8.6	37.2 ± 8.7
25 Watts	37.2 ± 9.3	37.9 ± 9.6	39.6 ± 10.5	41.9 ± 11.3	42.4 ± 11.9
40 Watts	39.0 ± 9.9	40.7 ± 10.7	44.0 ± 11.9	46.0 ± 13.4	49.1 ± 15.7
60 Watts	46.5 ± 11.9	47.7 ± 12.5	52.2 ± 14.9	53.4 ± 17.5	60.3 ± 19.2
Rest, Δ AIR	0.0 ± 0.0	0.77 ± 5.8	1.5 ± 5.8	1.4 ± 6.2	3.2 ± 6.3
25 Watts, Δ AIR	0.0 ± 0.0	0.65 ± 3.5	2.4 ± 3.7	4. 7 ± 4.5	5.2 ± 7.4
40 Watts, Δ AIR	0.0 ± 0.0	1.72 ± 4.4	4.9 ± 5.5	7.0 ± 8.8	10.1 ± 11.0
60 Watts, Δ AIR	0.0 ± 0.0	1.16 ± 4.7	5.6 ± 6.6	6.9 ± 9.7	13.7 ± 11.8
Overall, Δ AIR	*0.0 ± 0.0*	*1.1 ± 4.6*	*3.6 ± 5.7*	*5.0 ± 7.7*	*8.1 ± 10.1*
Rest, %Δ AIR	0.0 ± 0.0	2.6 ± 17.5	4.3 ± 17.7	5.2 ± 17.3	11.6 ± 20.8
25 Watts, %Δ AIR	0.0 ± 0.0	2.7 ± 11.3	6.8 ± 9.8	12.6 ± 13.1	15.4 ± 19.3
40 Watts, %Δ AIR	0.0 ± 0.0	4.8 ± 12.0	13 3 ± 13.9	19.1 ± 21.8	27.1 ± 26.2
60 Watts, %Δ AIR	0.0 ± 0.0	3.1 ± 10.0	13.4 ± 20.7	14.4 ± 16.8	30.8 ± 26.6
Overall, %Δ AIR	*0.0 ± 0.0*	*3.3 ± 12.8*	*9.4 ± 16.2*	*12.8 ± 17.8*	*21.2 ± 24.2*

Time-to-peak Ejection (ms)	1.9%	5.1%	9.8%	14.9%	19.2%
Rest	179.5 ± 13.9	177.3 ± 13.8	177.4 ± 18.1	176.2 ± 15.2	171.2 ± 14.7
25 Watts	159.5 ± 11.0	158.0 ± 10.2	155.8 ± 12.3	151.0 ± 12.0	147.7 ± 10.4
40 Watts	149.8 ± 11.2	150.0 ± 11.2	146.1 ± 12.6	141.5 ± 12.3	137.2 ± 11.5
60 Watts	134.5 ± 11.3	135.5 ± 11.1	131.4 ± 12.3	128.1 ± 9.6	124.5 ± 8.7
Rest, Δ AIR	0.0 ± 0.0	-2.20 ± 10.1	-2.1 ± 10.4	-3.4 ± 9.4	-8.4 ± 12.2
25 Watts, Δ AIR	0.0 ± 0.0	-1.53 ± 4.8	-3.8 ± 7.3	-8.5 ± 4.9	-11.8 ± 6.4
40 Watts, Δ AIR	0.0 ± 0.0	0.12 ± 7.4	-3.7 ± 3.4	-8.3 ± 5.7	-12.7 ± 4.6
60 Watts, Δ AIR	0.0 ± 0.0	1.01 ± 4.1	-3.1 ± 3.7	-6.3 ± 4.5	-10.0 ± 4.4
Overall, Δ AIR	*0.0 ± 0.0*	*-0.65 ± 6.95*	*-3.17 ± 6.7*	*-6.6 ± 6.6*	*-10.7 ± 7.6*
Rest, %Δ AIR	0.0 ± 0.0	-1.1 ± 5.6	-1.2 ± 5.6	-1.8 ± 5.4	-4.5 ± 6.6
25 Watts, %Δ AIR	0.0 ± 0.0	-0.9 ± 3.2	-2.3 ± 4.4	-5.4 ± 3.1	-7.3 ± 4.0
40 Watts, %Δ AIR	0.0 ± 0.0	0.2 ± 5.2	-2.5 ± 2.3	-5.6 ± 3.9	-8.5 ± 3.0
60 Watts, %Δ AIR	0.0 ± 0.0	0.8 ± 3.2	-2.3 ± 2.8	-4.6 ± 3.3	-7.3 ± 3.0
Overall, %Δ AIR	*0.0 ± 0.0*	*-0.2 ± 4.4*	*-2.1 ± 4.0*	*-4.3 ± 4.2*	*-6.9 ± 4.5*

Table 26 (continued). Combined effects of carbon monoxide exposure and upper-body hand-crank exercise.

O_2 Consumption (ml/min)	1.9% COHb	5.1% COHb	9.8% COHb	14.9% COHb	19.2% COHb
Rest	427.4 ± 76.1	411.5 ± 95.1	444.4 ± 70.0	479.8 ±175.9	464.2 ± 96.3
25 Watts	868.6 ±105.2	840.5 ±114.5	889.3 ±158.1	882.7 ±138.6	924.6 ±127.7
40 Watts	1001.8 ±118.5	976.4 ±114.9	1040.8 ±131.2	1016.0 ±127.3	1072.0 ±130.4
60 Watts	1347.1 ± 88.2	1273.3 ±126.3	1335.5 ±141.2	1316.4 ± 89.5	1387.9 ±121.6
Rest, Δ AIR	0.0 ± 0.0	-12.1 ± 75.6	36.0 ± 68.4	43.4 ±139.3	60.6 ± 88.0
25 Watts, Δ AIR	0.0 ± 0.0	-11.6 ± 39.5	37.6 ± 93.5	26.8 ± 86.0	89.6 ±100.1
40 Watts, Δ AIR	0.0 ± 0.0	-2.8 ± 59.6	63.9 ± 70.0	39.5 ± 67.9	100.3 ± 94.7
60 Watts, Δ AIR	0.0 ± 0.0	-58.0 ± 80.8	6.4 ±119.5	-10.9 ± 42.9	60.5 ±118.1
Overall, Δ AIR	*0.0 ± 0.0*	*-21.1 ± 65.9*	*36.0 ± 87.6*	*24.7 ± 94.7*	*77.7 ± 96.8*
Rest, %Δ AIR	0.0 ± 0.0	-2.2 ± 16.8	10.6 ± 17.6	11.0 ± 30.1	16.5 ± 22.5
25 Watts, %Δ AIR	0.0 ± 0.0	-1.6 ± 5.1	3.9 ± 10.8	3.0 ± 10.9	10.8 ± 11.7
40 Watts, %Δ AIR	0.0 ± 0.0	-0.3 ± 6.2	6.6 ± 7.1	4.2 ± 9.8	10.6 ± 9.7
60 Watts, %Δ AIR	0.0 ± 0.0	-4.6 ± 6.6	0.4 ± 8.9	-0.9 ± 3.3	4.6 ± 8.7
Overall, %Δ AIR	*0.0 ± 0.0*	*-2.2 ± 9.4*	*5.4 ± 11.7*	*4.3 ± 16.4*	*10.6 ± 14.1*

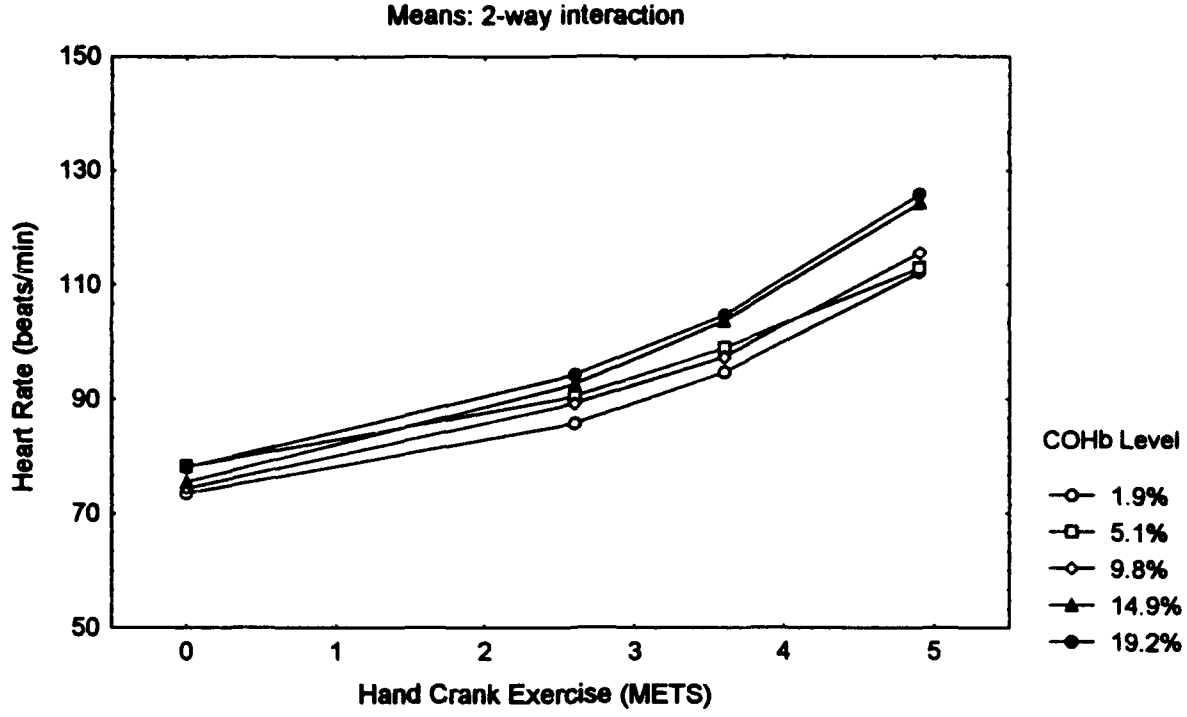
CO_2 Production (ml/min)	1.9%	5.1%	9.8%	14.9%	19.2%
Rest	374.9 ±117.1	315.9 ± 63.6	340.5 ± 64.2	370.3 ±127.2	357.4 ± 63.1
25 Watts	742.8 ±114.1	690.2 ± 88.9	732.5 ±115.1	722.7 ±101.1	769.5 ±107.8
40 Watts	911.2 ±133.3	861.1 ±101.8	927.6 ±119.2	898.5 ± 90.6	954.7 ±134.4
60 Watts	1299.8 ±120.6	1202.2 ± 96.2	1283.9 ±138.2	1261.6 ± 65.4	1341.0 ±100.5
Rest, Δ AIR	0.0 ± 0.0	-28.5 ± 60.9	-0.6 ± 77.1	9.1 ± 91.3	21.7 ± 75.5
25 Watts, Δ AIR	0.0 ± 0.0	-22.4 ± 36.6	9.0 ± 59.1	9.1 ± 71.3	59.0 ± 82.5
40 Watts, Δ AIR	0.0 ± 0.0	-12.9 ± 51.2	39.3 ± 57.4	27.2 ± 86.4	69.5 ±101.1
60 Watts, Δ AIR	0.0 ± 0.0	-69.3 ± 93.8	-11.6 ±125.6	-1.5 ± 44.9	57.7 ±117.8
Overall, Δ AIR	*0.0 ± 0.0*	*-33.3 ± 64.3*	*9.0 ± 81.9*	*11.0 ± 72.1*	*52.0 ± 92.1*
Rest, %Δ AIR	0.0 ± 0.0	-5.8 ± 18.7	3.3 ± 21.5	4.2 ± 25.0	10.5 ± 24.4
25 Watts, %Δ AIR	0.0 ± 0.0	-3.3 ± 5.4	1.1 ± 8.2	1.3 ± 10.3	8.5 ± 11.7
40 Watts, %Δ AIR	0.0 ± 0.0	-1.6 ± 5.9	4.5 ± 6.3	3.5 ± 9.8	8.1 ± 11.3
60 Watts, %Δ AIR	0.0 ± 0.0	-5.4 ± 7.6	-0.8 ± 10.3	-0.1 ± 3.6	4.8 ± 9.6
Overall, %Δ AIR	*0.0 ± 0.0*	*-4.0 ± 10.4*	*2.0 ± 12.4*	*2.2 ± 13.8*	*8.0 ± 14.7*

Table 26 (continued). Combined effects of carbon monoxide exposure and upper-body hand-crank exercise.

