EFFECTS OF SHORT-TERM EXPOSURE TO CARBON MONOXIDE IN SUBJECTS WITH CORONARY ARTERY DISEASE

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Twenty-six non-smoking male subjects with stable angina pectoris were studied to determine is exposing them to carbon monoxide would reduce their ability to exercise. On two separate days, subjects were exposed to either carbon monoxide (100 ppm) or to clean air in a random crossover, double blind protocol. The exposures to carbon monoxide elevated carboxyhemoglobin levels in the subjects to approximately 3%. After exposure, the subjects performed an incremental exercise stress test on a cycle ergometer until the point at which they noted the onset of angina.

The time required before the onset of angina was significantly less in subjects exercising after exposure to carbon monoxide. These results indicate that carbon monoxide exposures reduces the exercise tolerance in people with angina even at the relatively low exposure levels achieved in this study.

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Disclaimer

The statements and conclusions in this report are those of the contractor and not necessarily those of the California Air Resources Board. The mention of commercial products, their source or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products.

Summary and Conclusions

Current air quality standards for CO are based on findings of neurobehavioral effects in subjects exposed to CO in which carboxyhemoglobin (COHb) levels (percent saturation of hemoglobin by CO) was increased about 2% above baseline levels, which are normally in the range of 1 to 2% COHb for non-smoking people in urban areas. Some evidence indicated that carboxyhemoglobin concentrations in the 3% to 5% of saturation range can affect an individuals ability to detect small changes in his/her environment (vigilance) and may reduce reaction time slightly. These findings have not proven to be reproducible at COHb levels below 5%. Later studies, however, identified persons with angina and other cardiovascular diseases as the groups at greatest risk from low-level ambient exposures. Studies of the provocation of anginal pain by CO exposure in subjects with stable angina pectoris indicated that effects could be seen at levels of about 2% to 3% COHb saturation (Aronow et al. 1981; Anderson et al. 1973). The veracity of the Aronow data has been questioned and thus the data base upon which CO air quality standards are founded has been substantially weakened. We therefore undertook to study the effects of low-level CO exposure on a group of individuals with ischemic heart disease characterized by stable, exercise-induced angina pectoris. The study was not an exact replication of previous studies; the design was to confirm subjective measures, such as time to angina onset, with more objective measures of exercise tolerance.

Twenty-six non-smoking male subjects with stable angina pectoris were studied on two separate days, to determine if exposure to carbon monoxide reduced their ability to exercise, compared to clean air. The exercise protocol was similar to that reported by Aronow (1981). In the present study, the exposure levels were higher and subjects did not perform exercise tests before exposure to clean air or CO; only post-exposure tests were done. Subjects were exposed for one hour, in a random crossover, double blind protocol, to either carbon monoxide (CO, 100 ppm) or to clean air. The CO exposure was designed to raise COHb to about 3% of saturation. Subjects performed an incremental exercise stress test on a cycle ergometer until the point at which they noted the onset of angina. All of the subjects in this study were able to exercise to the point of onset of angina. None exhibited ECG changes or other symptoms of a magnitude sufficient for exercise to be stopped by the cardiologist administering the test. During exercise, work rates were increased by 25 watts at 3 minute intervals; the initial

work rate was 50 watts. Carboxyhemoglobin was measured before exposure to clean air or CO, after exposure, and after exercise.

Measurements of minute ventilation, oxygen uptake, carbon dioxide output and respiratory quotient (R) were made, averaged over 30 second intervals and updated on a minute-by-minute basis. Heart rate and blood pressure were monitored during the last 30 seconds of each 3 minute exercise period. The time to onset of angina and the duration of angina were also recorded.

Carbon monoxide exposure reduces exercise tolerance in people with angina even at the relatively low exposure levels achieved in this study. For the study group, taken as a whole, the 1 hr exposure to CO (100 ppm) resulted in an increase of carboxyhemoglobin from 1.4% (after clean air) to 3.0% (after CO) (Table 4) and the time to onset of angina was reduced by 6.9%, from 6.50 min to 6.05 min, respectively (Table 5). The difference in time to angina was significant in a 1-tailed paired "t"-test ($p=0.032$). The mean duration of angina was increased by 6.8%, from 1.46 min to 1.56 min, but this difference was not significant. The CO-induced reductions in time to onset of angina found in this study are similar to those reported by Anderson, et al. (1973) and by Aronow and Isbell (1973) for subjects with COHb levels raised to about 3%. Parameters related to exercise and respiratory gas exchange also exhibited changes indicating that CO exposure reduced the ability of subjects to exercise, however the differences in mean values between clean air and CO exposures were not significantly different at the $p<0.05$ level. The data are summarized in Table 6. There was a negative correlation (Table 7) between a subject's body mass and the change in his time to onset of angina. There was also a negative correlation between the percent change in COHb following exposure and body mass; heavier subjects had lower increases in COHb. We therefore separately analyzed data for subjects whose body masses were within 3 standard errors of the mean body mass (ie. subjects with body masses <95 kg). The results for these 19 subjects of mass 95 kg and below are also shown in Tables 5 and 6. Carboxyhemoglobin levels were increased from 1.5% at baseline to 2.9% after the subjects breathed 100 ppm CO for 1 hour. The time to angina was reduced 11.3%, which was significant, statistically ($p = 0.002$). The duration of anginal pain was increased 10.0%. This change was not, however, statistically significant. The exercise data also showed decremental changes; the rate of oxygen uptake was reduced 3.2%, which was significant ($p=0.032$).

Subjects appeared to enter anaerobic metabolism earlier in exercise after CO. Figure 2 shows the respiratory exchange ratio (R) as a function of time during the exercise stress test. Respiratory exchange ratio tends to be higher on the CO day than on the clean air day during the exercise period. The value of R typically increases during exercise as the subject approaches the anaerobic threshold; in this study we observed that the increase in R begins earlier after CO exposure than after clean air. This indicates a more rapid onset of anaerobic metabolism in CO-exposed subjects.

The data obtained in this study are consistent with the hypothesis that CO exposure induces exercise-precipitated angina and reduces exercise tolerance; more research is needed to elucidate the mechanisms responsible.

Recommendations

The data presented here demonstrate that low-level exposure to CO can significantly reduce exercise tolerance in subjects with stable angina, at carboxyhemoglobin levels of about 3% of saturation. These findings are in agreement with those previously reported by Aronow and Isbell (1973) and Anderson et al. (1973). In addition, we have confirmed the more subjective measures such as time to angina and duration of angina with objective measures of exercise tolerance. We also noted that, in CO-exposed subjects, systolic blood pressure was substantially increased in those subjects who were able to achieve relatively high levels of exercise prior to the onset on angina, compared to clean air exposures.

This finding suggests that oxygen demands by peripheral muscle tissue under exercise stress combined with CO exposure may be met by increased blood flow at higher blood pressures, prior to the onset of angina, in these subjects with cardiovascular disease. In this study of relatively impaired individuals, very few were able to exercise for more than 7 minutes, the point at which the divergence is noticeable between the clean air and CO curves. It would be useful to study a group of less severely impacted people with coronary artery disease, who might be able to exercise longer than the group studied in this program. It would also be useful to obtain blood pressure readings at intervals more frequent than every 3 minutes.

General Background, Scope, and Purpose of the Project

Our understanding of the mechanisms by which CO exerts its influence on man's health is still incomplete. CO reversibly reacts with proteins, competing with oxygen for binding sites on hemoglobin and myoglobin molecules, thus compromising the ability of these proteins to transport oxygen. Relatively small decreases in hemoglobin oxygen-carrying ability resulting from 3% to 5% carboxyhemoglobin levels can apparently cause changes which can be measured by neurobehavioral testing methods and can also reduce an individual's exercise tolerance, or ability to perform work.

Initially, the National Ambient Air Quality Standard was established based upon neurobehavioral effects. Psychomotor performance, measured in terms of visual threshold (McFarland, et al. 1944), flicker fusion frequency (Lilienthal, et al. 1946), and time perception (Beard and Wertheim, 1966), were reported to be degraded at levels of CO exposure sufficient to elevate carboxyhemoglobin (COHb) levels in the blood to about 5%. Later attempts to validate results at CO exposure concentrations near ambient levels produced equivocal results, and the health effect basis for an ambient CO standard was shifted to findings of reduced exercise tolerance and inducement of anginal pain in subjects with coronary artery disease.

Exercise tolerance in healthy individuals was reported to be impaired after subjects breathed 100 ppm CO for one hour, increasing COHb from 1.7% at baseline to 3.95% after exposure, and decreasing mean exercise time to exhaustion from 11.63 minutes to 11.04 minutes (Aronow and Cassidy, 1975). Horvath, et al. (1975) also reported that CO exposure reduced exercise tolerance in healthy individuals; approximately 4.9% and 7.0% reductions were observed when COHb levels reached 3.3% and 4.3%, respectively.

