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Carbon Monoxide Exposure of Subjects with Documented Cardiac Arrhythmias

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Includes the Commentary of the Institute's Health Review Committee

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HEI HEALTH EFFECTS INSTITUTE

The Health Effects Institute, established in 1980, is an independent and unbiased source of information on the health effects of motor vehicle emissions. HEI studies all major pollutants, including regulated pollutants (such as carbon monoxide, ozone, nitrogen dioxide, and particulate materials), and unregulated pollutants (such as diesel engine exhaust, methanol, and aldehydes). To date, HEI has supported more than 120 projects at institutions in North America and Europe.

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HEI Statement

Synopsis of Research Report Number 52

Carbon Monoxide and Cardiac Arrhythmias

BACKGROUND

Carbon monoxide is a ubiquitous air pollutant. Exposures can occur from cigarette smoke, poorly ventilated combustion sources, motor vehicles, and industrial processes. Outdoor carbon monoxide concentrations vary from 2 to 4 parts per million (ppm) near heavily traveled roads to levels in excess of 40 ppm in highway tunnels. The U.S. Environmental Protection Agency has set National Ambient Air Quality Standards for carbon monoxide of 9 ppm averaged over eight hours and 35 ppm averaged over one hour. Despite reductions in ambient carbon monoxide concentrations during the last decade, 22 million people live in areas of the United States that exceed the carbon monoxide standard.

Inhaled carbon monoxide binds to hemoglobin in red blood cells to form carboxyhemoglobin, reducing the oxygen carrying capacity of hemoglobin, and thereby reducing the delivery of oxygen to the heart and other tissues. The concentration of carboxyhemoglobin in blood correlates with the dose of carbon monoxide a person has been breathing and thus represents an excellent biomarker for recent carbon monoxide exposure. Typical blood carboxyhemoglobin levels are less than 1% in healthy nonsmokers not exposed to carbon monoxide, approximately 2% in exercising subjects who inhale 35 ppm carbon monoxide for one hour, and between 3% and 8% in smokers or workers in certain occupational settings.

Exposure to high concentrations of carbon monoxide is known to be lethal. The effects of exposure to low levels of carbon monoxide are also of public health and regulatory concern because some data indicate that carboxyhemoglobin levels as low as 2% to 4% adversely affect cardiovascular function in individuals with coronary artery disease. People with arrhythmias (abnormal heartbeats) are also potentially at risk from carbon monoxide exposure. Although some arrhythmias are harmless, other types can cause sudden death. The differences between asymptomatic irregular heartbeats and life-threatening arrhythmias are complex and incompletely understood. The Health Effects Institute sponsored two studies (one study by Sheps and coworkers [1991], which was presented in HEI Research Report Number 41, and the study reported here) to examine whether there is a link between carbon monoxide exposure and arrhythmias in subjects with coronary artery disease.

APPROACH

Drs. Chaitman, Dahms and coworkers studied 25 men and 5 women, aged 45 to 77 years, all of whom were nonsmokers with stable coronary artery disease and who had moderate levels of ventricular arrhythmias. In this study, evidence of cardiac arrhythmias was defined as 30 or more abnormal heartbeats per hour. Most of the subjects were taking medications for heart disease. The subjects were exposed for one hour to air only or to air containing one of two levels of carbon monoxide sufficient to produce 3% or 5% carboxyhemoglobin; these carboxyhemoglobin levels were maintained for an additional 90 minutes. Blood carboxyhemoglobin was measured using highly accurate gas chromatographic techniques. Subjects were monitored continuously for arrhythmias by Holter monitors, which record the electrical activity of the heart. They were monitored for a total of 20 hours while at rest, during a brief exercise period, during recovery from exercise, and during their usual activities.

RESULTS AND IMPLICATIONS

In this study, a two-and-a-half-hour exposure to carbon monoxide did not increase the frequency of cardiac arrhythmias, nor did it affect heart rate or blood pressure. Subgroup analyses did not detect any significant effects of carbon monoxide exposure on the frequency of abnormal heartbeats in those individuals who had elevated levels of arrhythmias or those with exercise-induced myocardial ischemia (reduced blood supply to the heart muscle).

The results of this study suggest that short-term exposure to carbon monoxide, leading to small elevations in carboxyhemoglobin levels, does not promote arrhythmias. The present exercise test results differ from the findings of Sheps and coworkers. They reported that a single exposure of subjects with coronary artery disease to carbon monoxide, leading to approximately the same levels of carboxyhemoglobin as in the present study, did increase the frequency of ventricular arrhythmias, but only during a short exercise test at the higher carboxyhemoglobin level. In resting subjects, the carbon monoxide exposures had no effect on the frequency of arrhythmias or other physiologic end points.

The results of both studies apply to subjects who have stable coronary artery disease and are on medication. It is not possible to predict the effect of similar exposures to carbon monoxide in subjects with more severe coronary disease, subjects with untreated arrhythmias, or those exposed to carbon monoxide for longer periods.