Ventilation (l/min)	1.9% COHb	5.1% COHb	9.8% COHb	14.9% COHb	19.2% COHb
Rest	16.4 ± 5.0	15.8 ± 1.9	14.9 ± 3.6	15.6 ± 1.9	15.7 ± 3.3
25 Watts	26.1 ± 3.3	26.2 ± 1.5	26.0 ± 3.1	27.5 ± 2.0	26.9 ± 3.9
40 Watts	30.3 ± 2.4	31.1 ± 2.0	30.7 ± 3.3	32.3 ± 3.4	32.3 ± 4.0
60 Watts	40.7 ± 3.7	40.3 ± 1.8	40.6 ± 5.2	42.4 ± 4.1	43.0 ± 6.4
Rest, Δ AIR	0.0 ± 0.0	0.72 ± 1.7	0.23 ± 3.2	0.62 ± 2.9	0.99 ± 3.3
25 Watts, Δ AIR	0.0 ± 0.0	1.22 ± 3.4	0.44 ± 2.0	2.42 ± 3.8	1.53 ± 3.1
40 Watts, Δ AIR	0.0 ± 0.0	1.71 ± 3.5	0.64 ± 1.8	2.89 ± 4.4	2.36 ± 3.5
60 Watts, Δ AIR	0.0 ± 0.0	0.44 ± 4.3	-0.09 ± 3.2	2.73 ± 4.9	2.70 ± 4.2
Overall, Δ AIR	*0.0 ± 0.0*	*1.0 ± 3.2*	*0.31 ± 2.5*	*2.2 ± 4.0*	*1.9 ± 3.4*
Rest, %Δ AIR	0.0 ± 0.0	6.3 ± 12.0	1.7 ± 22.6	6.9 ± 20.2	7.6 ± 21.7
25 Watts, %Δ AIR	0.0 ± 0.0	6.1 ± 15.3	2.0 ± 9.4	11.1 ± 17.2	6.3 ± 13.4
40 Watts, %Δ AIR	0.0 ± 0.0	6.3 ± 12.6	2.0 ± 6.6	10.3 ± 15.5	8.0 ± 12.1
60 Watts, %Δ AIR	0.0 ± 0.0	2.0 ± 12.4	-0.3 ± 7.7	7.5 ± 13.7	6.4 ± 10.0
Overall, %Δ AIR	*0.0 ± 0.0*	*5.2 ± 12.5*	*1.4 ± 12.5*	*9.0 ± 16.0*	*7.0 ± 14.1*

Resp. Exchange Ratio	1.9%	5.1%	9.8%	14.9%	19.2%
Rest	0.86 ± 0.15	0.76 ± 0.10	0.77 ± 0.09	0.77 ± 0.07	0.77 ± 0.08
25 Watts	0.87 ± 0.06	0.86 ± 0.09	0.83 ± 0.06	0.82 ± 0.05	0.85 ± 0.04
40 Watts	0.92 ± 0.06	0.89 ± 0.03	0.90 ± 0.04	0.91 ± 0.05	0.89 ± 0.05
60 Watts	0.97 ± 0.04	0.95 ± 0.03	0.97 ± 0.06	0.97 ± 0.03	0.97 ± 0.06
Rest, Δ AIR	0.0 ± 0.0	-0.04 ± 0.11	-0.05 ± 0.07	-0.28 ± 0.67	-0.04 ± 0.05
25 Watts, Δ AIR	0.0 ± 0.0	0.01 ± 0.07	-0.03 ± 0.04	-0.02 ± 0.06	-0.01 ± 0.03
40 Watts, Δ AIR	0.0 ± 0.0	-0.02 ± 0.03	-0.02 ± 0.02	0.01 ± 0.06	-0.03 ± 0.03
60 Watts, Δ AIR	0.0 ± 0.0	-0.01 ± 0.04	-0.02 ± 0.02	0.00 ± 0.03	-0.01 ± 0.04
Overall, Δ AIR	*0.0 ± 0.0*	*-0.01 ± 0.07*	*-0.03 ± 0.04*	*-0.07 ± 0.34*	*-0.02 ± 0.04*
Rest, %Δ AIR	0.0 ± 0.0	-3.9 ± 13.9	-5.5 ± 8.8	-4.5 ± 9.1	-4.2 ± 6.1
25 Watts, %Δ AIR	0.0 ± 0.0	1.3 ± 8.2	-3.2 ± 4.1	-2.4 ± 7.4	-1.4 ± 3.1
40 Watts, %Δ AIR	0.0 ± 0.0	-1.8 ± 3.5	-2.1 ± 1.8	1.0 ± 6.1	-2.9 ± 2.8
60 Watts, %Δ AIR	0.0 ± 0.0	-1.4 ± 4.6	-1.6 ± 2.1	0.4 ± 3.2	-0.6 ± 3.8
Overall, %Δ AIR	*0.0 ± 0.0*	*-1.4 ± 8.3*	*-3.1 ± 5.0*	*-1.4 ± 6.8*	*-2.3 ± 4.1*

PANEL A



PANEL B

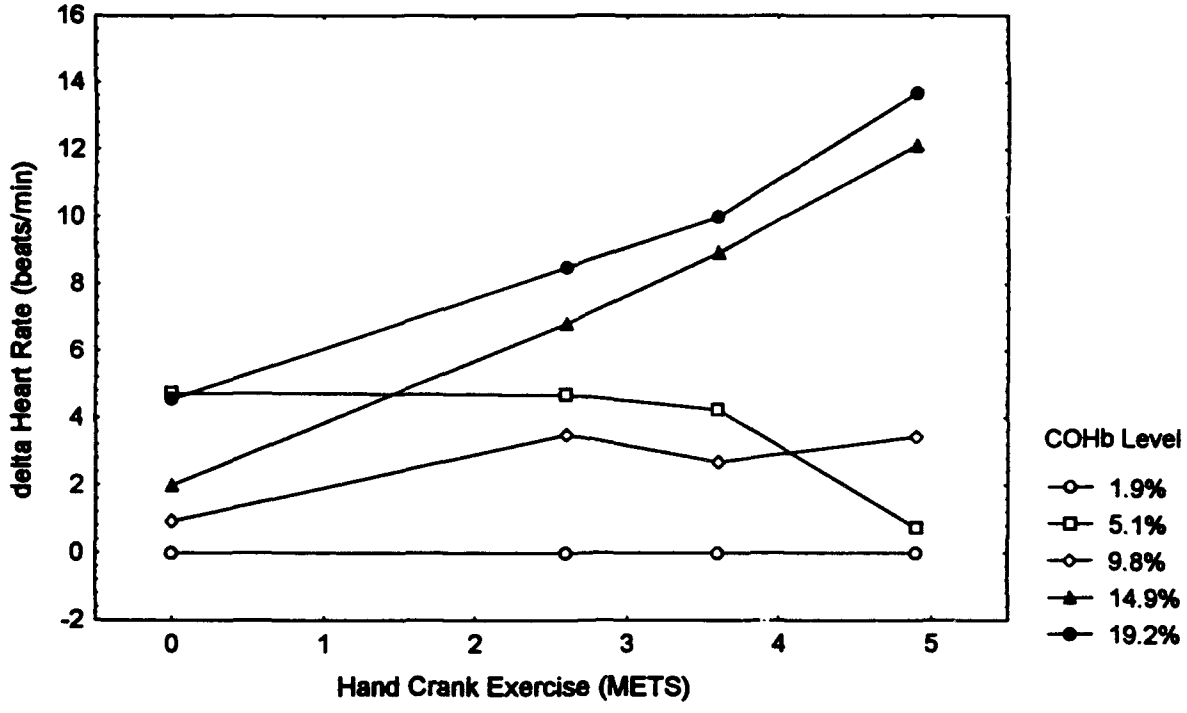
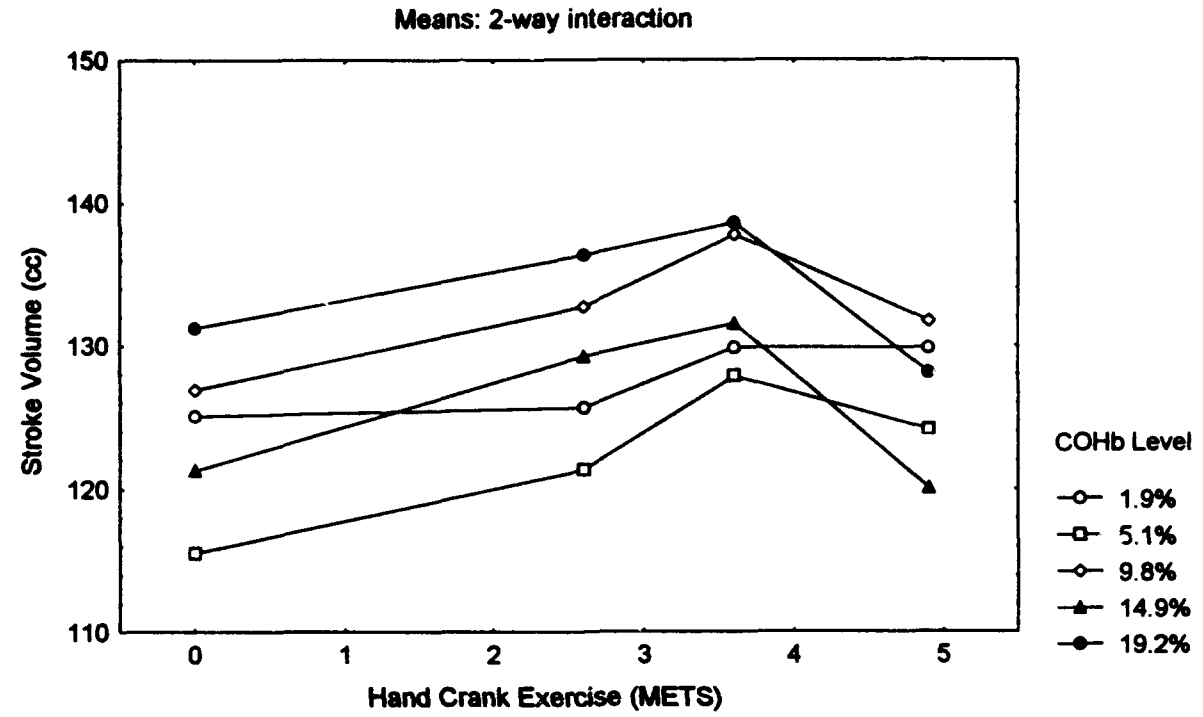


Figure 17. Mean heart rate response during hand-crank exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