Individuals with ischemic heart disease were found to be especially sensitive to the effects of CO. Aronow and Isbell (1973) reported that exposure to low levels of CO significantly reduced the ability of individuals with coronary artery disease to exercise. Subjects exposed to 50 ppm CO for two hours increased their COHb levels from a baseline of 1.0% to a level of 2.7% and the time of onset of exercise-induced angina pectoris was shortened from 3.74 minutes (observed

after subjects breathed clean air) to 3.13 minutes (observed after CO exposure). A study by Anderson, et al. (1973) showed a decreased exercise tolerance in persons with stable angina pectoris following exposure to CO sufficient to cause a mean increase in COHb of 1.6%. While these data indicated a consistant pattern of adverse health effects induced by low-level CO exposure, the quality of the data reported by Aronow and his colleagues was questioned. An EPA review panel examined the available Aronow data base and found that, because records were inadequately kept, it was not possible to validate Aronow's findings, leaving the health-related basis for the ambient CO standard on less stable ground. We therefore undertook to study of the effects of low-level CO exposure on a group of sensitive individuals with cardiovascular disease. The study was not an exact replication of any of the previous studies; the design was to combine subjective measures, such as time to angina onset, with objective physiological measures related to changes in exercise tolerance.

Subjects with cardiovascular disease and stable angina were exposed to 100 ppm CO or to clean air in a double-blind protocol. The subjects exercised on a cycle ergometer until the start of angina pectoris. During exercise, and a subsequent 8 minute recovery period, measurements were made of respiratory gas exchange and ventilation rates. Objective endpoints of exercise tolerance, such as oxygen uptake and CO_2 expiration, were obtained in addition to time to onset of angina or duration of angina. Twenty six subjects were studied.

Methods

Subject Recruitment and Selection

Subjects with stable angina pectoris and without evidence of pulmonary disease or anemia were recruited for this study. Prospective subjects were identified from records at the VA Hospital in Long Beach, CA and from outpatient cardiology clinics at the University of California, Irvine's Medical Center in Orange, California. Subjects with previously diagnosed chronic lung diseases were not considered as candidates. Stable angina was defined as pain or discomfort in the area of the chest (with or without radiation to other areas), precipitated by exertion of more than usual effort and relieved by rest or sublingual nitroglycerine, and with no recent changes in frequency, duration, time of appearance or precipitating factors (Lee,1980). Subjects were required to be non-smoking for at least 6 months prior to study and to have pulmonary function in the range normal for individuals of their age, weight, height and sex.

Finding and recruiting suitable subjects was one of the most difficult facets of performing this study. About 450 prospective subjects were identified from their medical records or by physician referrals. Each potential subject was contacted and interviewed by telephone to determine if he matched our selection "profile." Of these 450, 54 candidates were identified and invited to participate in a laboratory screening test. A total of 26 volunteers participated in the study. Three of the subjects were non-smokers and the rest were ex-smokers for at least 6 months prior to study. The subjects' ages ranged from 49 to 66 years. All subjects provided informed consent before any laboratory procedures were undertaken (including screening tests).

As part of the laboratory screening process, the subject's heart rate, blood pressure and temperature were taken and the subject was asked to complete a questionnaire which elicited information relevant to the subject's health, smoking habits, living conditions, and other factors which might relate to the subject's exposure to CO in his own environment. Pulmonary function was tested using a water-sealed spirometer (Warren E. Collins, Inc.). Forced vital capacity (FVC), forced expiratory volume at 1.0 second ($FEV_{1.0}$), and the ratio $FEV_{1.0}$/FVC were determined. The mid-expiratory flow rate was also measured. Subjects with FVC's and $FEV_{1.0}$'s at 80% or more of those predicted (Morris, et al. 1971), for comparable individuals in good health, were candidates for this study.

A physician reviewed the medical history and performed a limited physical examination prior to exercise testing. The exercise stress test was monitored by a physician, and controlled by the same technician, in all cases. The screening test exercise protocol was the same as that followed for the exposure tests (described in detail in a later section).

Exposure Testing of Subjects

Each subject was assigned to one of two groups, at random, and tested on two occasions separated by an interval of one week. Each test consisted of an exposure followed by an exercise stress test. One of the groups received clean air first and CO second, while the order of exposure was reversed in the second group. Neither the subjects, nor the exercise physiology staff, were informed of the exposure atmosphere. This randomized crossover design was therefore performed in a "double blind" manner, which controlled for subjective biases on the parts of the subjects and the research staff, and additionally for objective bias such as order effects or training effects.

The protocol was designed to minimize the possible influence of confounding factors such as variations in the taking of medication, differences in subject's carbohydrate loading before exercise tests, and possible uncontrolled exposure to CO during transit to the laboratory on the two exposure test days. We therefore telephoned subjects on the evening prior to each exposure test and reminded them to take their medication on schedule and to record the time. The subjects were instructed not to eat anything in the morning (a light, standardized breakfast snack was provided at the laboratory). Subjects were picked up on the morning of a test and transported to the laboratory in a van equipped with a clean air "tent." This helped to minimize the effects of extraneous CO exposure even when the subject was driven in heavy traffic conditions. Concentrations of CO in the tent averaged about 2 to 3 ppm during transit.

Prior to exposure, each subject received a routine chest examination, his blood pressure and heart rate were checked, a resting ECG was obtained, and a series of pulmonary function tests was performed. The results were evaluated by a physician. Samples of blood and breath were collected and analyzed to determine the subject's baseline COHb level. If there were no contraindications to

proceeding with the exercise test, the subject was given a light snack (fruit, cheese, a muffin, and juice or other non-caffeinated beverage).

The subjects were exposed, at rest, to either clean air or CO (100 ppm) for one hour. At the end of the exposure period, a second resting ECG, blood, and breath samples were obtained to evaluate the post-exposure COHb level, and the subject performed an exercise stress test, as described below.

All data were stored in a computer data base for subsequent statistical analyses. The double blind character of the study was preserved by coding the atmosphere as either A or B (neither of which was identified as to composition) and by withholding the results of the blood and breath sample analyses until the study was completed.

Atmosphere Generation and Exposure System

Carbon monoxide (1% in air) was metered from a cylinder of compressed gas into a flow of clean, HEPA filtered air. The gases were mixed in a chamber and delivered to a low-deadspace respiratory mask at atmospheric pressure. The mask was fitted with one-way valves to separate inspiratory and expiratory flows. Excess exposure atmosphere and expired gases were vented to a fume hood and exhausted from the room. CO concentrations in the inspired air were monitored continuously during exposure from a point upstream of the mask. Exposures were performed at rest; subjects read, watched TV, or reclined. Subjects were requested to stay awake during the exposure period, and technicians roused any subjects that appeared to be drowsing.

Atmosphere Monitoring

Carbon monoxide concentrations were monitored using an infrared absorption spectrophotometric method (Dasibi Model 3003). The monitor was calibrated daily against gas mixtures of known, certified CO concentrations. Monthly quality assurance assays were performed by the California Air Resources Board personnel, using standards traceable to the National Bureau of Standards. Breath samples were analyzed using an electrochemical detector (Ecolyzer) which was calibrated in a manner similar to that described above.

Exercise Testing

Subjects performed an exercise stress test similar to that described by Aronow (1981). Subjects were seated on an electomagnetically-braked cycle ergometer, a low-deadspace respiratory mask was fitted carefully over their nose and mouth, the mask's seal was tested to eliminate leaks, and the subject was instructed to breathe quietly and normally. Respiratory gases were monitored continuously; oxygen by an electrochemical detector and carbon dioxide by an infrared analyzer. These gas monitors were calibrated daily against gas mixtures of known, certified composition. The mixtures were also checked, independently, against a mass spectrometer which had been calibrated against certified, gravimetrically prepared, gas standards. Expired gas flow was monitored on a breath-by-breath basis using a turbine pneumotachometer. The data from the gas analyzers and the pneumotachometer were acquired by a microcomputer (Commodore Model 1032) interfaced with an analog to digital converter. The computer provided "real-time" measurements of minute ventilation, oxygen uptake, and carbon dioxide output, and also computed average values which were updated every 30 seconds. Electrocardiographic tracings (ECG) were taken during the last 30 seconds of each one minute exercise period. Tracings were evaluated to quantify the numbers of abnormal beats (preventricular contractions [PVC's]), changes in ST segments and T-waves, and to accurately count the heart rate. Blood pressure was taken during the last minute of each 3 minute work level increment, and at three minute intervals during the recovery phase.