This Statement is a summary, prepared by the Health Effects Institute (HEI) and approved by the Board of Directors, of a research project sponsored by HEI from 1987 to 1989. This study was conducted by Dr. Bernard R. Chaitman and associates of St. Louis University School of Medicine. The following Research Report contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee. CHAITMAN 52

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TABLE OF CONTENTS

Research Report Number 52

Carbon Monoxide Exposure of Subjects with Documented Cardiac Arrhythmias

Bernard R. Chaitman, Thomas E. Dahms, Sheila Byers, Lisa W. Carroll, Liwa T. Younis, and Robert D. Wiens

INVESTIGATORS' REPORT

Carbon Monoxide Exposure of Subjects with Documented Cardiac Arrhythmias

Bernard R. Chaitman, Thomas E. Dahms, Sheila Byers, Lisa W. Carroll, Liwa T. Younis, and Robert D. Wiens

ABSTRACT

The impact of low-level carbon monoxide exposure on ventricular arrhythmia frequency in patients with ischemic heart disease has not been thoroughly studied. The issue is of concern because of the potential proarrhythmic effect of carbon monoxide in patients with ischemic heart disease. We studied 30 subjects with well-documented coronary artery disease who had an average of at least 30 ventricular ectopic beats per hour over a 20-hour monitoring interval. By using appropriate inclusion and exclusion criteria, subjects were selected and enrolled in a randomized double-blind study to determine the effects of carbon monoxide exposure on ventricular arrhythmia frequency at rest, during exercise, and during ambulatory activities. The carbon monoxide exposure was designed to result in 3% or 5% carboxyhemoglobin levels, as measured by gas chromatography. The carbon monoxide exposure protocol produced target levels in 60 minutes, and the levels were maintained for an additional 90 minutes to provide adequate time to assess the impact of carbon monoxide on the frequency of ventricular ectopic beats. The data on total and repetitive ventricular arrhythmias were analyzed for seven specific time intervals: (1) two hours before carbon monoxide exposure; (2) during the two-hour carbon monoxide or air exposure; (3) during a two-hour rest period; (4) during an exercise period; (5) during an exercise recovery period; (6) six hours after carbon monoxide or air exposure; and (7) approximately 10 hours after exposure, or the remaining recording interval on the Holter monitor.

There was no increase in ventricular arrhythmia frequency after carbon monoxide exposure, regardless of the level of carboxyhemoglobin or the type of activity. During steady-state conditions at rest, the number of ventricular ectopic beats per hour was 115 ± 153 (SD) for room air exposure (0.7% carboxyhemoglobin), 121 ± 171 for the lower carbon monoxide exposure (3.2% carboxyhemoglobin), and 94 ± 129 for the higher carbon monoxide exposure (5.1% carboxyhemoglobin). The frequency of complex ventricular ectopy was not altered at the levels of carbon monoxide studied. Secondary analysis of the impact of carbon monoxide on ventricular ectopic beat frequency stratified by baseline ejection fraction, baseline ventricular ectopic beat frequency, and exercise-induced ST-segment changes did not indicate an effect of carbon monoxide on ventricular arrhythmias.

In conclusion, low levels of carbon monoxide exposure resulting in blood levels of 3.2% and 5.1% carboxyhemoglobin, as measured by gas chromatography, do not have a proarrhythmic effect on patients with coronary artery disease and frequent ventricular ectopy. However, patients with symptomatic ventricular arrhythmias and symptomatic myocardial ischemia were excluded from the present study.

BACKGROUND

Approximately 350,000 Americans die suddenly each year from a wide variety of cardiovascular-related causes. Catheterization of cardiac arrest survivors reveals that many individuals have extensive coronary disease, usually with prior myocardial infarction. Ambulatory electrocardiogram recording at the time of death has confirmed that most sudden cardiac deaths are due to ventricular fibrillation, which is usually preceded by ventricular tachycardia; high-density ventricular ectopic beats (VEBs)* are frequent. In the early post-infarction phase, complex ventricular ectopy is identified as a predictor of mortality, independent of and additive to the prognostic value of the left ventricular ejection fraction. Antiarrhythmic drug treatment of ventricular arrhythmias in the post-infarction phase is controversial, and increased mortality has been reported in patients with VEB suppression treated with Class 1C antiarrhythmic drugs. The prognostic importance of VEBs in patients with chronic ischemic heart disease who have not had a recent myocardial infarction is less certain, with some studies reporting increased risk in patients with exercise-induced

This Investigators' Report is one part of the Health Effects Institute Research Report Number 52, which also includes a Commentary by the Health Review Committee, and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Bernard R. Chaitman, St. Louis University School of Medicine, Division of Cardiology, 3635 Vista Avenue at Grand Boulevard, P.O. Box 15250, St. Louis, MO 63110–0250.

* A list of abbreviations appears at the end of this report for your reference.

ventricular ectopy (Califf et al. 1983) and others reporting no increase in risk (Sami et al. 1980).

Carbon monoxide exposure can provoke or aggravate cardiac arrhythmias in laboratory animals and susceptible human subjects when carboxyhemoglobin (COHb) blood levels are substantially elevated. The impact of mild to modest levels of carbon monoxide (CO) exposure on cardiac arrhythmia frequency has not been well studied. In a series of animal experiments, DeBias and colleagues (1973) produced myocardial infarction in monkeys and were able to lower the threshold for induced ventricular fibrillation after exposing the monkeys to 100 parts per million (ppm) CO for six hours (COHb saturation of 9%). Kaul and associates (1974) produced digitalis-induced ventricular tachycardia in anesthetized dogs and found increased sensitivity to ventricular arrhythmias after exposure to 0.5% CO (COHb saturation of approximately 20%). Aronow and coworkers (1978) investigated the effect of breathing 100 ppm CO or purified air for two hours on the ventricular fibrillation threshold in 21 dogs with acute myocardial injury caused by ligation of the left anterior descending coronary artery. At mean COHb levels of 1.1% (control), the mean ventricular fibrillation threshold was 15.0 mA. At mean COHb levels of 6.3%, the ventricular fibrillation threshold was significantly decreased to 8.1 mA ($p<0.001$). Foster (1981) studied eight dogs using bipolar epicardial electrocardiograms (ECGs) during six minutes of left anterior descending coronary artery occlusion before and after CO exposure, which produced COHb levels of 6.8% to 14.6%. In this study, the epicardial ECG showed no change in the degree of ischemic myocardial conduction slowing after CO exposure and no increased incidence of spontaneous ventricular tachycardia. Vanoli and colleagues (1989) studied 16 dogs one month after healed anterior myocardial infarction at concentrations of COHb ranging from 5% to 15%. Malignant arrhythmias were not enhanced in the conscious dogs at any of the COHb levels tested. The data from the animal studies remain controversial, although the bulk of evidence does not point to an increase in ventricular arrhythmias after moderate levels of CO exposure.