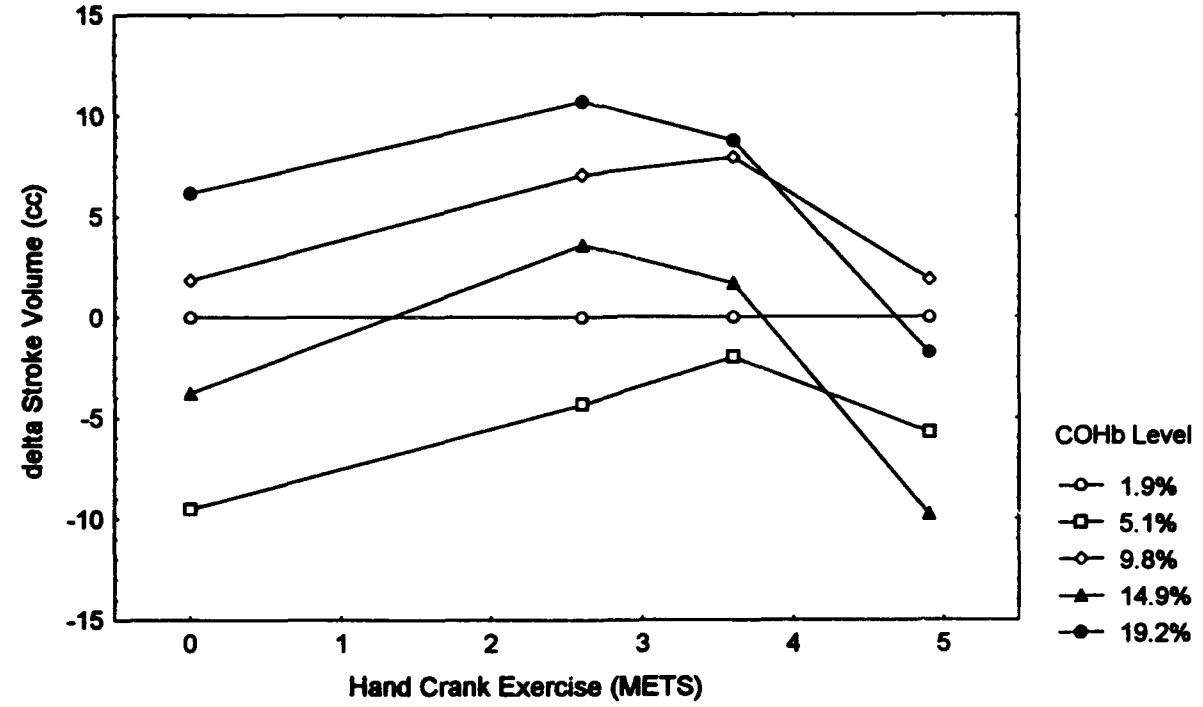
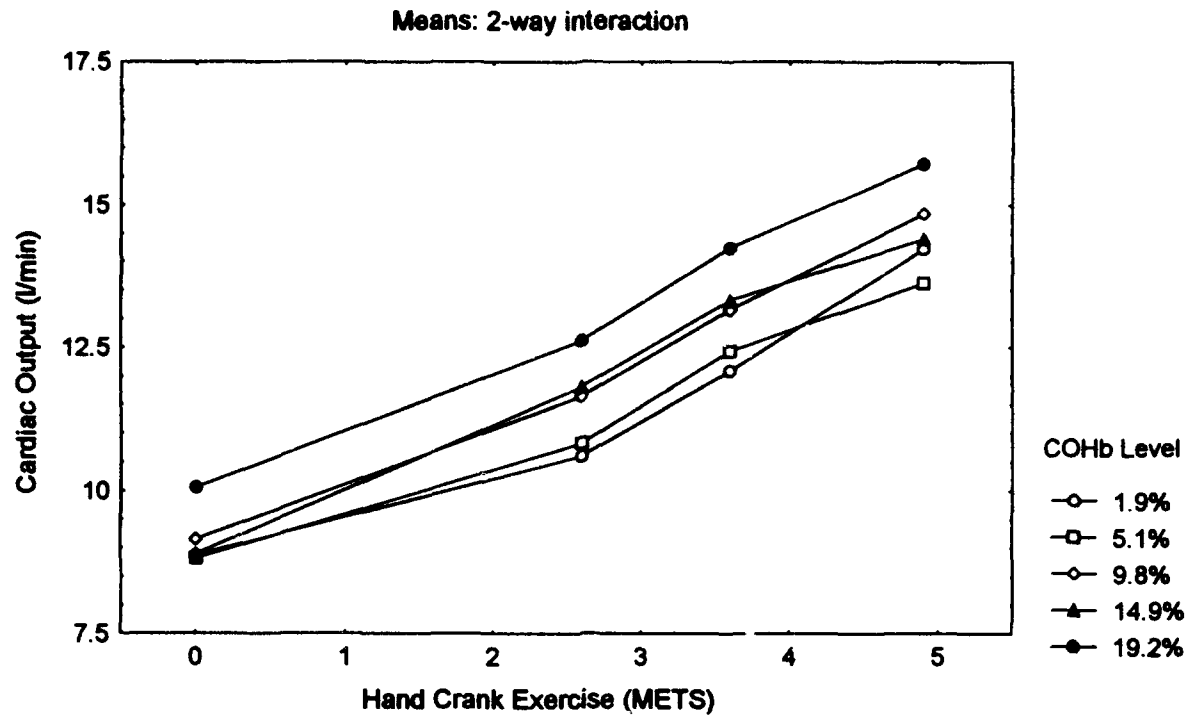


Figure 18. Mean stroke volume response during hand-crank exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

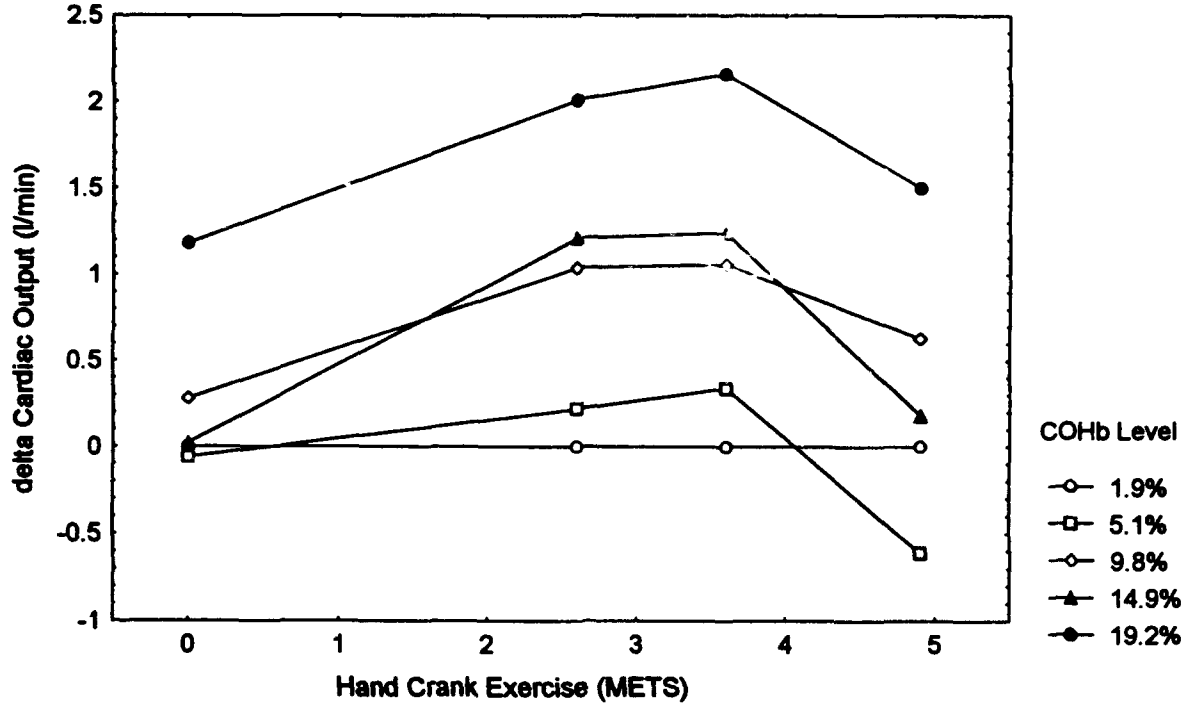
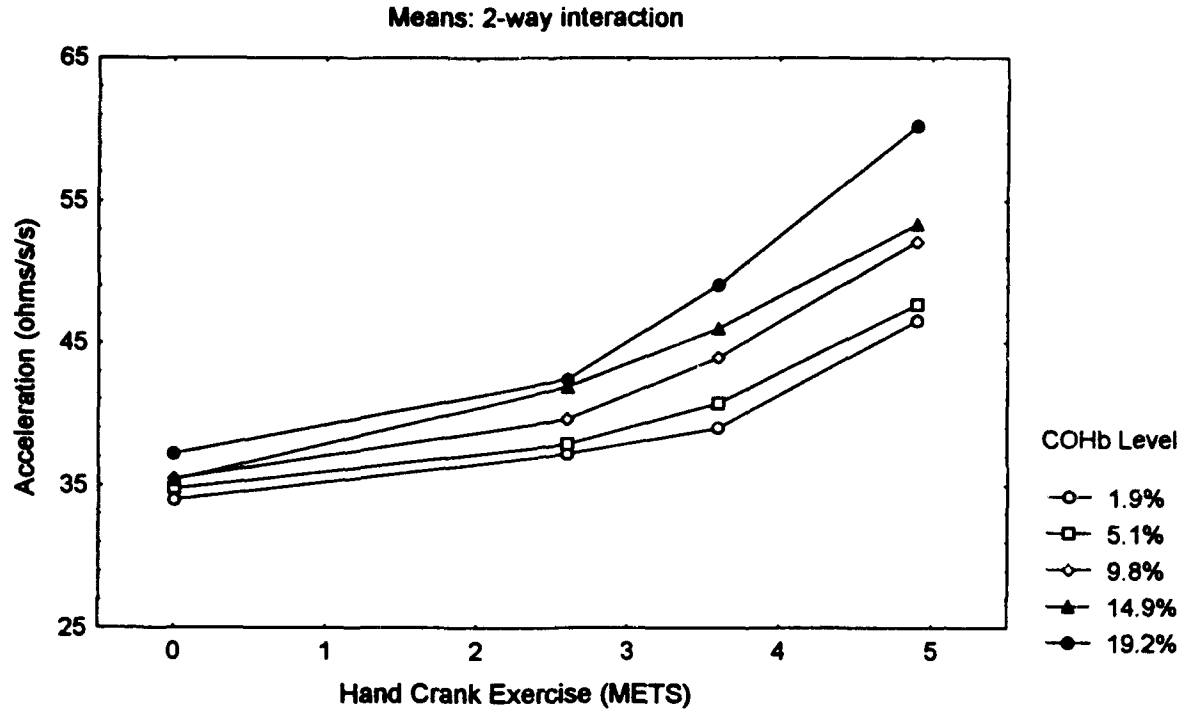


Figure 19. Mean cardiac output response during hand crank exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