The exercise test consisted of three segments; the warmup period (5 minutes), the stress test (to the point of onset of angina pectoris or stopped if other symptoms of ischemia were noted by the physician monitoring the ECG), and the recovery period (8 minutes). The five minute warmup allowed the subject to become acclimated to the test facility, and also allowed the gas sampling instrumentation time to reach equilibrium. At the end of 5 minutes the subject was told to pedal the ergometer at 60 RPM (indicated by a meter in the subject's view). The work rate was started at zero load to allow the subject to reach his stride, and then increased to 50 watts. The work rate was increased by 25 watt increments each 3 minutes until the termination of the test by the subject at the start of his angina. One subject, who developed angina after his CO exposure, did not have angina on the clean air day and terminated his test at the point of exhaustion. This subject was not included in the study. None of the tests were

stopped by the physician for reasons other than onset of angina. The time to angina was recorded and the subject was told to remain on the cycle and to indicate when the pain went away. Blood pressure, pulse rate, and respiratory gas exchange data were also recorded at the time of onset of angina. The duration of anginal pain was recorded. The subject remained on the cycle throughout the 8 minute recovery period; ECG, blood pressure, and respiratory gas data were recorded, as described above. Following completion of the exercise test, blood and expired gas samples were obtained, for later analysis for COHb and expired CO, respectively.

Analysis of Carboxyhemoglobin in Blood

Venous blood samples were collected three times on each of the exposure test days; on arrival at the laboratory before exposure (to obtain baseline data, and to verify that the subject had not been smoking recently), after the 1 hour exposure, and after exercise. The blood samples were placed on a rotary mixer until they were analyzed. An IL282 CO-Oximeter (Instrumentation Laboratories) was used to determine concentrations of total hemoglobin, oxyhemoglobin, carboxyhemoglobin (COHb), methemoglobin, and the volume percent of oxygen in blood. The CO-Oximeter was calibrated daily against standards obtained from Fisher Scientific. These standards consisted of dye solutions with colligative properties similar to human blood and with light absorption characteristics similar to hemoglobin.

Interlaboratory Comparison Tests

There has been controversy regarding the applicability of the IL282 CO-Oximeter to the measurement of blood carboxyhemoglobin levels below 5%. The method that is best accepted for low-level COHb concentrations is the gas chromatographic (GC) technique described by Horvath and Dahms (1967). With the cooperation of the Health Effects Institute, and with Dr. Dahms' reference laboratory in St. Louis, we have participated in an interlaboratory comparison program in which blood samples prepared and analyzed by GC and IL282 in Dr. Dahms' laboratory are shipped to our laboratory for analysis. The samples are submitted without identification (blind) and the results are returned to St. Louis for decoding. Our IL282 results compared well with those of the reference lab;

concentrations of the check samples ranged from 0.6% to 8% COHb. The average deviation from the reference lab IL282 values was 0.08% COHb with a standard error of 0.077% COHb. While the IL282 data were apparently higher than those observed by the GC method, the bias appeared to be relatively constant.

Breath Sampling and Analysis for CO

As an independent measure of the COHb level in subjects, before exposure, after exposure, and after exercise, breath samples were obtained and analyzed using an Ecolyzer CO analyzer. Subjects were instructed to take a deep breath and to hold that breath for 20 seconds. The subject was then told to breathe out about half his lung volume (to clear the respiratory system deadspace) and then blow the rest into a plastic sampling bag. The breath samples were usually analyzed within 5 hours of collection. Standard gas samples kept in the bags for two days showed no appreciable decay.

Statistical Analyses

All of the data collected were organized in a computer data base using the University of California, Irvine Honeywell CP-6 facility. The mean values of respiratory and cardiovascular parameters for the 26 subjects were contrasted using one tailed paired "t"-tests and two factor analyses of variance (ANOVA) with repeated measures. The two factors analyzed were EXPOSURE (clean air or CO) and ORDER (clean air followed by CO; CO followed by clean air) Data for a subset of 19 subjects, with body weight less than 95 kg, were also analyzed using ANOVA with repeated measures. Statistical tests and data base manipulations were performed using the SPSS-X computer package.

Results

Subject Characteristics

The subjects' ages, weights and medications are summarized in Table 1. All of the subjects in the study were males with stable angina pectoris, as defined under Methods. The subjects' medications and dosage levels were constant for at least 3 months prior to screening. A medical history was obtained as part of the screening process. The subjects ranged in age from 49 to 66 years, with a mean age of 59 and a standard error (s.e.) of 1 year. The subjects ranged in weight from 69 kg to 114 kg with a mean of 89.6 kg and a s.e. of 2.5 kg. Seven of the 26 subjects (23.2%) were signficantly overweight, as defined by being more than 3 s.e. above the mean body weight in the range of about 95 to 115 kg.

The pattern of medication usage is summarized in Table 1. Most of the subjects received nitrates (73%) and/or beta-blocking drugs (58%) on a daily basis. Smaller percentages of the subjects took calcium channel blockers (38%), diuretics (31%), anti-arrhythmics (15%), potassium chloride (15%), anti-coagulents (11%), and vasodilators (8%). Other medications used include dyazide, alpha-methyl-DOPA, clonidine, allopurinol and insulin.

About 54% of the subjects had had an angina attack within three days prior to their initial screening study. The remaining subjects reported a range of from 4 days to more than 4 months since their last attack of angina. Seventeen of the subjects had had a myocardial infarction, ranging in time from 1 year to 13 years prior to this study. Nine of the subjects reported having had coronary bypass surgery.

The subjects presented a broad spectrum of angina symptoms. Most (22%) felt the pain in the anterior chest area, however some occasionally felt pain in other parts of their body. For example, 8 felt pain in the region of their jaw, neck or throat, 11 felt pain in their left arms, and 3 felt pain in their right arms. When asked to rate the severity of their angina, 14 reported that their angina was "mild," 10 reported "moderate" and 2 reported "severe."

Smoking History

Most of the subjects (18 out of 26) were ex-cigarette smokers, five were ex-pipe smokers, and 3 never smoked. The average cigarette-smoking subject had smoked 1.4 packs of cigarettes per day; for the group, the range was from 0.1

packs per day to about 3 packs per day. The subjects reported having smoked in the range of 4 and 40 years, and all had quit at least 8 months prior to our screening study.

Evaluation of Screening Data

Pulmonary Function

Subjects' pulmonary function data obtained during screening tests are summarized in Table 2. All of the subjects had pulmonary function values comparable for individuals of their sex, age and height. Forced vital capacity (FVC) was between 80 and 100% of that predicted for their age group; forced expiratory volume at 1.0 second ($FEV_{1.0}$) was also between 80 and 100%. The subjects reported no previous history of lung disease or of anemia.

Cardiovascular Data

All of the subjects selected to participate in the study received an exercise stress test and their respiratory and cardiovascular functions were evaluated. All subjects were able to exercise to some degree; their performance on the test was limited by the onset of angina. Those subjects who were unable to exercise to the point of angina because of other limitations, muscle fatigue or ventilatory problems, were not included in the study group. Cardiovascular data are summarized in Table 3. Carboxyhemoglobin levels in these subjects ranged from 0.3% to 2.6%, with a mean of 1.5% (Table 4). These values are reasonable for non-smoking individuals who live in an urban area.

Exercise Physiology

The subjects were quite diverse with respect to their ability to perform exercise. Most were able to exercise strenuously enough to cross their anaerobic threshold, the point at which the demand for oxygen exceeds the body's ability to absorb and transport it, resulting in a shift from aerobic (citric acid cycle) to anaerobic metabolic pathways in which muscle glycogen is converted to lactic acid (Fruton and Simmonds, 1961). The respiratory exchange ratio, R, at the point of onset of angina averaged 1.13 with a s.e. of 0.03; R values greater than 1.0 indicate that the rate of CO_2 elimination exceeds the rate of O_2 intake. The

average subject achieved a minute ventilation rate of 48.6 Lpm, equivalent to a moderate level of exercise. Subjects exercised for periods ranging from 2 to 10 minutes before the onset of angina, with a mean and s.e. of 6.45 ± 0.51 minutes.

Exposure of Subjects to CO

Subjects were exposed to CO (100 ppm) or clean, filtered air, while at rest, and wearing a respiratory mask. Exposures were controlled within ± 2% variation in CO concentration; the mean CO concentration was 100.5 ± 1.8 ppm. On clean air test days, the CO concentration averaged 2.0 ± 1.5 ppm.

The COHb levels (percent of saturation of hemoglobin by CO) in subjects after clean air and CO exposures are summarized in Table 4. Subjects averaged 1.4% COHb before CO exposure but rose to 3.0 ± 0.1% COHb after 1 hour exposure to 100 ppm CO. The subsequent exercise study was performed with the subjects breathing room air; their COHb levels dropped slightly to 2.8±0.1% during exercise. Carbon monoxide was not supplemented during exercise to maintain the COHb levels; subjects breathed room air which was less than 5 ppm CO

Effects of CO Exposure on Cardiovascular Responses

Data were obtained on 26 subjects; group means for clean air and CO exposure days were obtained for each subject on a minute-by-minute basis and at the angina point for the response variables. As shown in Table 5, the time to onset of angina was decreased by 6.9% following CO exposure and the duration of angina was increased by 6.8%, relative to clean air controls. These changes are in the direction of an adverse affect and the change in time to angina is significant (one-tailed paired "t") at the $p<0.05$ level. The change in duration is not statistically significant. The decrease in double product (2.4 %), indicating an average reduction of throughput of blood by the heart, was not statistically significant.