Knelson (1972) reported ventricular arrhythmias in 2 out of 26 persons ranging in age from 41 to 60 who were exposed to 100 ppm CO for four hours (resultant COHb saturation, 5% to 9%). Cardiac arrhythmias were not observed in 12 subjects ranging in age from 25 to 36 years, after a similar protocol. Anderson and colleagues (1973) used ambulatory electrocardiographic monitoring and exercise stress testing to assess the effects of a randomized four-hour exposure (face mask) to air, 50 ppm CO and 100 ppm CO in 10 men with stable angina pectoris. In contrast with the findings of Knelson (1972), Anderson and colleagues (1973) found no significant cardiac arrhythmias at average COHb saturations of 2.9% and 4.5%, respectively (measured by end-tidal CO concentrations). Aronow and coworkers (1972) conducted an observational analysis of 10 men with stable angina pectoris participating in 90 minutes of Los Angeles freeway travel in winter. Ambient CO levels in the moving car averaged 53 ppm, producing an average increase in arterial COHb saturations from 1.12% to 5.08%. Ambulatory ECG findings revealed that 3 out of 10 patients had ischemic ST depression greater than 1 mm or 0.1 mV, and a fourth patient had very frequent premature ventricular beats.

Evans and associates (unpublished data) collected 6- to 8-hour ambulatory ECGs from 65 New York City toll collectors whose mean age was 48 years and who were exposed chronically to levels of CO that produced average COHb saturations of 2.9% in nonsmokers and 5.0% in smokers (Ayres et al. 1973, 1979). These data, collected in the early 1970s, were obtained with a single-channel ambulatory recorder and were analyzed with less sophisticated computer systems than currently available. Nevertheless, ventricular arrhythmias were surprisingly frequent. Of the 65 men, 16 (25%) had at least 5 VEBs per hour; 9 of the 16 men had at least 15 VEBs per hour; and 12 of the 16 men had multifocal premature ventricular beats.

In the studies cited above, baseline measurements were not available to determine ventricular arrhythmia frequency. Thus, the threshold at which ventricular irritability may or may not increase remains to be determined in carefully controlled experiments. Hinderliter and colleagues (1989) studied 10 subjects with ischemic heart disease and no ventricular ectopy during baseline monitoring. Of the 10 subjects, 8 had exercise-induced myocardial ischemia. However, ventricular arrhythmias during exercise testing or in the five hours after exercise were not precipitated during CO exposure at levels resulting in 4% and 6% COHb measured by IL-282 CO-Oximeter. In a subsequent study at the same institution, Sheps and associates (1990) studied patients with ischemic heart disease and ventricular ectopy. They reported the effects on ventricular arrhythmias after CO exposure resulting in 4% and 6% COHb. At rest, CO exposure did not significantly increase the frequency of singular or multiple ventricular ectopic beats. However, during exercise, at the 6% COHb level, but not the 4% COHB level, ventricular ectopy in singular and multiple VEBs increased significantly. Thus, the only clinical data available in patients with ambient ventricular ectopy at rest and coronary artery disease are from this study at a single center, which demonstrates increased ventricular ectopy at 6% COHb levels (CO-oximeter measurement) during a brief (less than 20 minutes) period of exercise.

Carbon monoxide is a common pollutant to which subjects may be exposed on an almost daily basis. The present study was designed to assess the impact of low-level CO ex-

posure in patients with evidence of coronary artery disease, but largely without symptomatic myocardial ischemia or symptomatic ventricular arrhythmias, who have demonstrated a potential for frequent ventricular ectopy prior to CO exposure.

EXPERIMENTAL METHODS

SUBJECT POPULATION

Potential subjects were identified from a retrospective review of the daily logs of patients referred to St. Louis University School of Medicine for ambulatory electrocardiography from January 1986 through December 1989. Nonsmoking subjects with ischemic heart disease and chronic ventricular arrhythmias (defined as at least 30 VEBs per hour, averaged over 20 hours) were screened for enrollment in the study. Patients with child-bearing potential, severe renal or hepatic insufficiency, second or third degree atrioventricular nodal block, history of recent angina at rest, severe uncontrolled hypertension, valvular heart disease, decompensated congestive heart failure, intermittent claudication, hemodynamically significant ventricular tachyarrhythmia, or serious intraventricular conduction delays were excluded. Patients with artificial pacemakers, left bundle-branch block, or atrial fibrillation were excluded because each of these conditions interfered with arrhythmia analysis using electrocardiographic techniques. Patients on antiischemic and antiarrhythmic drug therapy were permitted in the study, and the dosing and timing regimens for their medications remained constant on test days.

After inclusion and exclusion criteria were assessed, 68 suitable subjects were invited to participate in a screening test that included a 20-hour ambulatory electrocardiogram and symptom-limited exercise test to confirm the presence of at least 30 VEBs per hour, to verify patient compliance, and establish the quality of the subject's medical history documents. Of the 68 patients, 35 did not meet the criterion of having at least 30 premature ventricular complexes per hour, averaged over 20 hours, and were not enrolled in the study.