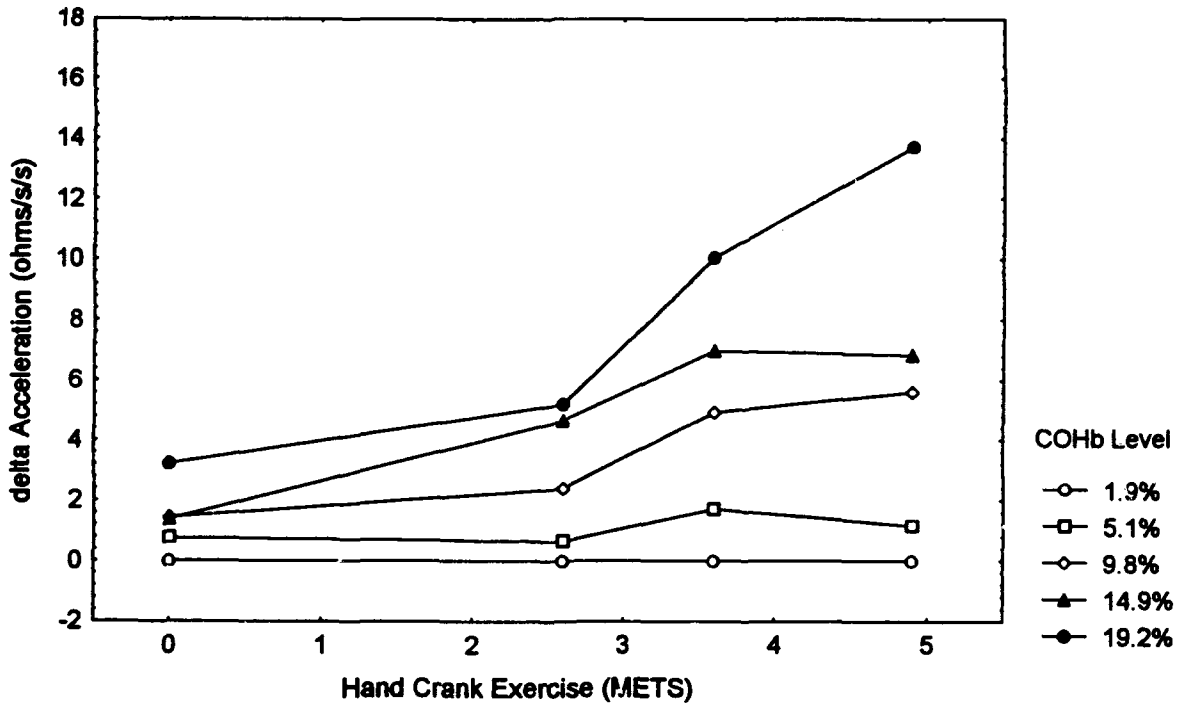
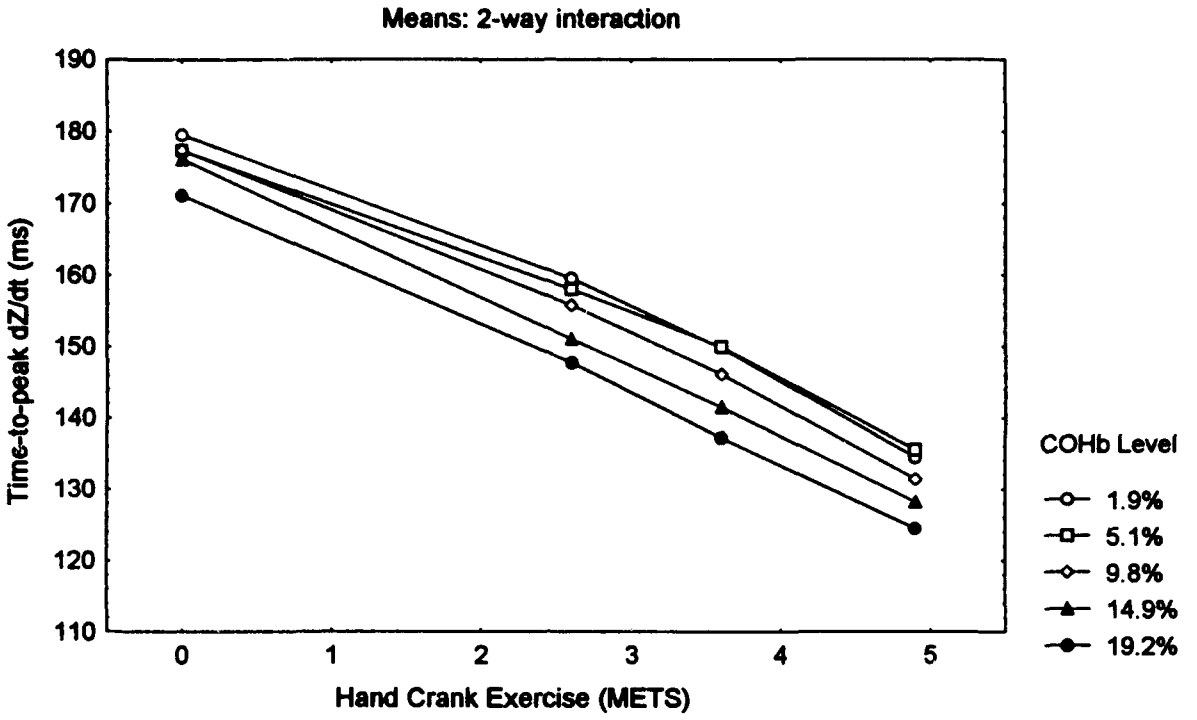


Figure 20. Mean ICG acceleration response during hand crank exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

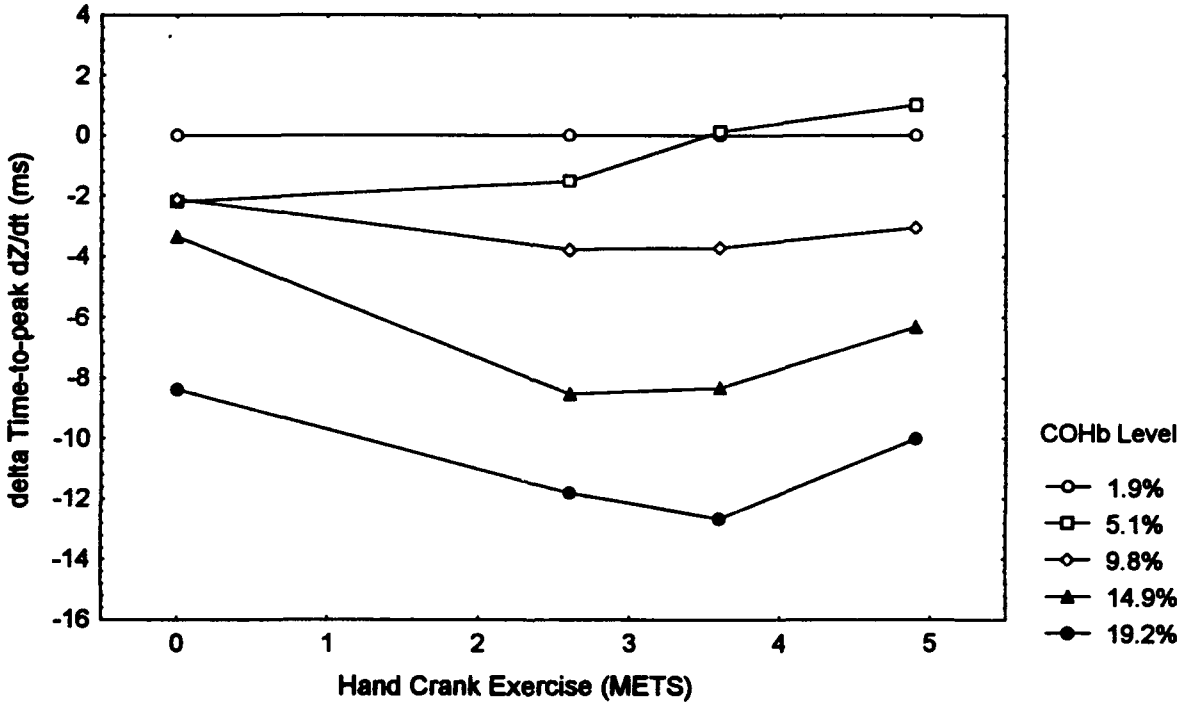
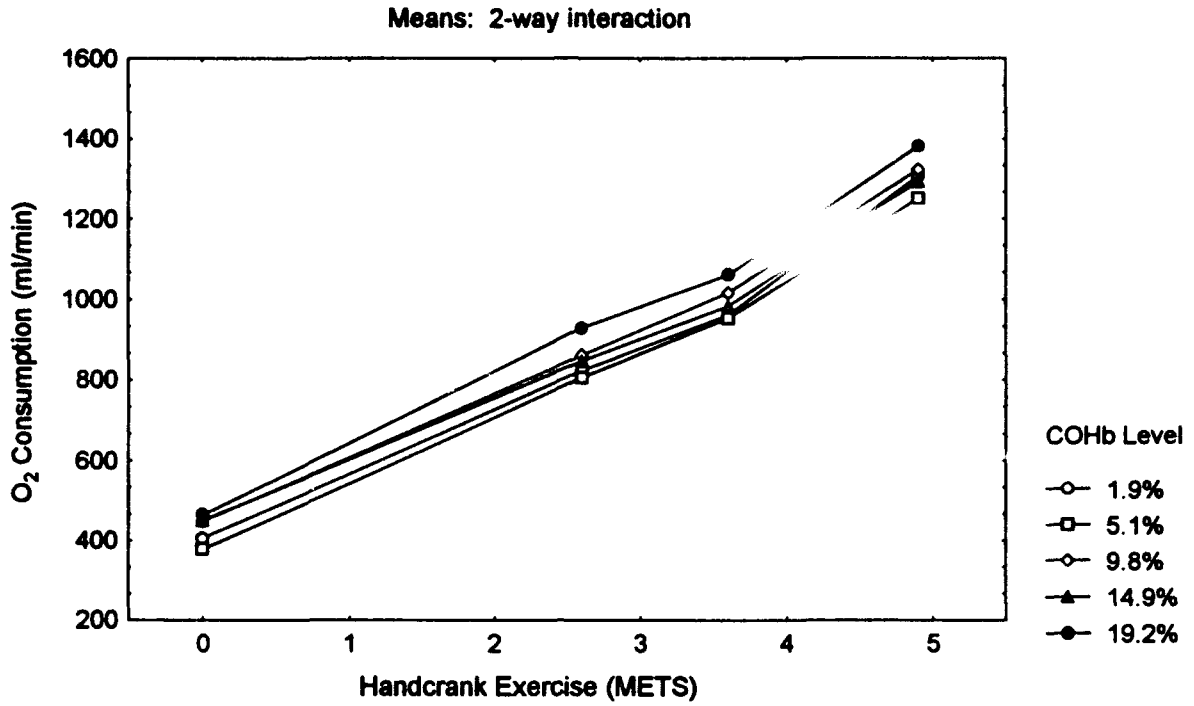


Figure 21. Mean time-to-peak velocity response during hand crank exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