Seven of the subjects showed small depressions of the ST segment of their ECG's at the point of angina on both test days, and one subject showed ST segment depression only on the clean air day. The depressions averaged 0.4 ± 0.6 mm on both the clean air and CO exposure days. The differences were not significant. There were no significant changes in group mean heart rate or

systolic blood pressure at the angina point; heart rates averaged 105 ± 21 bpm and 104 ± 21 bpm, and blood pressure averaged 178 ± 24 mm Hg and 177 ± 27 mm Hg, for clean air and CO exposure days, respectively. None of the subjects exhibited preventricular contractions (PVC's) at the angina point.

Respiratory data measured at the angina point are summarized in Table 6. Minute ventilation (Lpm), oxygen uptake (Lpm) and CO_2 output (Lpm) were all decreased slightly. The differences were not significant for the entire group of 26 subjects, but the change in oxygen uptake (V_{O2}) was significant for the subset of 19 subjects with body weight less than 95 kg.

Some of the variables within the data set were strongly inter-related. We therefore explored the possibility of confounding influences in the data by examining the matrix of correlation coefficients. Key relationships are summarized in Table 7 for the "independent" variables age, weight, dosage of nitrate (NITRATE) medication, and for the "dependent" variables, the differences between the clean air day and CO exposure day values for time to angina (DELTTA), duration of angina (DELDA), carboxyhemoglobin level (DELCOHb), oxygen uptake rate ($DELVO_2$), and respiratory exchange ratio (DELR).

The strongest underlying relationship within the set of data was the correlation between weight and the difference in COHb (clean air - CO) among the subjects. The correlation coefficient is significant at the $p<0.01$ level, and indicates that heavier subjects tended to show smaller increases in COHb following their 1 hour exposure to 100 ppm CO than subjects of lesser weight. This finding can be partially explained by the fact that the volume of blood in an individual is directly proportional to his body mass (Dittman and Grebe, 1958). Since, for a given rate of CO intake, COHb concentration should be inversely proportional to blood volume, we might expect heavier subjects to achieve lower percent saturations of hemoglobin by CO, for a given exposure concentration and duration. The data may therefore suggest a causal relationship; the heavier subjects had lower COHb levels, hence they might also show less response due to CO on their time to angina. Examining the weights of the subjects it was observed that 7 of the 26 weighed 95 kg or more, and could be considered substantially overweight using the criterion that subjects should be within 3 standard errors of the mean subject population weight. The subject numbers for the overweight individuals are "flagged" in Tables 5 and 6 by the symbol '@'. Removal of the data for these 7

individuals from the means reduced the number of subjects in the more homogeneous subset to 19. The means for clean air and CO exposure days and the significance levels for one-tailed paired "t"-tests are shown in Tables 5 and 6, for the entire group of 26 subjects and for the sub-sample of 19 subjects with body masses less than 95 kg. The one-tailed test was used because the hypothesis being tested is that CO exposure reduces a subject's ability to exercise and because it is unlikely that CO will act to improve exercise tolerance. Thus, a one-tailed test is appropriate. The percent differences between clean air and CO exposure days, for all of the variables in Tables 5 and 6, changed in the direction indicating that exercise tolerance was reduced after CO, relative to clean air. This was true for the entire group; the sub-sample of 19 subjects with body masses <95 kg showed effects in the same direction but with greater magnitude, and with increased levels of statistical significance.

Exposure to carbon monoxide significantly reduced the time to onset of angina; 6.9% for the group as a whole ($p=0.032$) and 11.3% for the sub-sample of 19 individuals ($p=0.002$). Oxygen uptake, at the point of angina, was reduced 2.3% for the group as a whole ($p=0.063$) and 3.2% for the sub-sample ($p=0.032$). Percent differences for the other variables were not statistically significant at the $p=0.05$ level, but in general showed trends in the direction of decrement of function.

The group mean values for the 19 subjects for seven cardiopulmonary variables are summarized in Table 8. These data were used to test the hypothesis that exposure to CO produced changes in the direction of an adverse effect in 2 factor analyses of variance with repeated measures. The two factors tested were atmosphere (clean air or CO) and order of exposure (clean air on the first exposure or clean air on the second exposure). The levels of significance for the two-tailed ANOVA are also shown in Table 8. The average time to angina was reduced from 6.55 minutes to 5.80 minutes, a difference of 0.75 minute, which was statistically significant ($p<0.004$). This represents an 11% change in the exercise tolerance of subjects with stable angina pectoris after exposure to CO sufficient to raise their carboxyhemoglobin level to about 2.7%. The average duration of angina was increased by about 10%, however this difference was not statistically significant. Ventilatory parameters (minute ventilation, oxygen uptake rate, and CO output rate) were all reduced; the differences were small (3 to 5%) and only the changes in O_2 uptake rate approached significance ($p<0.065$). Heart rate, blood pressure and double product (a measure of blood ejection volume)

were all slightly reduced, however none of the differences achieved statistical significance. All of the changes observed are consistent with the hypothesis that CO exposure reduces exercise tolerance. The order in which exposure was presented did not significantly affect the outcome.

The effect of CO on ability to exercise for all 26 subjects is presented in Figure 1 in the form of a dose-response relationship, where dose is "dose" of exercise, in minutes, and response is the percent of subjects experiencing angina after a given duration of exercise. The response curve for CO-exposed subjects is shifted to the left, relative to clean air-exposed subjects. This presents in graphic form the conclusion drawn from the group mean values discussed above; CO reduced the ability to exercise in subjects with stable angina.

The data obtained for some of the key cardiopulmonary variables for the subject population over the course of the exercise protocol are summarized in Figures 2 through 5. The abscissa of each graph shows the time during the exercise period; during this time, the subject pedals at 60 rpm and the work rate is increased by 25 watts every three minutes. Figures 2 through 5 all end at 10 minutes of exercise, the maximum exercise time of any of the subjects after CO exposure. (As shown in Figure 1, one subject exercised for 12 minutes after his clean air exposure.) The numbers of subjects represented by each data point on the graphs vary; as exercise time increases, the number of subjects participating decreases. Each data point represents those subjects for which both clean air and CO-exposure day values were obtained; the graphs thus represent "paired" comparisons. These Figures provide a picture that is complementary to the data summarized in Table 8.

The respiratory exchange ratio (R) is examined in Figure 2. There is a tendency for the R to be higher at any given moment of exercise when subjects were given CO as compared to clean air. Thus subjects tended towards anaerobic metabolism at an earlier time after CO exposure than after clean air. Since, as a group, the subjects exercised for shorter durations after CO than after clean air, the group mean R values were lower on the CO-exposure day, even though minute-by-minute R values were higher for CO exposure compared to clean air exposure. The oxygen uptake rates for CO and clean air exposures are compared in Figure 3. The two curves appear identical, except for the last (9 min) data point. Thus CO exposure does not appear to alter the rate of oxygen uptake; the difference in

group mean values shown in Table 8 most likely represents the fact that subjects exercised for shorter durations after CO, hence climbing lower on the O_2 uptake curve (shown in Figure 3). The rate of output of CO_2 is shown in Figure 4. There appears to be greater output on the CO-exposure day than on the clean air day, but the differences between each of the paired data points were not statistically significant, using the paired "t"-test.

The diastolic and systolic blood pressures are shown in Figure 5. The blood pressure results show that the subjects who were able to exercise for longer times (>7 min), tended to exhibit higher blood pressures on the CO day than on the clean air day. The systolic pressure difference after 9 min of exercise (CO - Clean Air) was small (9 mm Hg) but was statistically significant ($p<0.05$). Because of the small number of subjects who were able to exercise for this extended period, it is difficult to attribute clinical significance to this finding, at this time, although it is suggestive of an important physiological consequence of CO exposure in this sensitive population.

Discussion

This study demonstrates that low-level exposure to CO can significantly reduce exercise tolerance in subjects with stable angina, at an average carboxyhemoglobin level of 2.9% of saturation. These findings agree with those previously reported by Aronow and Isbell (1973) and Anderson et al. (1973). In addition, we have confirmed the more subjective measures such as time to angina and duration of angina with objective measures of exercise tolerance. We also noted that, in CO-exposed subjects, systolic blood pressure was substantially increased in those subjects who were able to work relatively strenuously prior to the onset of angina, compared to clean air exposures. The difference between CO and clean air days became apparent in blood pressure measurements at 6 (12 subjects) and 9 (4 subjects) minutes of exercise. Blood pressure readings taken at intervals more frequent than 3 minutes and the use of subjects better able to exercise strenuously would provide more definitive data, however the findings do suggest that CO exposure stresses the cardiovascular system during exercise.