Thirty-three subjects consented and participated in the randomized trial. Three male subjects were removed from analysis: one was unable to complete the series of test days, one had ambulatory electrocardiographic data that were noninterpretable, and one had an elevated COHb level upon arrival at the laboratory. The study population consisted of the remaining 30 patients, 25 men and 5 women (Table 1). The average age of the subject population was 65 (range 45 to 77) years. Of the 30 subjects, 28 had angiographic evidence of coronary artery disease. The diagnosis of ischemic heart disease for the other two subjects was made on the basis of a previous history of myocardial infarction or abnormal exercise electrocardiogram, and a thallium defect. Cardioactive medication, ejection fraction measurements, and the presence or absence of exercise-induced angina or ST-segment changes on the screening exercise test are found in Table 1.

PROTOCOL

One week was permitted between the screening day and entry into the protocol. During this week, the subjects were shown the environmental chamber, which is located within the Cardiology Division at the University Hospital. Appropriate medication and an electrical defibrillator were available immediately outside the chamber. The test conditions and the protocol requirements were explained. At this time, all subjects also signed a written informed consent form, which had been approved by the Human Research Committee at St. Louis University School of Medicine.

When the subject entered the protocol, a complete medical history was obtained, and a complete physical examination was conducted, including 12-lead ECG, chest x-ray, routine biochemical screening, complete blood count, venous COHb, CO uptake rate, spirometry, echocardiogram, and treadmill exercise test. On each test day (Figure 1), two procedures were performed to allow data gathering throughout the protocol period: an electrocardiographic recorder was placed on the subject to record 20 hours of continuous ambulatory ECG patterns; and an indwelling venous catheter was inserted to allow blood COHb levels to be measured at designated intervals.

Three days of testing with a maximum of seven days be-

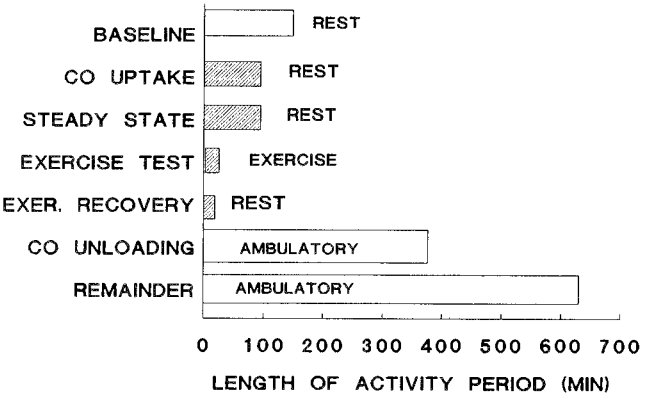

Figure 1. Protocol of each double-blind randomized exposure day, demonstrating the average length of each monitoring period. The periods when the subject was not exposed to chamber levels of CO are indicated with open bars; hatched bars indicate exposure periods in the chamber. The activity level of the subjects is also noted on the figure. The order of monitoring periods starts at the top.

Table 1. Clinical and Baseline Characteristics of Study Population

Subject[a]	Gender, Age	Coronary Arteries with Stenosis ≥ 70%	Myocardial Infarction	Medication[b]	Ejection Fraction (%)	Angina and ST-Segment Depression[c]	Thallium[d]	Arrhythmia Profile: Mean VEBs per Hour	Arrhythmia Profile: Paired Beats per 20 Hours	Arrhythmia Profile: Ventricular Tachycardia Total per 20 Hours
1	M, 75	2	No	AA	26	No; 1.2 mm	No	41	44	0
2	M, 70	1	No	N, CaB	58	Yes	Yes	59	44	0
3	M, 63	2	No	CaB	58	No	No	148	0	0
4	M, 62	—	No	BB	66	No; 2.0 mm	Yes	74	118	0
5	M, 61	—	Yes	N,CaB	49	No	No	45	16	6
7	M, 70	1	Yes	Dig	25	No	Yes	321	208	3
9	M, 54	2	Yes	BB, AA, Dig	32	No; 2.3 mm	Yes	37	22	0
10	M, 69	1	No	CaB	55	No	No	57	2	0
11	M, 65	1	No	BB, CaB, AA, Dig	38	No	No	34	8	0
12	M, 67	1	Yes	No anti-angina	39	No; 1.2 mm	No	196	362	3
13	M, 51	3	Yes	BB, CaB, AA	47	No	Yes	82	0	5
14	F, 67	2	No	CaB	71	No	No	31	18	0
15	M, 70	3	No	CaB	55	No	No	31	6	0
16	M, 51	1	Yes	BB	44	No	No	65	0	0
17	M, 71	1	No	No anti-angina	55[e]	No	No	253	240	21
18	M, 55	1	Yes	N, Dig	30	Yes	Yes	61	1	0
19	M, 60	2	No	Dig	38	No	No	72	11	3
20	F, 71	1	No	CaB	46	No	No	66	0	0
21	M, 70	3	Yes	No anti-angina	33	No	No	39	14	4
22	F, 74	3	No	BB, Dig	43	No; 1.0 mm	Yes	53	8	0
23	M, 65	2	No	BB	59	No; 1.5 mm	Yes	45	34	0
25	F, 67	3	No	CaB, N	32	No	Yes	174	468	61
26	M, 77	1	No	Dig, AA	48	No; 1.8 mm	Yes	103	2	0
27	M, 67	1	No	CaB	46	No	Yes	36	0	0
28	M, 61	2	No	Dig	28	No	No	266	252	15
29	M, 70	3	Yes	No anti-angina	31	No	Yes	51	16	5
30	M, 64	1	No	CaB	55	No; 1.8 mm	No	148	18	0
31	F, 64	2	No	BB	53	No; 1.3 mm	No	50	30	7
32	M, 68	1	No	BB, Dig	39	No	Yes	795	718	6
33	M, 45	3	Yes	Dig	32	No	No	55	26	0

[a] Patients 6, 8, and 24 were removed from analysis for technical reasons (see text).