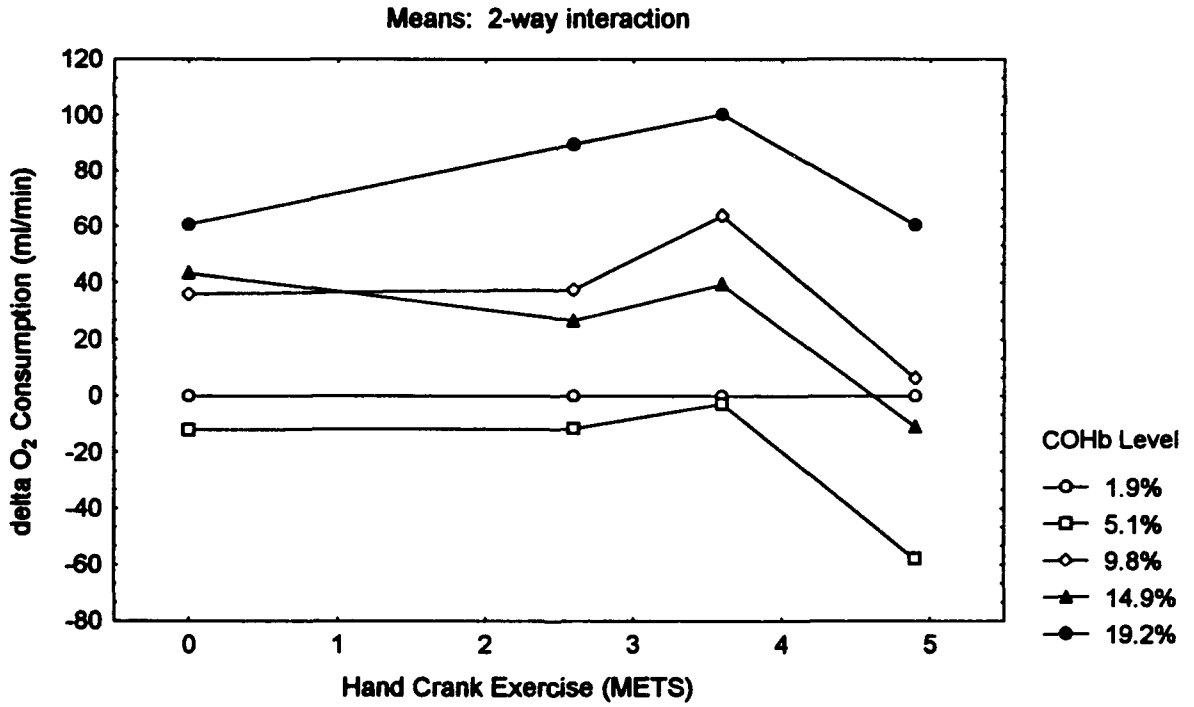
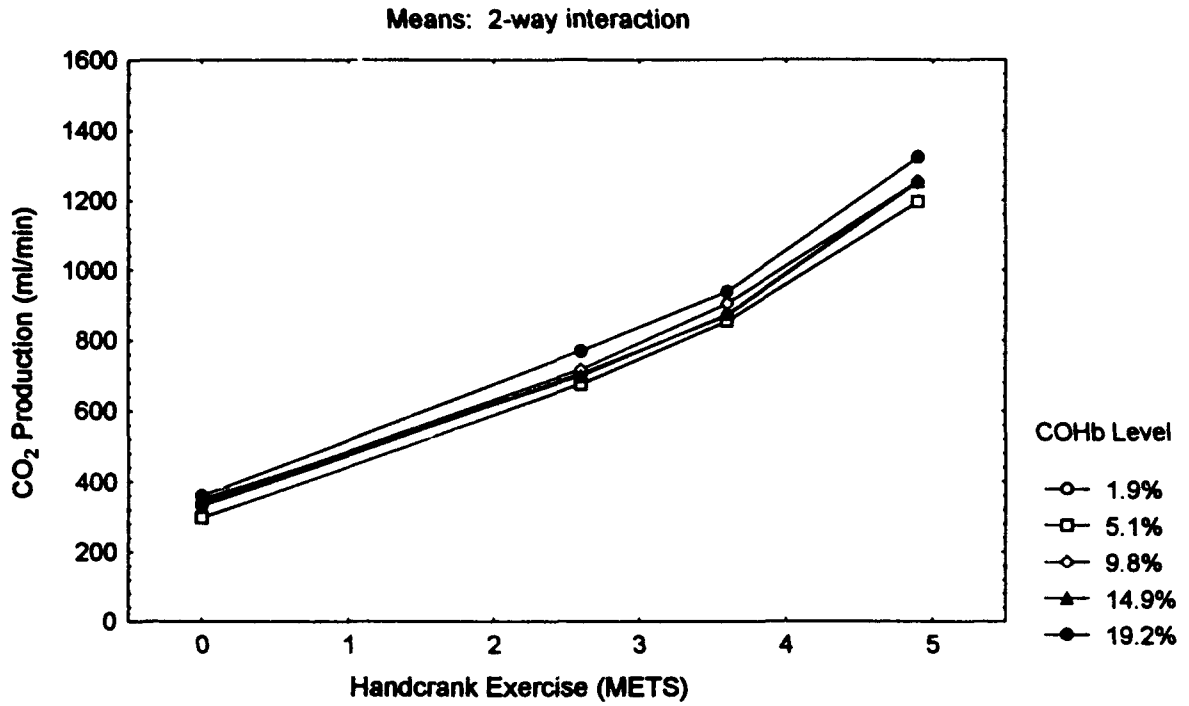


Figure 22. Mean oxygen consumption response during hand crank exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

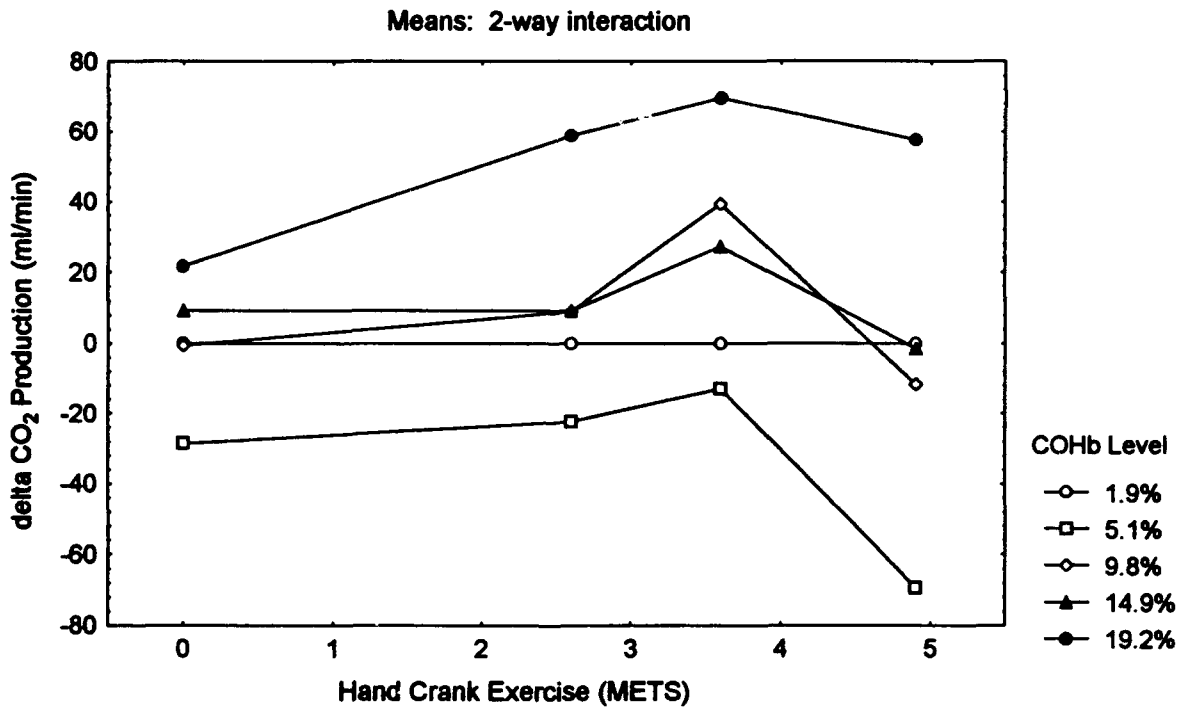
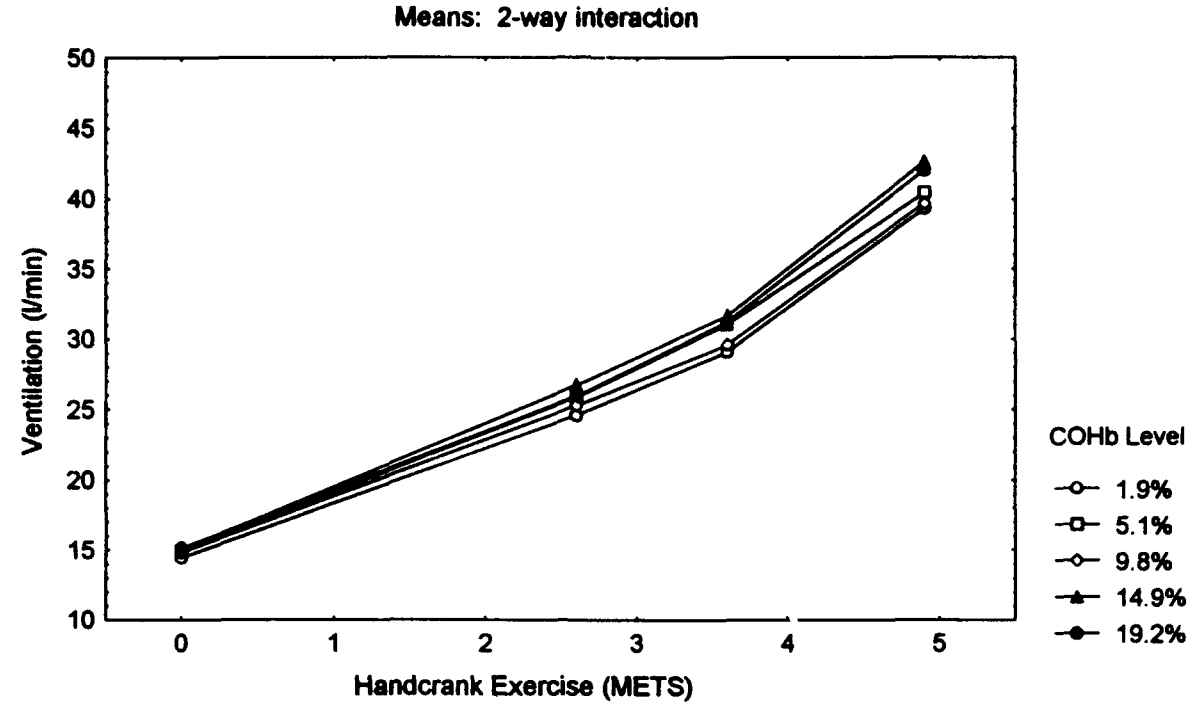


Figure 23. Mean carbon dioxide production response during hand crank exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