There were some differences between the protocol used in our study and those used by Aronow and co-workers. They achieved COHb levels of about 2.7 to 2.9% of saturation by exposing subjects for 2 hours to 50 ppm CO. In our study we exposed subjects to 100 ppm for 1 hour, achieving comparable COHb levels. It is unlikely that this difference significantly altered the outcome of the study. In our study, the subjects who were tested were possibly less severely limited by their disease than those in the Aronow (1981) study. Our subjects were exercised according to the protocol described by Aronow, however they were able to exercise considerably longer than Aronow's subjects; 6.5 minutes versus 4.8 minutes, respectively, and thus presumably represented a more healthy group than did Aronow's.

The sensitivity of the subjects to CO insult, as indexed by the reduction in time to angina (TTA) after exposure, was correlated to the dosage levels (mg/day) of the medications taken. For example, 4 subjects were on anti-arrhythmics and there was a significant ($p<0.05$) negative correlation between TTA and drug dose. Thus, subjects on high doses of anti-arrhythmics showed less effects due to CO. Subjects on high doses of nitrates, however, appeared to show the opposite effect, i.e., a strong positive correlation ($p<0.05$). Those subjects on high doses of nitrates showed more effects attributable to CO. The nitrate

dose level, however, was closely linked to subjects'weight. In future studies, it would appear to be useful to control for these interactions in some appropriate statistical design, and thus account for the protective effects of medication.

There was substantial variation between subjects with respect to baseline COHb levels, even on days when they were driven to our laboratory under clean air conditions. There did not appear to be any relationship between baseline COHb and response to CO exposure in our study group. Thus, within the relatively narrow range of COHb observed in urban residents, there did not appear to be evidence of acclimatization to CO exposure.

Environmental factors which might relate to subject's baseline COHb levels were evaluated. Air quality data for each subject's place of residence have not been acquired. Most of the subjects were residents of Orange County, California. Some, however, lived as far away as Riverside. Most of the subjects lived in a home with a gas water heater (65%), about 58% of the subjects used a gas stove, as opposed to an electric stove, and 34% had a gas space heater, of some sort. Of those 17 subjects with gas water heaters, 7 had outdoor units. Four of the subjects lived in homes with other individuals who smoked regularly. There did not appear to be any relationship of this factor to baseline COHb levels. All of the subjects drove motor vehicles, however only about 45% claimed to drive more than one hour per day. Most of the subjects drove during daylight hours, but only 5 (or 20%) drove during rush hours. No pattern linking these environmental factors to baseline COHb levels was apparent from analyses of correlation patterns.

More research is needed to thoroughly investigate the phenomena we have observed. Studies to better understand the mechanisms responsible for the earlier onset of anaerobic metabolism which we observed should be undertaken. In addition, studies in which more detailed information on blood pressure, heart rate, and efficiency of blood movement by the heart will help to clarify the observations made in this study.

To conclude, exposure of subjects with stable angina pectoris to carbon monoxide resulted in a more rapid onset of exercise-induced anginal pain and a longer duration of pain than when the same subjects were exposed to clean air. The subjects also experienced more stress after CO exposure, as evidenced by a

higher blood pressure at the end of the exercise period. The level of carboxyhemoglobin in the CO-exposed subjects was about 3% of saturation, a level which can be achieved during normal exposure to polluted ambient air in urban environments.

Table 1: Subject Characteristics and Medication Usage

Subject	Age	Weight	Nitrates	Beta-Blockers	Insulin	Anti-Arrhythmics	Diuretics	Vaso-Dilators	Anti-Coagulents
1	59	73.2	.	.	40	.	.	.	.
2	65	100.5	.	125	37	.	30	.	.
3	61	87.6	.	.	.	.	.	.	6.1
4	58	114.2	16	160	.	.	.	.	.
5	59	88.4	16	.	.	.	20	.	.
6	64	78.7	16	.	.	.	160	.	.
7	65	83.2	8	.	80	.	.	.	.
8	62	74.8	20	.	.	.	.	.	.
9	63	88.9	.	.	.	.	.	.	.
10	64	99.8	16	.	.	.	50	.	.
11	54	109.6	4	80	45	.	50	.	.
12	60	87.6	25	60	.	.	.	.	.
13	49	85.6	24	50	.	750	.	.	.
14	62	79.2	.	.	.	.	.	.	.
15	61	92.2	4	120	.	.	.	.	.
16	51	113.6	10	200	.	.	.	.	.
17	52	84.0	12	5	.	4000	.	.	.
18	66	82.0	6	.	.	7500	20	.	.
19	65	105.8	6	120	.	.	100	.	.
20	59	87.7	40	.	.	.	.	.	12.5
21	52	109.0	4	160	.	.	.	.	.
22	52	90.6	16	150	.	6000	.	.	.
23	56	72.5	.	50	.	.	.	.	.
24	62	88.8	16	120	.	.	.	.	.
25	58	69.0	.	.	.	.	125	2	.
26	54	82.2	13	240	.	.	.	75	1.0
TOTAL NUMBER	26	26	19	14	4	4	8	2	3

Table 2 -- Pulmonary Function in 26 Subjects with Cardiovascular Disease

	Mean	S.E.	% of Predicted Mean	% of Predicted S.E.
FVC (liters)	4.16	.14	93.70	2.57
$FEV_{1.0}$ (liters)	2.98	.10	94.20	3.08
FEV/FVC (%)	71.68	1.59	---	---
MMFR (ml/m)	149.50	12.89	81.21	7.32

Table 3 -- Cardiovascular Data Obtained During Screening
(n = 26; mean ± s.e.)

Cardiovascular Function	At Rest	At Angina Point
Heart Rate (bpm)	69.90 ± 3.13	114.42 ± 4.70
Systolic B.P.	133.26 ± 3.99	179.68 ± 5.67
Diastolic B.P.(mm Hg)	89.40 ± 9.78	98.10 ± 11.60
PVC's *	0	0
ST Segment Changes **	0	0.32 ± 0.13
Carboxyhemoglobin (%)	1.26 ± 0.10	1.22 ± 0.09

Notes: * preventricular contractions
** depression of electrocardiographic ST segment in mm displacement

Table 4: Carboxyhemoglobin in Blood (%COHb Saturation)

Subject	Clean Air Exposure			CO Exposure		
	(1)	(2)	(3)	(1)	(2)	(3)
1	1.6	1.4	1.4	2.3	--(4)	3.4
2	2.6	2.1	1.6	0.3	3.0	3.0
3	1.4	1.4	--(4)	1.4	3.1	2.6
4	1.3	1.1	1.2	1.6	2.6	2.4
5	2.6	1.9	1.8	1.3	3.0	3.1
6	0.8	0.9	1.1	1.1	2.9	2.8
7	1.0	1.2	1.1	1.8	3.2	2.5
8	1.5	1.6	1.6	1.4	3.1	3.0
9	1.8	2.0	1.4	1.3	2.5	2.3
10	1.2	1.0	1.4	1.2	3.1	3.1
11	1.8	1.9	2.0	1.8	3.0	2.6
12	1.5	1.0	0.9	1.4	2.7	2.5
13	2.1	1.9	2.2	2.4	3.8	2.9
14	1.2	1.3	1.3	1.9	3.0	2.7
15	--(4)	1.0	1.0	1.7	2.3	2.7
16	1.6	2.1	2.5	2.0	3.1	3.8(5)
17	1.3	1.1	1.0	--(4)	2.5	2.2
18	0.9	0.8	1.1	1.0	2.6	2.6
19	1.2	1.1	1.3	1.1	2.9	2.9
20	1.7	0.3	0.3	1.3	2.8	2.8
21	1.7	2.3	1.5	0.7	3.1	2.2
22	1.9	1.5	1.5	1.6	2.5	2.4
23	1.4	1.1	1.1	1.4	3.7	3.2
24	1.5	0.9	1.0	1.1	3.0	2.8
25	1.2	1.0	1.1	1.4	2.9	2.7
26	1.2	1.7	1.4	2.0	3.6	2.9
Mean ± s.e.	1.5 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	3.0 ± 0.1	2.8 ± 0.1

Notes:
(1) Pre Exposure
(2) Post Exposure
(3) Post Exercise
(4) Sample Lost
(5) Small Sample (1 reading only)