[b] AA = anti-arrhythmic; BB = beta blocker; CaB = calcium channel blocker; N = nitrate; Dig = Digitalis.

[c] Horizontal or downsloping ST-segment depression.

[d] Positive exercise thallium stress test.

[e] Ejection fraction from contrast ventriculogram.

tween test days permitted double-blind randomized exposure to either room air or two levels of carbon monoxide. The physician and nurse who supervised the exercise test were blinded as to test conditions.

To assess adequately baseline arrhythmia frequency, the exposure day protocol included a 120-minute period of rest before exposure, and at least a 60-minute period of rest during which the blood COHb level was maintained at steady-state with the subject at rest. This allowed us to evaluate the effect of COHb on arrhythmia frequency at rest.

A symptom-limited maximum exercise test was performed using a modified Naughton protocol after reaching steady-state COHb levels, as detailed below.

CARBON MONOXIDE PROTOCOL

All personnel other than the exposure chamber operator were blinded to the randomized order of the chamber CO levels. Subjects were exposed randomly either to air or to CO at one of two levels to produce 3 percent (low) or 5 percent (high) blood COHb after one hour of exposure. The chamber level of CO needed to achieve each COHb level was calculated from each subject's pretest uptake rate determined in the week preceding randomization.

A preexposure blood sample was drawn and analyzed immediately using an IL-282 CO-Oximeter (Instrumentation Laboratories, Lexington, MA) to measure the baseline level of COHb. If the COHb level measured by CO-Oximeter

could be adjusted to a gas chromatography value that was below 1.0%, the subject continued through the protocol. If a subject did not meet this criterion, the investigator noted that the resting COHb was excessive and attempted to determine the exposure source. Repeat blood samples were drawn to verify the COHb level, and the subject was instructed as to how best to eliminate all environmental sources of CO exposure before retesting. A 72-hour period was used to readmit the subject back into the protocol. One subject failed the retest conditions and was removed from the analysis.

Blood COHb levels were determined for each subject from venous samples before, during, and after exposure to CO or air. After 60 minutes of exposure, the chamber level of CO was lowered to 0 to 35 ppm atmospheric CO to maintain the peak percentage of blood COHb for an additional 90 minutes, which included 60 minutes of steady-state exposure, the treadmill exercise test, and an immediate post-exercise phase (Dahms et al. 1975). Blood samples were taken to verify the body burden level of CO at 30 minutes and 60 minutes of the steady-state phase of exposure, and after exercise.

The duration of the treadmill exercise test used to assess the impact of CO exposure on cardiac arrhythmias during exercise ranged from 3.75 to 18.5 minutes. Arrhythmia frequencies were monitored during the six-hour post-exposure phase, when the subjects followed their normal daily routine but still had elevated COHb levels based upon known rates of CO elimination, and for the approximate 10 hours of remaining ambulatory electrocardiographic recording when the COHb levels would have returned to baseline conditions.

MEASUREMENT OF CARBON MONOXIDE IN BLOOD

For operational purposes, immediate estimation of COHb levels was required; this was accomplished with an IL-282 CO-Oximeter. Previous studies in this laboratory have demonstrated that at the low levels of COHb used in this study, the CO-oximetry values of COHb are approximately 0.7% to 1% COHb higher than gas chromatography levels. The CO-Oximeter uses optical wavelengths that result in a significant influence of oxyhemoglobin on the COHb values. In a series of experiments carried out before the study, the effect of oxyhemoglobin on the average individual COHb readings was determined. All COHb readings were corrected for the influence of oxyhemoglobin. The reported CO-Oximeter COHb values represent means of three from a series of five determinations (high and low values were discarded), and this mean value was corrected to an average oxyhemoglobin level of 56%.

The effective CO dose each subject received during the exposure phase was based upon blood COHb levels. The primary measurement of the amount of CO bound to hemoglobin was made by gas chromatography (Dahms and Horvath 1974). All blood samples were collected as follows: from the antecubital vein, a 7-mL sample was drawn in a 10-mL sterile plastic syringe containing sodium heparin (10 units/mL of blood). The samples were mixed by repeated inversion or rotation and a 2-mL aliquot was analyzed by CO-Oximetry within 15 minutes. The remaining sample volume in the syringe (5 mL) was hemolyzed with dry saponin (Sigma Chemical Co., St. Louis, MO) and stored in the dark at 4°C until analyzed. Previous experiments demonstrated no effect of the hemolytic agent or storage on the CO content of samples (Allred et al. 1989a). All samples were analyzed within seven days of collection.

The chromatographic analysis consisted of quantitatively adding 200 µL of hemolyzed blood to a 1.8-mL sealed reaction vial containing 100 µL each of 1 N lactic acid and 0.5 M potassium ferricyanide solution, 10 µL of caprylic alcohol as an antifoam agent, and a magnetic stir bar. The reagents were degassed with the carrier gas, 99.995% helium, before adding the blood. The blood and reagents were mixed to achieve a vortex for three minutes while the head space (1.8 mL) was pressurized to the column pressure of 45 psig with helium. The head space was eluted onto the columns using a manual sampling valve. The columns were maintained at 70°C with a carrier flow rate of 100 mL/minute. The pre-columns and columns were in series in the following sequence: water stripper: 30 cm filled with 10- to 20-mesh Drierite (W.A. Hammond Drierite Co., Xenia, OH); Column 1: 90 cm filled with 80- to 100-mesh Porapak Q on firebrick (Anspec, Ann Arbor, MI); CO_2 stripper: 30 cm filled with 30- to 60-mesh 13x molecular sieve; and Column 2: 360 cm filled with 13x molecular sieve. The CO distribution curves were detected by thermal conductivity and quantified by peak height. A linear relationship between peak and height and peak area had been previously established with this method in this laboratory. Peak height has also been demonstrated to be linear over the entire range of physiologically possible CO contents. The gas chromatography system was calibrated with a known volume of certified standard gas (Matheson, E. Rutherford, N.J.) at standard temperature and pressure conditions. All measurements of CO content were made in triplicate, and the reported value is the average of each triplicate.