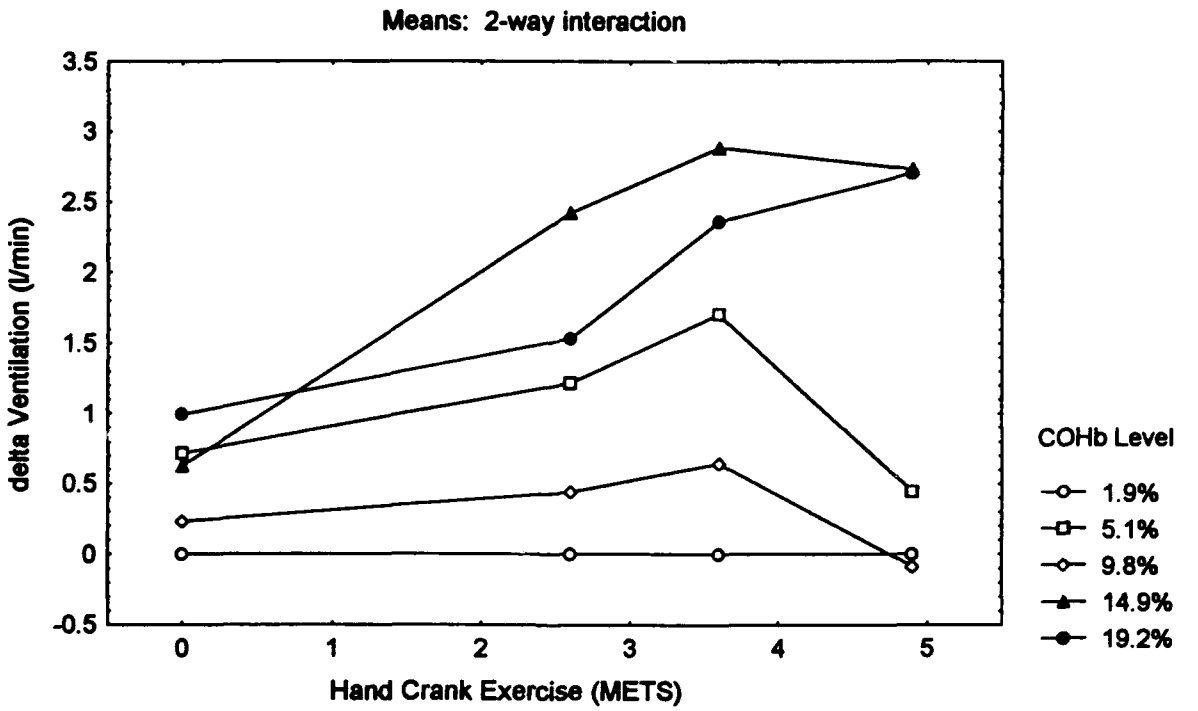
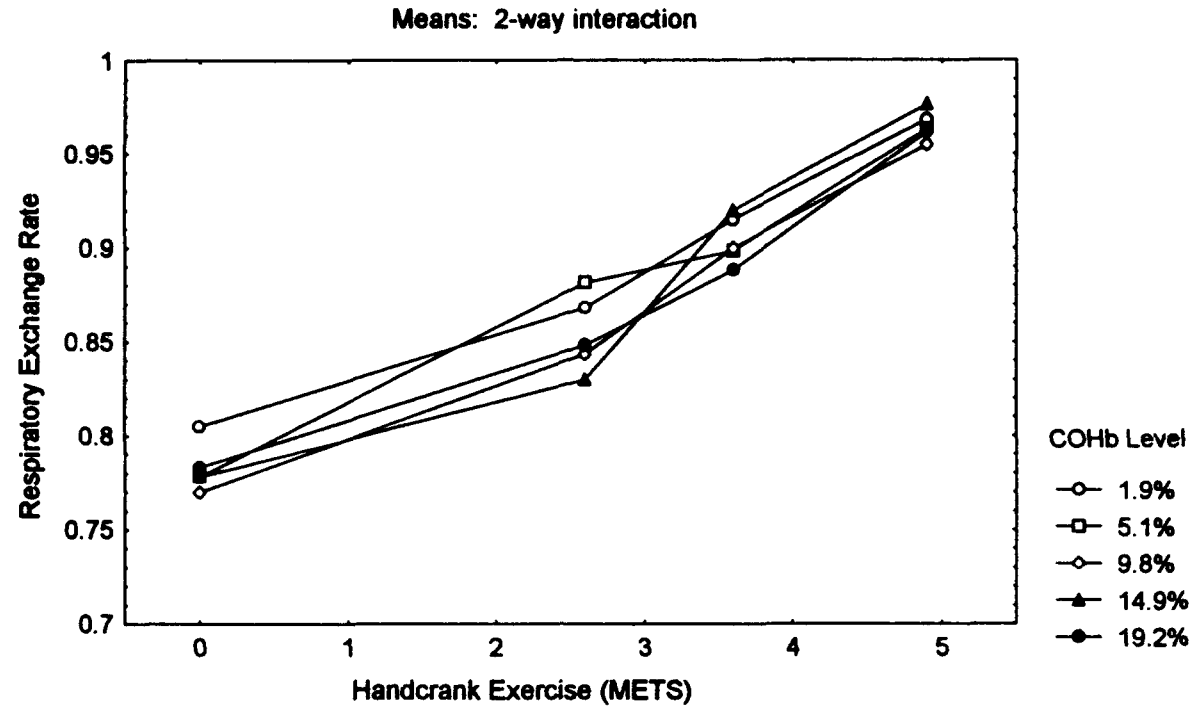


Figure 24. Mean ventilation response during hand crank exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

PANEL A



PANEL B

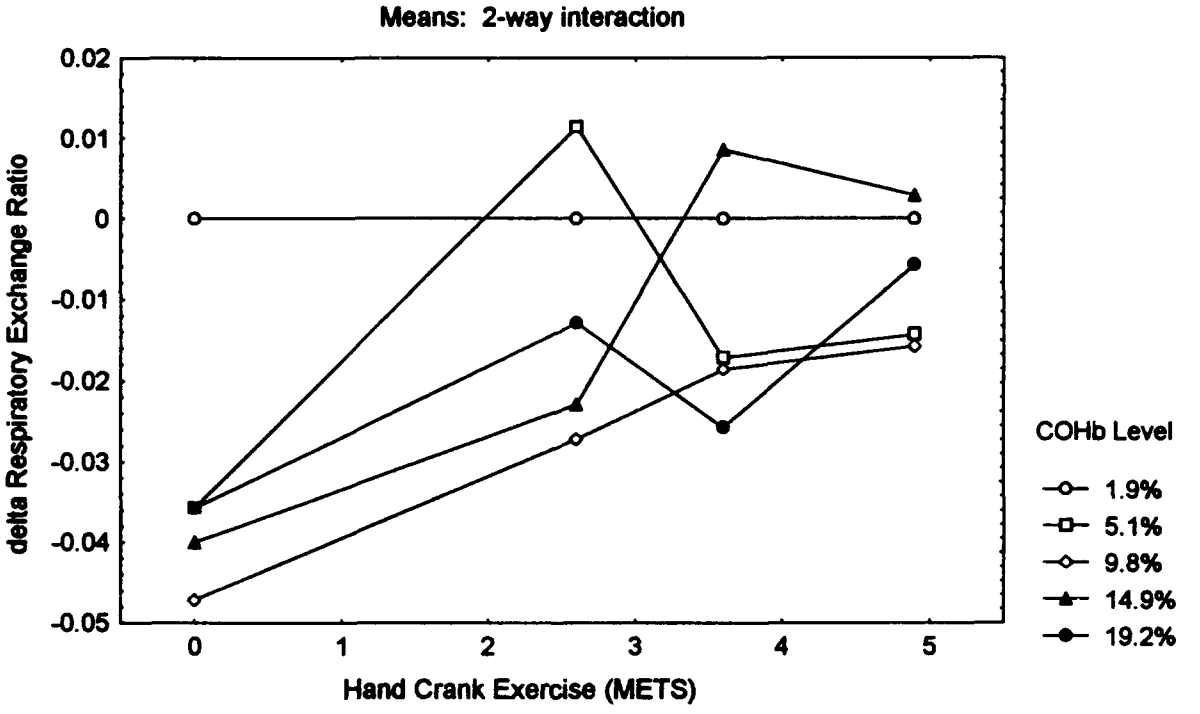


Figure 25. Mean respiratory exchange ratio response during treadmill exercise for air and CO exposures (Panel A). Effect of CO exposures on exercise response by mean paired-difference from air-exposure (Panel B).

2.5.5 Effects of CO Exposure on Cardiac Electrophysiology

Effects of CO exposure on myocardial ischemia

The effects of carbon monoxide exposure on myocardial ischemia were assessed by beat-by-beat analysis of ECG ST-segment depression. Episodes of one millimeter (0.1 mVolt) depression relative to ECG baseline (isoelectric segment between the P and Q waves) measured 80 ms after the J-point was the clinical threshold used for a positive ischemic response. Episodes of less than one millimeter depression were designated as subclinical ischemic responses.

Clinical or subclinical evidence of myocardial ischemia was observed on at least one experiment day in eight of the sixteen subjects (Tables 27 and 28). All of these subjects had ST-segment depression during both air and CO exposures, which is indicative of false-positive readings for these individuals.

Positive ischemic responses were observed in one subject only (subject #9), and had occurred during both air and CO exposures for both lower-body treadmill (Table 27) and upper-body hand-crank (Table 28) exercise. This subject also demonstrated subclinical ST depression for the remaining lower-body exercise segments and most of the upper-body exercise segments.

A repeated-measures ANOVA was performed to determine whether CO exposure increased the incidence of either clinical or subclinical ischemia. No significant effect was found for lower-body treadmill exercise nor for upper-body hand-crank exercise.

Effects of CO exposure on cardiac rhythm

The effects of carbon monoxide exposure on cardiac rhythm were assessed by tallying ventricular ectopic beats (VEBs) (Tables 29 and 30) and premature atrial contractions (PACs) (Tables 31 and 32) for each subject by air or CO exposure segment. VEBs and PACs occurring during O_2 recovery were included in the maximal exposure segment (15% or 20% COHb).

Very few episodes of ventricular ectopy (premature ventricular contractions) were observed. Only 5 episodes were found during air exposure and 6 during CO exposure. Of these eleven episodes, 5 single-beat and 2 double-beat episodes occurred during lower-body treadmill exercise, and 3 single-beat and 1 double-beat episodes occurred during upper-body hand-crank exercise. A repeated-measures ANOVA was performed to determine whether CO exposure increased the rate of VEBs. No significant effect was found for either lower-body treadmill exercise or upper-body hand-crank exercise.

Episodes of premature atrial contractions were more frequent than ventricular ectopic beats, although the number of events remained very small. Subject #9 was the only individual with frequent PACs (Tables 31 and 32). Discounting events occurring during O_2 recovery, however, his rate of PACs was similar across air and CO exposure. Many of the PAC episodes occurred during O_2 recovery, long after the completion of maximal CO exposure as COHb was being reduced. A repeated-measures ANOVA was performed to determine whether CO exposure increased the rate of PACs. No significant effect was found for either lower-body treadmill exercise or upper-body hand-crank exercise.

Table 27. Summary of ECG myocardial ischemia analysis in lower-body treadmill exercise listed by subject and exposure segment. Positive ischemic responses (≥1mm ST-segment depression) and subclinical ischemic responses (<1mm ST-segment depression) are indicated.

Subject (#)	Air Exposure	Air Exposure	Air Exposure	5% CO Exposure	10% CO Exposure	15% CO Exposure	20% CO Exposure
4							
5							
7							
9	≥1mm	<1mm	<1mm	<1mm	<1mm	≥1mm	<1mm
10	<1mm						
11	<1mm						<1mm
12							
13	<1mm				<1mm	<1mm	<1mm
14	<1mm	<1mm	<1mm	<1mm	<1mm	<1mm	<1mm
15							
16			<1mm				<1mm
17	<1mm	<1mm	<1mm	<1mm	<1mm	<1mm	<1mm
18							
19							
20		<1mm		<1mm		<1mm	
21							

Table 28. Summary of ECG myocardial ischemia analysis in upper-body hand-crank exercise listed by subject and exposure segment. Positive ischemic responses (≥1mm ST-segment depression) and subclinical ischemic responses (<1mm ST-segment depression) are indicated.

Subject (#)	Air Exposure	Air Exposure	Air Exposure	5% CO Exposure	10% CO Exposure	15% CO Exposure	20% CO Exposure
4							
5							
7							
9		<1mm	≥1mm	<1mm	<1mm	≥1mm	<1mm
10							
11							
12							
13		<1mm		<1mm	<1mm	<1mm	<1mm
14						<1mm	<1mm
15							
16							
17						<1mm	
18							
19							
20		<1mm		<1mm		<1mm	
21							

Table 29. Summary of ECG rhythm analysis for lower-body treadmill exercise. Episodes of ventricular ectopic beats (VEBs) are listed by subject and exposure segment.

Subject (#)	Air Exposure	Air Exposure	Air Exposure	5% CO Exposure	10% CO Exposure	15% CO Exposure	20% CO Exposure
4							
5							
7		1: 3rdEx		2: 3rdEx		1: 3rdEx	
9	2: 3rdEx						
10							
11							
12							
13							
14	1: rec			1: 2ndEx			
15							
16						1: O_2 rec	
17							
18							
19							
20							
21							

Table 30. Summary of ECG rhythm analysis for upper-body hand-crank exercise. Episodes of ventricular ectopic beats (VEBs) are listed by subject and exposure segment.

Subject (#)	Air Exposure	Air Exposure	Air Exposure	5% CO Exposure	10% CO Exposure	15% CO Exposure	20% CO Exposure
4							
5							
7	2: 3rdEx						
9							
10							1: O_2 rec
11							
12			n/a		n/a		n/a
13							
14							
15							
16							
17							
18		1: 1stEx				1: O_2 rec	
19							
20							
21							

restEx: Rest (standing) exercise segment
1stEx: First exercise segment (4.6 METS / 2.6 METS)
2ndEx: Second exercise segment (7.0 METS / 3.6 METS)
3rdEx: Third exercise segment (10.2 METS / 4.9 METS)
rec: recovery phase after exercise
O_2 rec: subject receiving oxygen therapy
n/a: Failure of ambulatory ECG recorder

Table 31. Summary of ECG rhythm analysis for lower-body treadmill exercise. Episodes of premature atrial contractions (PACs) are listed by subject and exposure segment.