Table 5: Angina-Related Changes After Exposure to CO

DAY	Time to Onset of Angina (min)		Duration of Angina (min)		Double Product* (bpm x mm Hg)	
	Clean Air	CO	Clean Air	CO	Clean Air	CO
Subject						
1	6.50	5.42	2.00	2.75	22990.00	26368.00
2@	8.02	6.50	1.40	2.00	21168.00	20188.00
3	9.90	9.90	1.27	.05	20440.00	21996.00
4@	7.25	9.38	.63	.78	18400.00	18000.00
5	12.00	9.40	.47	.80	26384.00	24381.00
6	3.92	3.45	.58	.43	26574.00	25400.00
7	3.57	2.93	.58	.27	18156.00	19320.00
8	7.38	7.22	.35	.42	20952.00	12324.00
9	4.72	4.13	.80	1.03	24408.00	22440.00
10@	5.42	7.32	.65	1.12	13224.00	15770.00
11@	9.12	9.78	1.95	1.63	25740.00	26910.00
12	7.77	6.77	3.45	4.48	13904.00	15088.00
13	6.17	3.72	.97	.73	10920.00	9480.00
14	5.38	5.62	1.62	1.47	23120.00	22968.00
15	3.92	4.97	3.62	5.67	15438.00	14400.00
16@	5.43	4.33	2.67	2.20	11696.00	12354.00
17	8.25	8.88	2.05	2.87	12848.00	15390.00
18	8.03	7.02	1.08	.92	22736.00	22800.00
19@	3.67	3.68	1.03	1.85	15770.00	14940.00
20	4.40	2.20	1.18	.77	15120.00	12740.00
21@	5.72	6.25	3.05	1.67	12040.00	12264.00
22	6.38	5.45	.90	1.38	12556.00	12900.00
23	10.47	9.83	3.85	3.55	31174.00	30816.00
24	6.82	4.83	.62	.58	15092.00	14700.00
25	5.55	5.55	.45	.42	27510.00	25284.00
26	3.27	2.88	.68	.75	18360.00	15744.00
All Subjects(N)	26	26	26	26	26	26
Mean	6.50	6.05	1.46	1.56	19105	18652
s.d.	2.26	2.37	1.06	1.36	5744	5737
% Difference	-6.9%		+6.8%		-2.4%	
1-tailed "t" probability	0.032		0.232		0.167	
Subjects <95kg (N)	19	19	19	19	19	19
Mean	6.54	5.80	1.40	1.54	19930	19186
s.d.	2.45	2.41	1.11	1.57	5834	5981
% Difference	-11.3%		+10.0%		-3.7%	
1-tailed "t" probability	0.002		0.184		0.117	

Notes * Double Product = Heart Rate x Sys. Blood Press. (index of blood flow rate)
@Body mass >95 kg.

Table 6: Exercise Respiratory Physiology Data at the Angina Point

	Ventilation Rate (V_e Lpm)		Oxygen Uptake (VO2 Lpm)		CO_2 Elimination (VCO2 Lpm)	
DAY	Clean Air	CO	Clean Air	CO	Clean Air	CO
Subject						
1	51.5	48.3	1.10	1.18	1.23	1.29
2@	51.7	45.6	1.61	1.38	1.81	1.60
3	71.0	68.5	1.58	1.54	1.87	1.89
4@	43.0	55.7	1.30	1.46	1.41	1.73
5	82.5	62.6	1.59	1.48	1.75	1.55
6	48.8	42.9	1.06	.97	1.25	1.15
7	34.2	36.4	1.14	1.23	1.12	1.16
8	45.0	54.1	1.16	1.15	1.32	1.39
9	31.7	36.2	1.35	1.21	1.28	1.34
10@	47.3	55.0	1.23	1.34	1.34	1.46
11@	71.1	75.3	1.80	1.83	2.18	2.23
12	50.0	43.1	1.34	1.21	1.43	1.28
13	45.9	37.0	1.04	.91	1.43	1.23
14	36.7	38.6	1.21	1.25	1.35	1.41
15	30.0	36.6	1.10	1.19	1.09	1.28
16@	34.7	32.6	1.14	1.14	1.15	1.13
17	64.2	68.2	1.37	1.40	1.55	1.59
18	54.6	55.4	1.41	1.34	1.64	1.69
19@	42.0	40.9	1.15	1.15	1.17	1.14
20	48.4	38.2	1.09	1.04	1.12	.96
21@	44.5	52.0	1.40	1.34	1.58	1.63
22	57.2	55.6	1.22	1.15	1.48	1.40
23	50.1	50.9	1.55	1.56	1.87	1.81
24	52.1	40.1	1.26	1.24	1.49	1.26
25	48.2	46.3	1.07	1.09	1.42	1.40
26	30.5	29.0	1.16	.92	1.12	.95
All Subjects						
(N)	26	26	26	26	26	26
Mean	48.7	47.9	1.29	1.26	1.44	1.42
s.d.	12.9	11.9	0.20	0.21	0.28	0.30
% Difference	-1.6%		-2.3%		-1.4%	
1-tailed "t" probability	0.275		0.063		0.231	
Subjects <95kg						
(N)	19	19	19	19	19	19
Mean	49.1	46.7	1.25	1.21	1.41	1.37
s.d.	13.6	11.4	0.18	0.19	0.24	0.25
% Difference	-4.9%		-3.2%		-2.8%	
1-tailed "t" probability	0.079		0.032		0.079	

Note: @ Body mass >95 kg.

Table 7: Correlations Among Selected Physiological and Cardiopulmonary Data in Total Study Population

	DELTTA	DELDA	DELCOHb	DELVO2	DELR	AGE	WEIGHT	NITRATES
DELTTA	1.0000	.1224	-.1028	.5964***	.4927**	-.0653	-.3131*	.4658**
DELDA		1.0000	-.0832	.1093	.0907	-.2184	.0662	.0552
DELCOHb			1.0000	.2532	-.5342***	-.1847	.5033***	-.5353***
DELVO$_2$				1.0000	-.0480	-.0821	-.1169	.2783
DELR					1.0000	-.0373	-.1982	.4557
AGE						1.0000	-.1775	-.0520
WEIGHT							1.0000	-.0007
NITRATE								1.0000

NOTES:
* P<0.1
** P<0.05
***P<0.01

Key: All differences computed as (clean air - CO) exposure day values

DELTTA: Difference in time to onset of angina
DELDA: Difference in duration of angina
DELCOHb: Difference in Carboxyhemoglobin saturation
DELVO$_2$: Difference in Oxygen uptake rate
DELR: Difference in ventilatory gas exchange ratio (V_{CO2}/V_{O2})
AGE: Years
WEIGHT: kg
NITRATES: mg/day

Table 8: ANOVA Comparisons of Cardiopulmonary Results
For Subjects of Body Weight <95 kg

	CLEAN AIR		CO EXP.			p level (2-tailed)	
	mean	s.d.	mean	s.d.	% change	EXPOSURE	ORDER
Time to Angina (min)	6.55	2.45	5.80	2.41	-11.4	.004	.289
Duration of Angina (min)	1.40	1.11	1.54	1.57	+10.0	.367	.541
Heart Rate (bpm)	110.90	20.40	108.10	21.60	-2.5	.149	.986
Systolic Blood Pressure	177.00	28.00	174.00	28.00	-1.7	.358	.688
Double Product (HR * BP)	19900.00	5800.00	19200.00	6000.00	-3.5	.233	.927
Minute Ventilation at the Point of Angina	49.08	13.65	46.74	11.44	-4.8	.159	.223
CO_2 Production (l/min)	1.41	.24	1.37	.25	-2.8	.159	.570
Oxygen Uptake (l/min)	1.25	.18	1.21	.19	-3.2	.065	.151
Number of Subjects	19		19				