The standard format for presenting CO levels in blood is the percentage of COHb, meaning the percentage of the hemoglobin binding sites that are available for binding to oxygen or CO (the equivalent of the oxygen combining capacity). The computation of COHb from CO content measured by gas chromatography required the measurement of the

CO combining capacity. The capacity was calculated on a routine basis from the hemoglobin content in each blood sample as measured by the standard cyanomethemoglobin technique. Each sample was measured in triplicate. The capacity was calculated using the stoichiometric ratio of the molar combining capacity of hemoglobin with CO as being 1:1. The capacity was calculated as follows: CO capacity = 1.389 (mL/g, STPD) × hemoglobin concentration (g/dL). On a routine basis, the actual CO capacity of freshly collected samples was measured and compared to the calculated value for the same sample. The average of these comparisons (calculated and measured) over the course of these experiments was 101%. Therefore, the internal standardization of this method of measuring COHb levels was clearly established.

CHAMBER CARBON MONOXIDE CONCENTRATION

The ambient CO level in our environmental chamber is less than 4 ppm. The chamber CO level inhaled by the subject during his or her entire visit to the laboratory was monitored continuously. A sample line was placed near the subject's head to measure the CO level using a nondispersive infrared analyzer (model 3501-5CA, Bendix Combustion Engineering, Lewisburg, WV). Before monitoring subjects each day, the analyzer was calibrated using U.S Environmental Protection Agency standard gases traceable to National Institute of Standards and Technology standards for CO (AIRCO, Detroit, MI).

AMBULATORY ELECTROCARDIOGRAPHIC TECHNIQUE

The screening consisted of continuous 20-hour ambulatory ECGs obtained on a portable 3-channel recorder, with electrodes placed in a bipolar V_1 and V_5 position. The recordings were made with Avionics model 459 recorders and analyzed on an Avionics Trendscriber (model 9100), which permitted individual programming of a multifactorial computer to recognize template configurations of normal and ectopic beats. Validity assessment, defined on a stratified hand-counted 150-hour ventricular ectopic beat database and a 50-hour supraventricular ectopic beat database, had determined a positive predictive accuracy of 94%, a sensitivity of 92%, and a false-positive rate of 6% for ventricular ectopic beats. Each recorder had an event marker that indicated critical time points during the experimental exposure. Thus, the event marker was used to signal the onset of the two-hour preexposure period, the end of the preexposure phase, the onset of exposure, the start of the steady-state phase, the onset of exercise, the end of exercise, and so on. Each ambulatory ECG was printed out with a fiber-optic printer, and the real-time printout was hand counted for ventricular arrhythmias. The entire recording was hand counted, except for the last phase of the recording, which started six hours after the completion of exercise. Ventricular arrhythmias during this last phase of the recording interval were analyzed by computer, unless there was a discrepancy between the computer measurements and hand counts for the subjects during the previous periods. This occurred in two patients in whom the last phase was also hand counted. The data obtained include an hourly count of total premature ventricular beats, ventricular couplets, and nonsustained (less than 30 seconds) and sustained ventricular tachycardia.

EXERCISE TESTING

A Modified Case II Marquette system was used to gather multiple-lead electrocardiographic data. Arrhythmia frequency was assessed during the exercise test using the continuous ambulatory ECG. The exercise test was a symptom-limited modified Naughton protocol. Subjects walked for two minutes at each stage of the exercise protocol; each stage was designed to increase the workload by an estimated 1 met (basal metabolic equivalent). The maximum potential workload using this protocol was 11 mets at 18 to 20 minutes of exercise. The presence of severe fatigue, dyspnea, dizziness, malignant ventricular arrhythmias, marked ST-segment depression from baseline (at least 3 mm or 0.3 mV), fall in systolic blood pressure of 20 mm Hg from the preceding reading, or progressive angina were indications for test termination. The presence of reproducible ischemic ST-segment depression (horizontal or downsloping ST-segment depression of at least 1 mm or 0.1 mV, compared with baseline) occurred during exercise in nine patients (Table 1).

DATA ANALYSIS

The primary question explored in this study was whether CO exposure resulting in 3% and 5% blood COHb levels, as measured by gas chromatography, had a significant impact on total and repetitive ventricular arrhythmia frequency. Seven specific time intervals were studied: (1) two hours before CO exposure (baseline); (2) during a two-hour CO or air exposure; (3) during a two-hour rest period (steady state); (4) during an exercise period; (5) during an exercise recovery period; (6) six hours after chamber exposure (CO unload); and (7) the remaining recording interval (approximately 10 hours). Exercise-induced ventricular arrhythmia frequency was a primary end point. The total number and type of ventricular arrhythmias recorded during the five minutes preceding exercise, during exercise, and during a

five-minute post-exercise phase were noted. The exercise level was similar on each of the three test days. However, because the exercise times were not precisely the same on each of the three recording days, ventricular arrhythmia count rates were adjusted for total exercise duration. This was done by dividing the total number of VEBs observed during the test by the duration of treadmill time in minutes, and multiplying this figure by 60 to provide an hourly VEB rate.