Subject (#)	Air Exposure	Air Exposure	Air Exposure	5% CO Exposure	10% CO Exposure	15% CO Exposure	20% CO Exposure
4	2: preEx		2: preEx		1: preEx	2: O_2 rec	2: O_2 rec
5							
7							
9	2: preEx 1: restEx 2: 1stEx 3: 2ndEx 24: 3rdEx 11: rec	16: preEx 1: restEx 18: 1stEx 12: 2ndEx 7: 3rdEx 21: rec	6: preEx 5: restEx 1: 1stEx 0: 2ndEx 2: 3rdEx 15: rec	4: preEx 2: restEx 7: 1stEx 8: 2ndEx 2: 3rdEx 22: rec	11: preEx 5: restEx 0: 1stEx 0: 2ndEx 2: 3rdEx 20: rec	3: preEx 2: restEx 14: 1stEx 19: 2ndEx 11: 3rdEx 9: rec 52: O_2 rec	12: preEx 0: restEx 0: 1stEx 0: 2ndEx 7: 3rdEx 25: rec 83:O_2 rec
10							
11	1: 3rdEx				1: 2nd rec		
12			2: preEx		2: preEx		2: O_2 rec
13					1: preEx	1: O_2 rec	
14							
15							
16	1: 3rdEx				1: preEx		
17							2: O_2 rec
18							
19							
20							2: O_2 rec
21				1: rec			1: O_2 rec

pre-Ex: Pre-exercise
restEx: Rest (standing) exercise segment
1stEx: First exercise level (4.6 METS)
2ndEx: Second exercise level (7.0 METS)
3rdEx: Third exercise level (10.2 METS)
rec: Recovery phase after exercise
O_2 rec: Subject receiving Oxygen therapy

Table 32. Summary of ECG rhythm analysis for upper-body hand-crank exercise. Episodes of premature atrial contractions (PACs) are listed by subject and exposure segment.

Subject (#)	Air Exposure	Air Exposure	Air Exposure	5% CO Exposure	10% CO Exposure	15% CO Exposure	20% CO Exposure
4	2: 3rdEx						
5							
7	1: rec						
9	2: 1stEx 1:2ndEx 10: rec	23:preEx 8: restEx 2: 1stEx 7: 2ndEx 19: 3rdEx 10: rec	14:preEx 4: restEx 0: 1stEx 11: 2ndEx 18: 3rdEx 25: rec	18:preEx 5: restEx 0: 1stEx 2: 2ndEx 4: 3rdEx 18: rec	12:preEx 2: restEx 1: 1stEx 12: 2ndEx 13: 3rdEx 14: rec	12:preEx 8: restEx 2: 1stEx 5: 2ndEx 10: 3rdEx 8:rec 63: O_2 rec	2:preEx 0: restEx 0: 1stEx 6: 2ndEx 15: 3rdEx 21: rec 39:O_2 rec
10							3: O_2 rec
11							1: O_2 rec
12			n/a		n/a		n/a
13							
14							4: O_2 rec
15						1: O_2 rec	
16							
17							
18			8: preEx			1:restEx 1: O_2 rec	
19	1:preEx						1:1stEx
20						2:rest 61: O_2 rec	9: O_2 rec
21							

preEx: Pre-exercise
restEx: Rest (sitting) exercise segment
1stEx: First exercise level (2.6 METS)
2ndEx: Second exercise level (3.6 METS)
3rdEx: Third exercise level (4.9 METS)
rec: Recovery phase after exercise
O_2 rec: Subject receiving Oxygen therapy
n/a: Failure of ambulatory ECG recorder

2.5.6 Modeling Cardiac Responses to CO Exposure and Exercise

Further analyses were conducted to determine whether a global model can be used to predict a particular output measure based upon COHb and exercise levels, or whether separate models are required for different subjects. In a global or fixed effects model, the coefficients are constant for all individuals, whereas in an individual or random effects model, some or all of the coefficients vary across individuals. A simple model with one independent variable can be used to illustrate this.

Let Y_{ij} denote the output measure for observation j of individual i, let X_{ij} denote the independent variable value for observation j for individual i, and let e_{ij} denote the random error term. The model for the ith individual can be written as

$$\begin{aligned} Y_{ij} &= A_{0i} + A_{1i}X_{ij} + e_{ij} \\ &= (A_0 + D_{0i}) + (A_1 + D_{1i})\, X_{ij} + e_{ij} \\ &= (A_0 + A_1X_{ij}) + (D_{0i} + D_{1i}X_{ij}) + e_{ij} \\ &= \text{(fixed effects)} + \text{(random effects)}. \end{aligned}$$

In the above, A_0 and A_1 (without the i subscripts) represent the global parameters and the D_{0i} and D_{1i} coefficients represent the individual's deviations from the global coefficients. The hypotheses of interest can be expressed as:

H0: A_{0i} are equal for all i OR H0: $D_{0i} = 0$ for all i.
H0: A_{1i} are equal for all i OR H0: $D_{1i} = 0$ for all i.

If the random effects coefficients are not significant, then the model reduces to a global model containing only coefficients for fixed effects across all individuals.

The actual data used in this analysis included five different output measures (RATE, S.V., C.O., ACCEL, and TZPEAK), two independent variables (COHb and exercise level), and two different types of exercise (hand-crank vs. treadmill). If we denote Y_i as a particular outcome measure for subject i performing a particular type of exercise, and X_1 as the measured COHb level, and X_2 as the nominal exercise level, then an initial model is the second-order response surface model (subscript j has been suppressed on the Xs):

$$\begin{aligned} Y_{ij} &= A_{0i} + A_{1i}X_{1i} + A_{2i}X_{2i} + A_{11i}(X_{1i})^2 + A_{22i}(X_{2i})^2 + A_{12i}X_{1i}X_{2i} + e_{ij} \\ &= [A_0 + A_1X_{1i} + A_2X_{2i} + A_{11}(X_{1i})^2 + A_{22}(X_{2i})^2 + A_{12}X_{1i}X_{2i}] + \\ &\quad [D_{0i} + D_{1i}X_{1i} + D_{2i}X_{2i} + D_{11i}(X_{1i})^2 + D_{22i}(X_{2i})^2 + D_{12i}X_{1i}X_{2i}] + e_{ij}. \end{aligned}$$

This model allows separate coefficients for individuals on all linear and quadratic terms as well as a separate intercept. Use of an ordinary multiple regression algorithm (e.g. SAS procedure GLM) to estimate the parameters will produce the same estimates as if a separate model were fit to each individual's data. However, the test statistics for testing significance of the D parameters are based on the pooled residual variance across all individuals.

A limitation in this model is that it treats each individual's data points as if they were independent observations when actually they are repeated measures on the same individual. This limitation was not considered to be a major problem, and BMDP random effects software was used to confirm the results obtained from the above model for selected output measures. The BMDP analyses were limited by the small number of subjects with data (16 with hand-crank data and 15 with treadmill data), and were only able to treat the intercept and linear terms as random effects.

The data analyzed for each individual is illustrated in Table 33. Separate databases were maintained for the hand-crank and treadmill data, and each database contained the five output measurements collected over three days with five nominal levels of COHb and four nominal levels of exercise within each COHb level. Actual values of COHb levels were used in the analysis rather than the nominal values. Three different dependent variables were analyzed for each output measure as follows:

Y = output measure for CO, ACCEL, RATE, SV and TZPEAK (28 observations per individual),

ΔY = difference in output measure from rest condition (21 observations per individual), and

$\Delta_{AE}Y$ = difference in output measure from air exposures segment (16 observations per individual).

The basic analytical approach for each dependent variable involved running the full model on all the data, examining the residuals for outliers, and deleting data accordingly. After the outliers were removed, the higher order random effects in the model were tested for significance and the model was reduced whenever possible. The objective was to obtain the lowest order model which would relate the observed values of the dependent variables to the levels of COHb and exercise.

Table 34 presents a summary of the results obtained for the quadratic and interaction random effects terms for the three dependent variables. With the exception of the $\Delta_{AE}Y$ for RATE, at least one of the random effects coefficients is significant at the .10 level for all of the models. These results indicate that a global model without individual coefficients cannot be used to predict the output measures based upon this data. BMDP random effects models were run on Y and $\Delta_{AE}Y$ for ACCEL, and the results indicate a positive variance component associated with the linear terms of COHb and exercise. Although the BMDP models could not test the higher order random terms, these results confirm the conclusion that individual-specific models must be used to characterize this data.

Table 33. Sample data analyzed in random effects model for each individual.

COHb Level*	Exercise Level**	Y (28 obs.)	ΔY (21 obs.)	Δ_{AE}Y (16 obs.)
0	Rest	Y1		
0	1st Ex	Y2	ΔY1=Y2-Y1	
0	2nd Ex	Y3	ΔY2=Y3-Y1	
0	3rd Ex	Y4	ΔY3=Y4-Y1	
0	Rest	Y5		
0	1st Ex	Y6	ΔY4=Y6-Y5	
0	2nd Ex	Y7	ΔY5=Y7-Y5	
0	3rd Ex	Y8	ΔY6=Y8-Y5	
5	Rest	Y9		Δ_{AE}Y1=Y9-(Y5+Y17)/2
5	1st Ex	Y10	ΔY7=Y10-Y9	Δ_{AE}Y2=Y10-(Y6+Y18)/2
5	2nd Ex	Y11	ΔY8=Y11-Y9	Δ_{AE}Y3=Y11-(Y7+Y19)/2
5	3rd Ex	Y12	ΔY9=Y12-Y9	Δ_{AE}Y4=Y12-(Y8+Y20)/2
15	Rest	Y13		Δ_{AE}Y5=Y13-(Y5+Y17)/2
15	1st Ex	Y14	ΔY10=Y14-Y13	Δ_{AE}Y6=Y14-(Y6+Y18)/2
15	2nd Ex	Y15	ΔY11=Y15-Y13	Δ_{AE}Y7=Y15-(Y7+Y19)/2
15	3rd Ex	Y16	ΔY12=Y16-Y13	Δ_{AE}Y8=Y16-(Y8+Y20)/2
0	Rest	Y17		
0	1st Ex	Y18	ΔY13=Y18-Y17	
0	2nd Ex	Y19	ΔY14=Y19-Y17	
0	3rd Ex	Y20	ΔY15=Y20-Y17	
10	Rest	Y21		Δ_{AE}Y9=Y21-(Y5+Y17)/2
10	1st Ex	Y22	ΔY16=Y22-Y21	Δ_{AE}Y10=Y22-(Y6+Y18)/2
10	2nd Ex	Y23	ΔY17=Y23-Y21	Δ_{AE}Y11=Y23-(Y7+Y19)/2
10	3rd Ex	Y24	ΔY18=Y24-Y21	Δ_{AE}Y12=Y24-(Y8+Y20)/2
20	Rest	Y25		Δ_{AE}Y13=Y25-(Y5+Y17)/2
20	1st Ex	Y26	ΔY19=Y26-Y25	Δ_{AE}Y14=Y26-(Y6+Y18)/2
20	2nd Ex	Y27	ΔY20=Y27-Y25	Δ_{AE}Y15=Y27-(Y7+Y19)/2
20	3rd Ex	Y28	ΔY21=Y28-Y25	Δ_{AE}Y16=Y28-(Y8+Y20)/2

* Actual measured COHb levels were used in the analysis.

** Exercise levels in METS (Treadmill/Hand-crank):
Rest: Standing/Sitting at rest (1.0 METS)
1st Ex: First exercise segment (4.6 METS / 2.6 METS)
2nd Ex: Second exercise segment (7.0 METS / 3.6 METS)
3rd Ex: Third exercise segment (10.2 METS / 4.9 METS)

Table 34. Significance levels for higher order random effects coefficients.