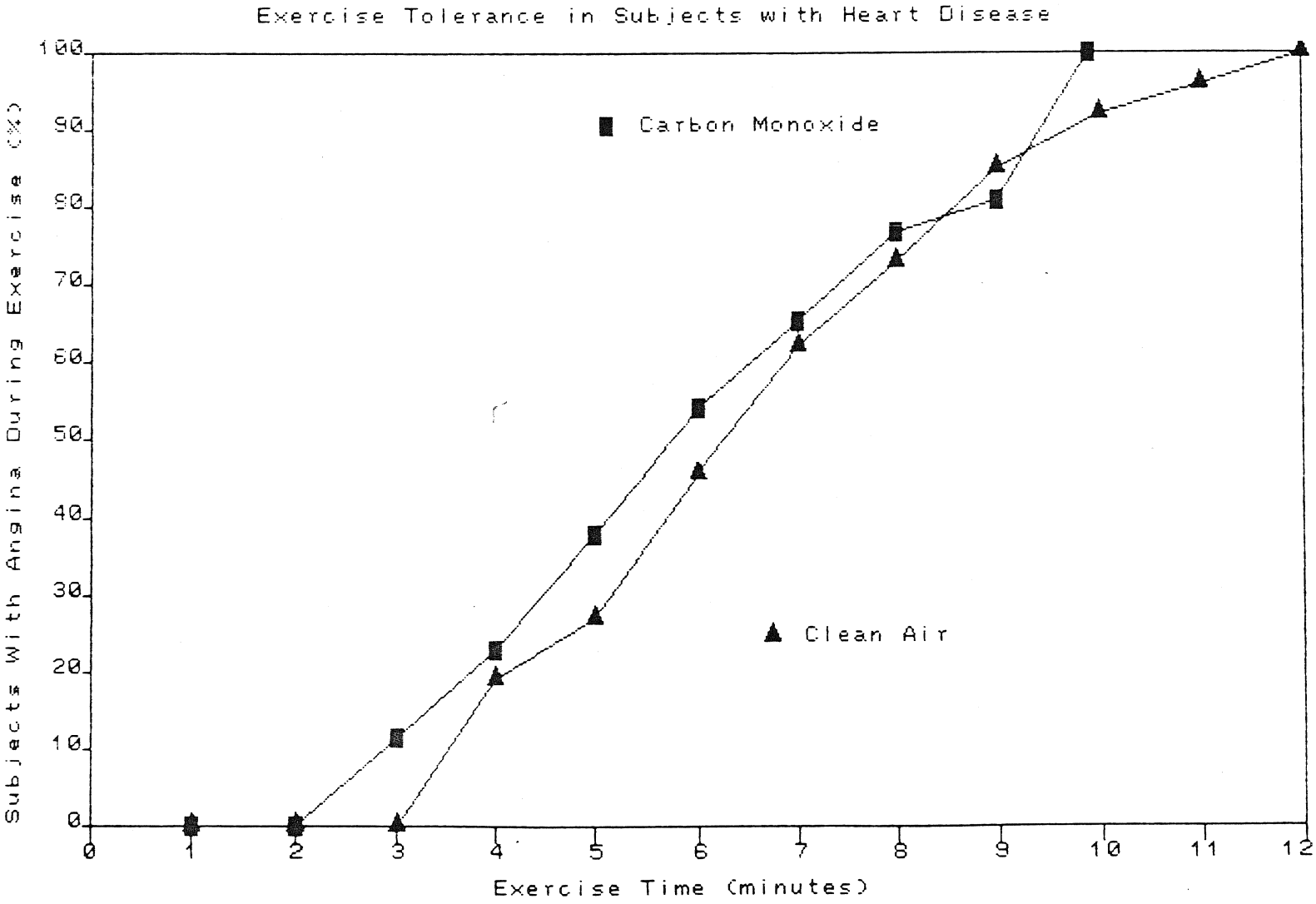

Figure 1. The ability of subjects with coronary artery disease to perform exercise is reduced relative to clean air by an earlier time to onset of angina pectoris.

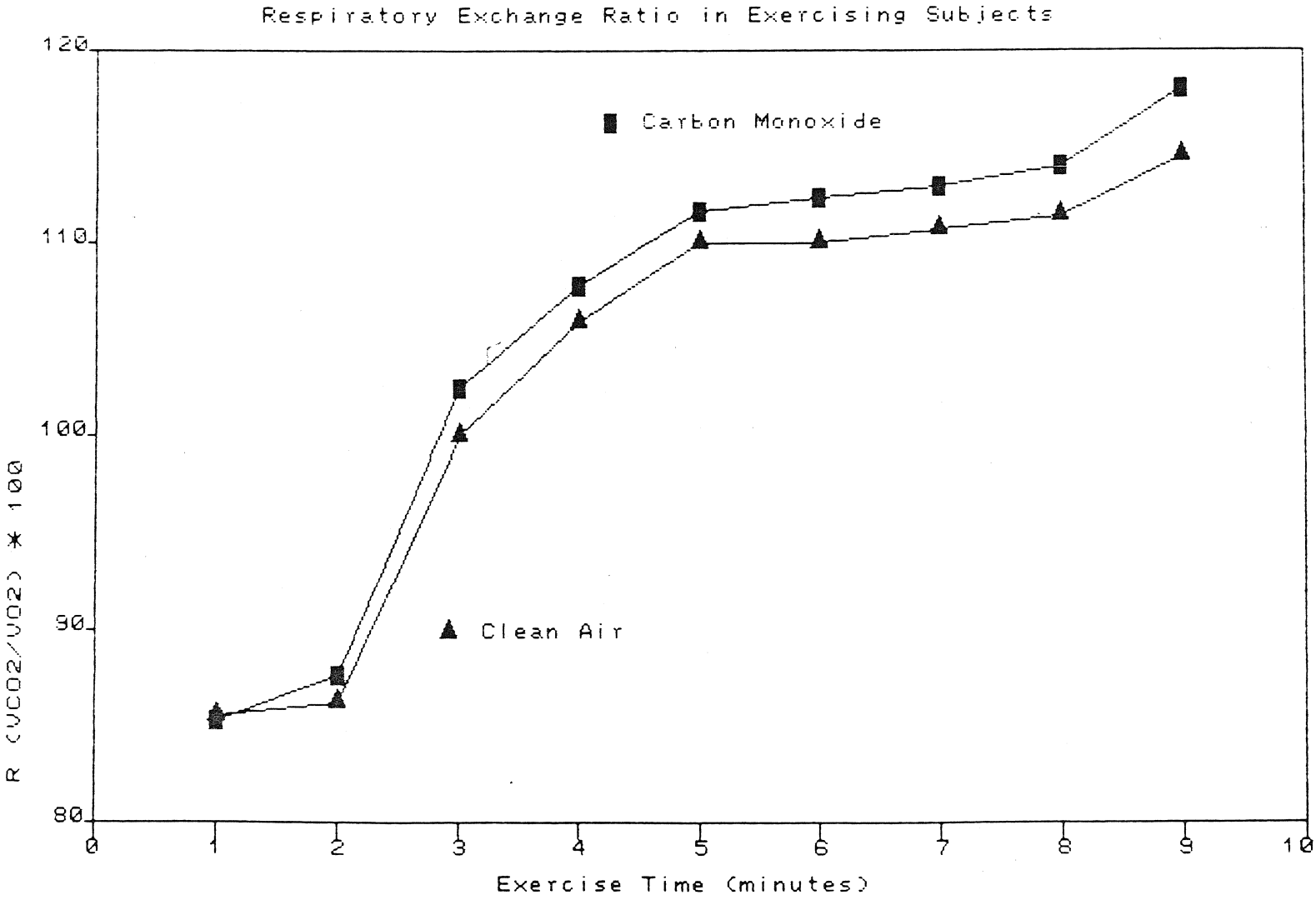

Figure 2. The respiratory exchange ratio indicates an earlier entry into anaerobic metabolism in subjects with coronary artery disease exposed to carbon monoxide, as compared with the same subjects exposed to clean air.

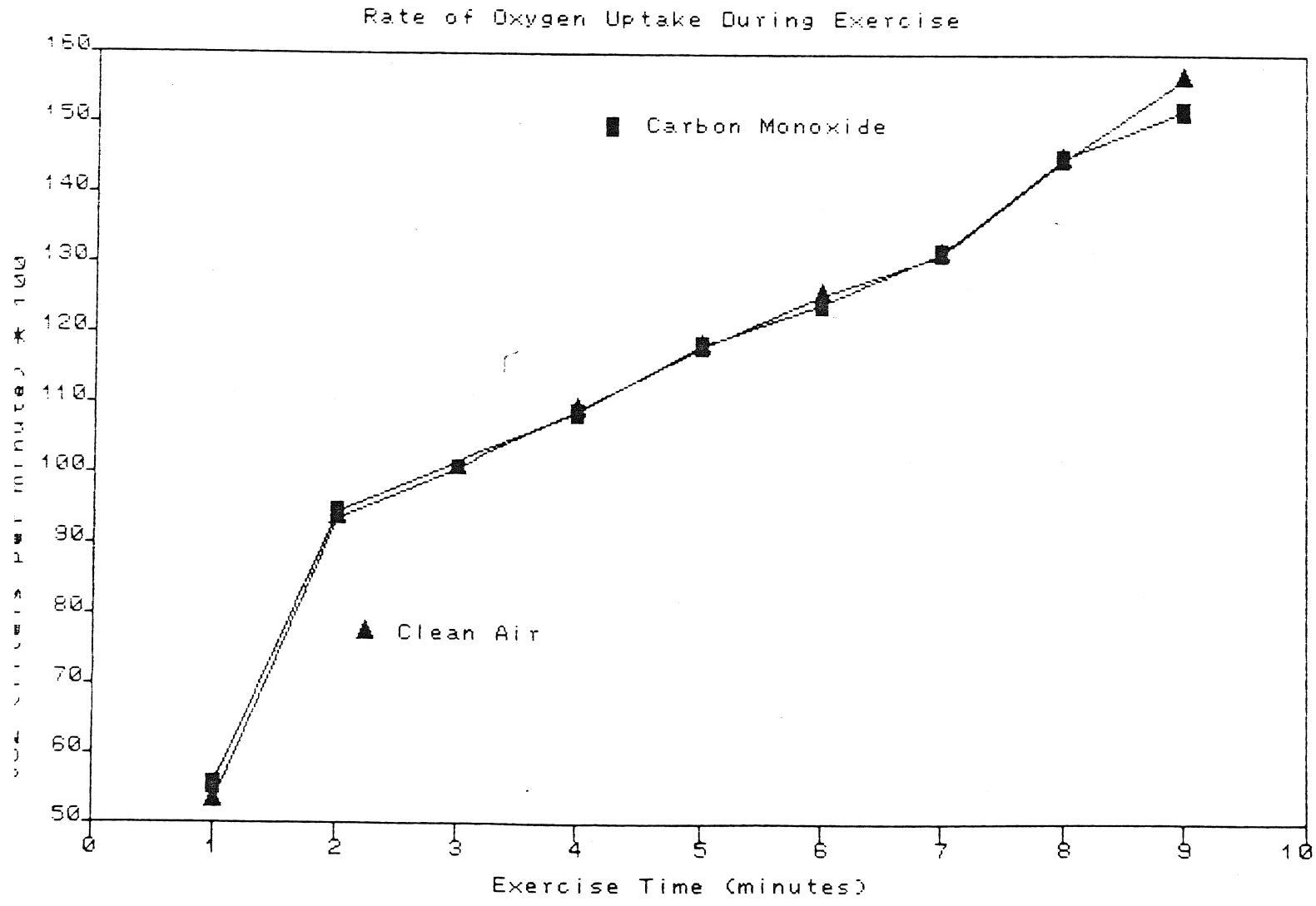

Figure 3. Rates of oxygen uptake during exercise appear comparable after exposures to clean air or carbon monoxide.