Differences in average hourly heart rate, number of premature ventricular beats, repetitive forms, and episodes of nonsustained and sustained ventricular tachyarrhythmia were compared using a two-way analysis of variance (ANOVA) (Dixon et al. 1988). Initial plots of the VEB data indicated that they were not normally distributed: there were outliers, and the data were skewed. Therefore, we used nonparametric statistical methods. The Friedman test (Woolson 1989) of the ANOVA for repeated measures was used; this is a nonparametric equivalent of a two-way ANOVA for this design and is an extension of the sign test for more than two matched groups. The Friedman test was used for the post-hoc pair-wise multiple comparisons. In addition, parametric statistical methods were used to analyze both the transformed data (log) and the group means of individual differences between the VEBs per hour data for each period corrected for the daily preexposure VEBs per hour. There were no differences observed between the analyses on the transformed data and the Friedman test on the ANOVA of the actual data.

For each of the three COHb conditions, the Friedman test was used to identify any statistically significant differences in the number of VEBs per hour during each of the above specified time intervals. The analysis was performed using all 30 subjects, and repeated after stratification by ejection fraction (ejection fraction less than than 40%, $n = 13$; ejection fraction greater than 40%, $n = 17$). Similar analyses were performed with the subjects stratified by those with at least 60 VEBs per hour ($n = 15$) or those with less than 60 VEBs per hour at baseline ($n = 15$), and by presence ($n = 11$) or absence ($n = 19$) of exercise-induced chest pain or abnormal exercise-induced ST-segment depression.

RESULTS

CHAMBER CARBON MONOXIDE AND BLOOD CARBOXYHEMOGLOBIN MEASUREMENTS

The average COHb levels during the CO exposure resulting in steady-state COHb levels on the three test days after 120 minutes of total exposure were 0.7%, 3.2%, and 5.1% for room air, target 3% (low), and target 5% (high) COHb levels, respectively (Table 2). In order to achieve the average 3.2% COHb level, 159 ± 25 (mean ± SD) ppm CO were required during rapid uptake, and 19.3 ± 0.8 ppm CO were required for maintenance levels. The average 5.1% COHb levels required 292 ± 31 ppm CO for rapid uptake and 31 ± 1.2 ppm CO for maintenance levels (Table 3). The group mean

Table 2. Carboxyhemoglobin Levels During Exposure to Carbon Monoxide as Measured by Gas Chromatography[a]

	Baseline (%)	120 Minutes of CO Exposure[b] (%)	1 Minute After Exercise (%)	5 Minutes After Exercise (%)
Room air exposure	0.73 ± 0.20	0.67 ± 0.13	0.60 ± 0.14	0.55 ± 0.28
Low-level CO exposure (target 3% COHb)	0.69 ± 0.12	3.24 ± 0.27	2.94 ± 0.30	3.26 ± 0.24
High-level CO exposure (target 5% COHb)	0.71 ± 0.18	5.24 ± 0.43	4.71 ± 0.46	5.13 ± 0.40

[a] Values are means ± SD for all subjects ($n = 30$).

[b] Includes one hour of uptake and one hour of steady-state exposure.

Table 3. Atmospheric Carbon Monoxide Levels During Exposure

	CO Levels During Exposure[a] (ppm)		
	Baseline	Uptake	Maintenance
Room air exposure (0.7% COHb)	< 1	< 1	< 1
Low-level CO exposure (3.2% COHb)	< 1	159.4 ± 24.8	19.3 ± 0.8
High-level CO exposure (5.1% COHb)	< 1	291.8 ± 30.5	30.5 ± 1.2

[a] Values are expressed as means ± SD.

values for percentage of COHb, as measured by the IL-282 CO-Oximeter, are found in Appendix Table A.1. The measured changes in COHb levels during the uptake and maintenance periods of the target 5% COHb exposure protocol are shown in Figure 2.

VENTRICULAR ARRHYTHMIA FREQUENCY AT REST

The mean numbers of VEBs per hour during the measurement periods when the subjects were at rest (seated) for the entire period are shown in Figure 3. The periods consisted of 133 minutes of rest, 60 minutes of CO uptake, and 60 minutes of COHb steady state. There were no significant differences in the number of VEBs per hour between the days for any of these periods at rest. These measured periods did not contain the intermittent bouts of exercise found in the later periods, when the subjects were ambulatory.

VENTRICULAR ARRHYTHMIA FREQUENCY ON DIFFERENT TEST DAYS

The mean numbers of VEBs per hour were similar at baseline and on each of the three test days (Table 4). In the aggregate, there were no significant differences in the mean numbers of VEBs per hour during the CO steady-state phase, CO unloading phase, and during the balance of the recording interval. However, there was a trend toward a decreased number of VEBs per hour at the highest CO exposure level (Table 4).

VENTRICULAR ARRHYTHMIA FREQUENCY AT BASELINE

The impact of CO exposure among subjects stratified by low (less than 60 VEBs per hour) and high (at least 60 VEBs per hour) levels of VEBs according to the baseline ambulatory ECG is illustrated in Table 5. There were no significant differences in ventricular ectopy frequency after CO exposure, regardless of the level of ventricular ectopy at baseline (Table 5). Similar results were obtained when the patients were stratified by 30 VEBs per hour, as shown in Appendix Table B.1.

EXERCISE-INDUCED ST-SEGMENT DEPRESSION OR ANGINA AT BASELINE

The effects of both levels of CO exposure were compared to those of room air in patients stratified by the presence or absence of exercise-induced ischemic ST-segment depression or angina at baseline (Table 6). There were no significant differences between room air and CO exposure days for the different activity intervals regardless of whether exercise-induced angina or ST-segment depression was present at baseline.