Dependent Variable	Hypothesis	RATE	S.V.	C.O.	ACCEL	TZPEAK
Y*	$D_{12i} = 0$, all i				H	
	$D_{11i} = 0$, all i		T	T		H
	$D_{22i} = 0$, all i	H, T	T	T	H, T	
ΔY	$D_{12i} = 0$, all i				H, T	H, T
	$D_{11i} = 0$, all i	H	H, T	H, T	H, T	
	$D_{22i} = 0$, all i					
Δ_{AE}Y**	$D_{12i} = 0$, all i				H	
	$D_{11i} = 0$, all i		T	T		H, T
	$D_{22i} = 0$, all i		H, T		H, T	

H = Hand-crank exercise coefficients significant at 0.10 level.
T = Treadmill exercise coefficients significant at 0.10 level.

* For hand-crank exercise, data for subject #13 excluded from analysis.

** For hand-crank exercise, data for subject #13 excluded from analysis.
For treadmill exercise, data for subject #7 excluded from analysis,
and Δ_{AE}Y15 for ACCEL and Δ_{AE}Y6 for TZPEAK set to missing for subject #16.

2.6 Discussion

The goal of this study was to demonstrate whether or not CO plus exercise can elicit measurable changes in the impedance cardiogram (ICG) in a pilot experiment. The experiment results presented in Section 2.5 strongly support the achievement of this goal. Furthermore, the results permit an analysis of the experiment hypotheses as stated in Section 1.3, particularly with regard to the comparative effects of CO exposure on upper-body and lower-body exercise.

Hypothesis 1: Cardiac contractility (i.e., ICG acceleration) exhibits a dose-response relationship to carbon monoxide exposure during exercise.

This study is the first to report on the effects of CO exposure on cardiac contractility during exercise in humans. Stewart et al. (1973) commented on preejection period as a measure of cardiac contractility at rest, but presented no statistical results. He reported that no general increase in contractility was found at rest after CO exposure, however, one subject had a 28% decrease in preejection time (i.e., increased contractility) that was reportedly associated with a precordial pounding sensation.

The primary cardiac contractility measurement in this study was the ICG-derived aortic blood acceleration. The relationship of the ICG acceleration to aortic blood acceleration (by Doppler echocardiography) has been validated in a previous study (Kizakevich et al., 1993a). A secondary measure of contractility reported was the time-to-peak ejection velocity (TZMAX). TZMAX correlates well with time-to-peak Doppler velocity, time-to-peak Doppler velocity acceleration (Kizakevich et al., 1993a), and time-to-peak left ventricular dP/dt (Mohapatra, 1981).

For both lower-body and upper-body exercise, cardiac contractility was increased slightly at rest and substantially in exercise after CO exposure. Upper-body exercise resulted in lower acceleration values throughout exercise and a lesser increase in exercise response after CO exposure than lower-body exercise. Overall ICG acceleration increased during treadmill segments by about 5, 10, 17, and 26 % and hand-crank segments by about 3, 9, 13, and 21% for nominal COHb levels of 5, 10, 15, and 20%. At almost every level of exercise, increasing COHb resulted in an increased ICG acceleration response, thus supporting the hypothesis of a dose-response relationship. Since individual differences in higher-order coefficients (Table 34) could not be resolved, however, a general (i.e., subject-independent) dose-response model could not be developed from these data.

Changes in contractility were not reflected in the TZMAX measure for lower-body exercise below 15% COHb. During upper-body exercise, mean decreases in TZMAX (increases in contractility) were observed throughout all levels of CO exposure and exercise, however, these changes were not statistically significant below 15% COHb. At equivalent exercise levels (~5 METS), TZMAX was shorter for hand-crank than for treadmill exercise, while heart rate, ventilation, and O_2 consumption were considerably higher. These differences support the concept that upper-body work is less efficient than lower-body work.

Although ICG acceleration was substantially enhanced after CO exposure at each level of exercise, the effect relative to air exposure was diminished at the highest level of treadmill exercise for 14.8% and 19.2% COHb. Reflecting this effect, TZMAX increased slightly at for 14.8% and 19.2% COHb in treadmill exercise relative to air exposure. In contrast, only TZMAX was negatively affected by increasing COHb at any level of hand-crank exercise, increasing slightly at 5 METS relative to air exposure. The differences in acceleration response trends (especially relative to air exposure) may have been due to the extremely high acceleration levels in attained during treadmill exercise.

It is unclear, therefore, whether the reduced ability to increase ICG acceleration over the air exposure during treadmill exercise was due to a direct effect of CO on cardiac contractility, reduced oxygen delivery, or intrinsic limitations of cardiac muscle performance. To resolve this question, maximal exercise stress tests would have to be done using the same individuals to determine their maximum acceleration capacity. Furthermore, additional CO studies at even higher levels (>20%COHb) might help elucidate whether CO has a direct limiting effect.

Hypothesis 2: Cardiac output exhibits a dose-response relationship to carbon monoxide exposure during exercise.

Cardiac output was determined noninvasively using an empirical formula relating pulsatile changes in thoracic electrical impedance (i.e., impedance cardiogram (ICG)) to changes in aortic geometry associated with cardiac ejection (Kubicek et al., 1966). The relationship of the ICG-derived cardiac output to invasive measurements (e.g., green dye and thermal dilution) has been validated in a many studies (Mohapatra, 1981; Demeter et al., 1988; Sherwood, 1993). For healthy, young subjects (like the CO study population), correlation of ICG and invasive cardiac output measurements range from 0.75 to 0.95, with the higher correlations generally occurring with exercise. ICG cardiac output estimates have an accuracy within 20% of true cardiac output, however, changes in ICG are believed to be considerably more accurate (Handelsman, 1989).

For both lower-body and upper-body exercise, cardiac output showed no difference at rest or in exercise at 5% COHb. For COHb≥10%, mean cardiac outputs increased with increasing CO exposure, however, these changes were not statistically significant in treadmill exercise. This lack of effect was likely do to the higher variability of cardiac output measurements in treadmill (Table 16) than in hand-crank (Table 26) exercise. After adjustment to the air exposure, however, cardiac output presented a more consistent, albeit nonlinear, CO response (Figures 10 and 19). Overall cardiac output increased during treadmill segments by about 8, 7, and 15 % and hand-crank segments by about 8, 7, and 17% for nominal COHb levels of 10, 15, and 20%.

The variability of CO responses are consistent with previously reported results (Penney, 1988). In resting subjects, Ayres et al. (1965) found no change in cardiac output at 5% and 10% COHb, while Vogel and Gleser (1972) found no change at 19% COHb. Other studies at rest found increases in cardiac output at 5%, 33%, and 48% COHb (Ayres et al., 1969; Asmussen and Chiodi, 1941; Chiodi et al. 1941), and were shown to be linearly related to COHb saturation (Stewart et al., 1973). In exercising subjects, Vogel and Gleser (1972) observed increased cardiac outputs after CO exposure.

In the present study, increasing COHb resulted in an augmented cardiac output at almost every level of exercise. Although these results support the hypothesis of a dose-response relationship, the lack of effect at rest and for COHb<10% would suggest a nonlinear, threshold model. Unfortunately, as with the ICG acceleration, individual differences in higher-order model coefficients (Table 34) could not be resolved and a general (subject-independent) dose-response model could not be developed.

Hypothesis 3: Short-term CO exposure resulting in 5-20% COHb does not induce pathological changes in ECG rhythm or waveshape in normal subjects.

Changes in ECG rhythm were assessed by tallying ventricular ectopic beats (VEBs) and premature atrial contractions (PACs) for each subject by air or CO exposure segment. The incidence of ventricular ectopy was extremely low, with only 14 premature beats observed throughout the experiment. Furthermore, no increase in frequency of resting or exercise-induced ventricular ectopy or PACs was observed after CO exposure. These findings are in accordance with exercise studies in coronary artery disease patients with no baseline ectopy (Hinderliter et al., 1989).

The effects of carbon monoxide exposure on myocardial ischemia were assessed by beat-by-beat analysis of ECG ST-segment depression. Clinical or subclinical evidence of myocardial ischemia was observed on at least one experiment day in eight of the sixteen subjects. Positive ischemic responses were observed in one subject only, occurring during both air and CO exposures and for both lower-body and upper-body exercise. All of the eight subjects had subclinical (<1mm) ST-segment depression during both air and CO exposures.

Only one study reports on ECG changes and myocardial ischemia after CO exposure in healthy men (Davies and Smith, 1980). In this experiment, marked ST-segment depression was observed in only one of 16 subjects at 2.5% COHb. None of the 15 subjects reaching 7.1% COHb presented evidence of myocardial ischemia. Other ECG findings were observed in these groups, including unequivocal P-wave changes in three of 16 subjects at 2.4% COHb and in six of 15 subjects at 7.1% COHb.

The results of the present study support the hypothesis that short-term CO exposure resulting in 5-20% COHb does not induce pathological changes in ECG rhythm or waveshape in normal subjects.

3.0 CONCLUSIONS

3.1 Significance

The completion of this research has resulted in new knowledge and benefits for both the military and civilian scientific communities. This investigation of the effects of carbon monoxide exposure on exercise combined both lower-body treadmill and upper-body hand-crank in an integrated study involving the same subjects for both types of exercise. While upper-body exercise is known to be less efficient, comparative analysis of the effects of CO exposure on upper and lower-body exercise had not been previously reported. Since CO exposure is not limited to persons performing lower-body exercise, better understanding of the effects on upper-body work is needed. This is specifically relevant for military personnel in vehicular weapons system (e.g., tanks, armored personnel carriers, air planes) who perform a variety of tasks in the sitting position while receiving CO exposures.

The primary conclusion of this study is that young, apparently healthy males (of military age) can perform submaximal upper and lower-body exercise without adverse health effects after CO exposures attaining 20% COHb. The experimental data also show that the cardiovascular system compensates for the reduced oxygen-carrying capacity of the blood by augmenting heart rate, cardiac contractility, and cardiac output for both upper-body and lower-body exercise. While this mechanism serves well in submaximal exercise, the enhanced cardiovascular response to exercise is not without physiological costs. The enhanced response begins to fail at higher levels of CO exposure and exercise, and although not tested in this study, must ultimately result in reduced maximal exercise capacity.

Another significant outcome of the study is the demonstrated utility of impedance cardiography for noninvasive assessment of cardiac function in environmental research. Although impedance cardiography has been an available research tool for almost 30 years, its application in the clinical and research environments has been limited by inadequate signal processing and waveform analysis techniques. Impedance cardiography technology developed at Research Triangle Institute (Kizakevich et al., 1989; 1993a; 1993b) was used to perform automatic waveform analysis at 60-second intervals across the CO study data sets at rest and during exercise (Section 2.4.2). These new methods facilitated the acquisition of cardiac hemodynamic data which could not otherwise be obtained in exercising subjects outside of the clinical cardiology laboratory. Moreover, since impedance cardiography systems have been developed for ambulatory applications (Kizakevich et al., 1993), the foundation is set for clinical and military acquisition of cardiac hemodynamic data in the field.

3.2 Suggestions for Future Work

Experience in this study leads to the following suggestions for future work:

- Replication of the study in women, with modification of the experiment design to investigate the effects of changes in blood volume and red cell volume associated with the menstrual cycle.
- Extend the range of CO exposures to attain 25%-30% COHb.
- Study the effects of varying inhalation rates of CO exposure on cardiac hemodynamics. For example, reach 10%, 15%, and 20% COHb in 2, 6, or 10 minutes.
- Evaluate behavioral performance (e.g., tracking task, cognitive skills) at 10%, 15% and 20% COHb shortly after high-submaximal upper-body and lower-body exercise.

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