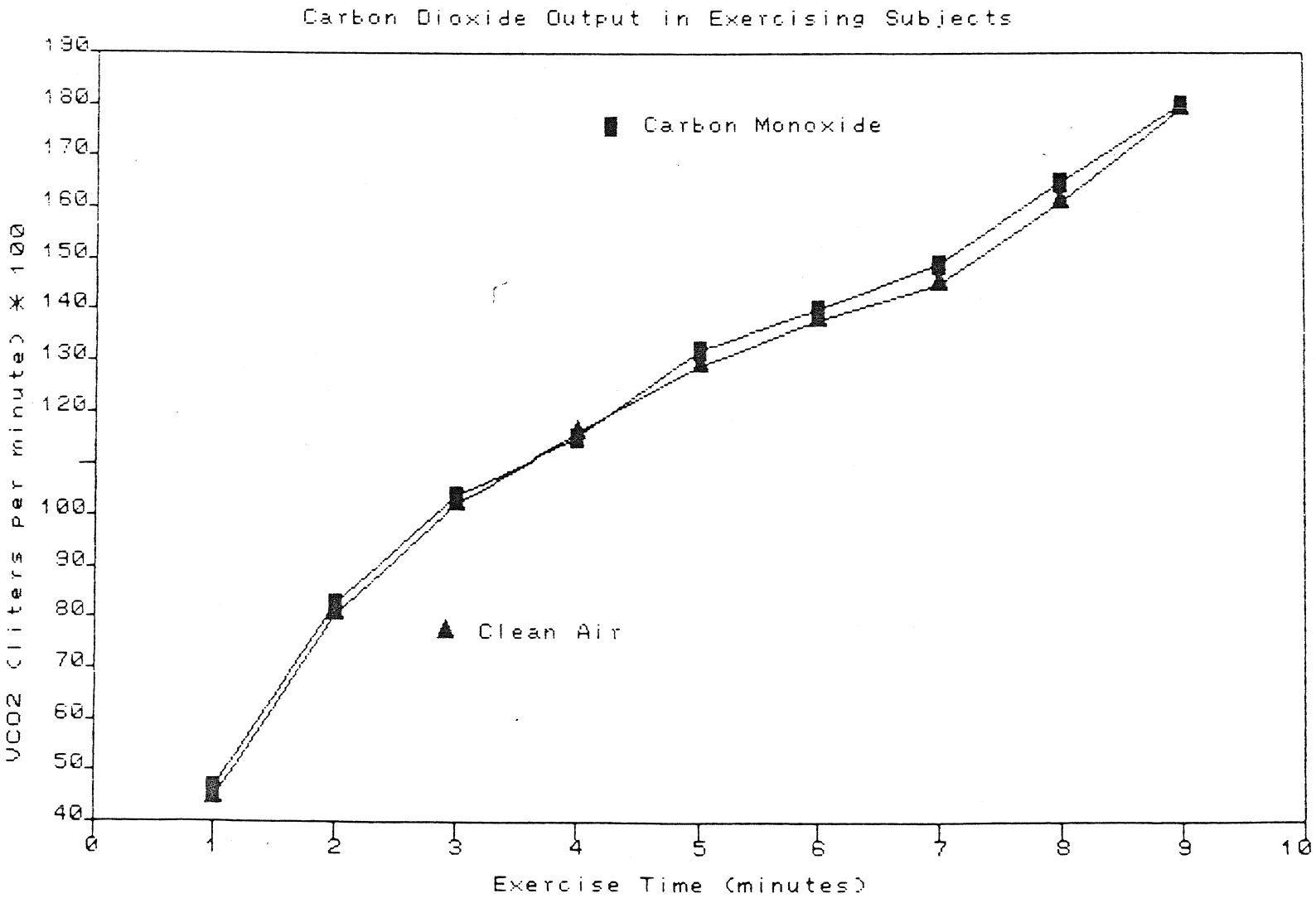

Figure 4. Rates of carbon dioxide output are slightly increased during exercise after subjects were exposed to carbon monoxide, as compared to clean air.

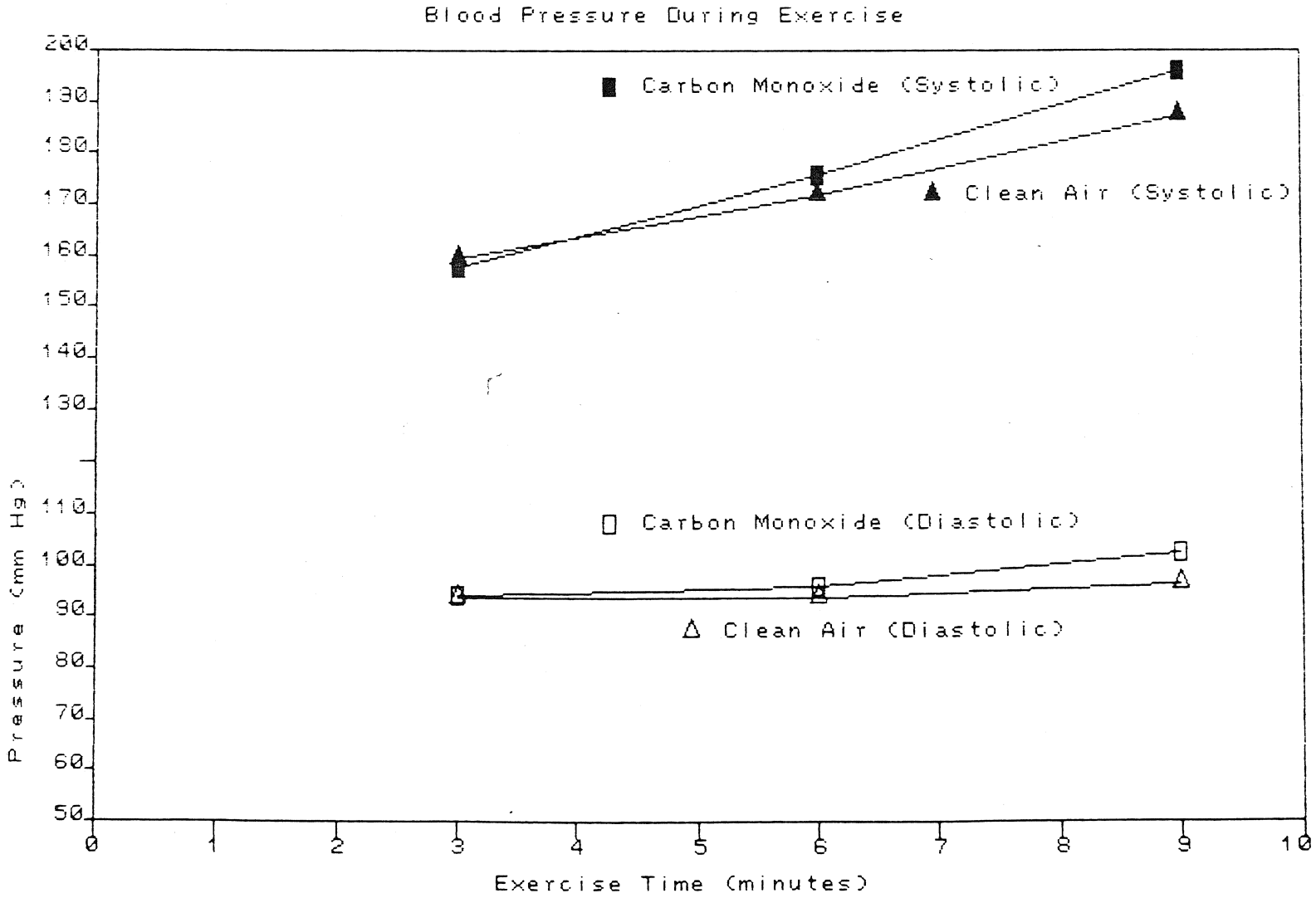

Figure 5. The rates of increase in blood pressure (both systolic and diastolic) were greater after CO exposure than after clean air exposure.

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