EJECTION FRACTION AT BASELINE

The effects of both levels of CO exposure were compared to those of room air in patients stratified by a low ejection fraction of less than 0.40, and an ejection fraction greater

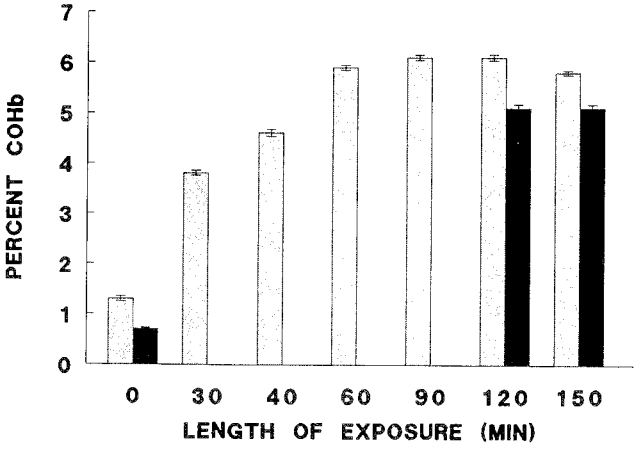

Figure 2. COHb values (measured by gas chromatography and CO-oximetry) during the course of the monitoring period for the 5% COHb target exposure. The values measured by gas chromatography are noted with solid bars; the values measured by CO-oximetry are noted with hatched bars. The data presented are group mean ± SEM values (n = 30).

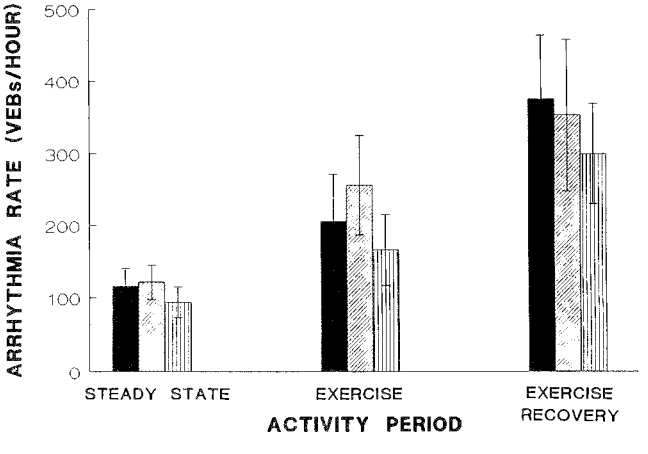

Figure 3. Combined effect of CO exposure and exercise on VEBs per hour, shown for the steady-state monitoring period before exercise (one hour), the exercise period (0.15 hours), and the exercise recovery period (0.12 hours). Group mean values (n = 30) and SEM are presented for all three randomized exposure conditions: room air (solid bars), 3.2% COHb (diagonally hatched bars), and 5.1% (vertically hatched bars).

Table 4. Effect of Carbon Monoxide Exposure on the Number of Ventricular Ectopic Beats per Hour by Activity Period

	Events per Hour by %COHb[a]		
Activity Period	0.7%	3.2%	5.1%
Baseline	116.0 ± 188.6	118.0 ± 175.2	107.4 ± 175.8
CO uptake	110.3 ± 193.4	105.6 ± 141.0	86.9 ± 108.2
COHb steady state	115.4 ± 152.5	121.2 ± 170.8	93.8 ± 128.5
Exercise test	205.7 ± 358.2	255.9 ± 375.2	166.3 ± 268.4
Exercise recovery	374.7 ± 489.6*	352.7 ± 575.9	299.1 ± 379.8
CO unload	183.9 ± 254.7*	193.5 ± 260.2	165.2 ± 192.8
Remainder	131.5 ± 257.0	136.7 ± 222.2	129.0 ± 236.5

[a] Values are expressed as means ± SD for all subjects (n = 30). All row p values for comparing 0.7% with 3.2% COHb and 0.7% with 5.1% COHb exceed 0.05. All column p values for comparing baseline with activity periods exceed 0.05, except those marked by an *.

Table 5. Effect of Carbon Monoxide Exposure on the Number of Ventricular Ectopic Beats per Hour by Activity Period and Stratified by 60 Ventricular Ectopic Beats per Hour on the Entrance Screening Day

	Events per Hour by %COHb[a]		
Activity Period	0.7%	3.2%	5.1%
Subjects with ⩽ 60 VEBs/hour (n = 15)			
Baseline	27.2 ± 19.2	33.3 ± 21.7	37.3 ± 38.4
CO uptake	26.4 ± 24.5	37.7 ± 30.7	31.2 ± 24.9
COHb steady state	41.8 ± 35.4	49.7 ± 41.8	40.9 ± 31.15
Exercise test	70.8 ± 86.6	117.9 ± 174.1	42.6 ± 44.1
Exercise recovery	159.1 ± 210.6	173.7 ± 222.2	226.3 ± 341.4
CO unload	54.5 ± 37.37	52.0 ± 40.5	60.1 ± 58.0
Remainder	39.5 ± 27.3	32.1 ± 24.0	35.1 ± 31.0
Subjects with > 60 VEBs/hour (n = 15)			
Baseline	204.9 ± 237.4	202.6 ± 218.6	177.4 ± 228.1
CO uptake	194.3 ± 248.6	173.4 ± 174.2	142.6 ± 130.4
COHb steady state	189.0 ± 187.9	192.7 ± 218.5	146.8 ± 165.1
Exercise test	340.6 ± 468.2	394.0 ± 470.1	289.9 ± 338.5
Exercise recovery	590.2 ± 593.8	531.7 ± 754.2	371.9 ± 413.5
CO unload	313.3 ± 311.6	335.1 ± 309.3	270.3 ± 223.5
Remainder	223.4 ± 343.5	241.3 ± 279.8	222.9 ± 309.9

[a] Values are expressed as means ± SD. All row p values for comparing 0.7% with 3.2% COHb and 0.7% with 5.1% COHb exceed 0.05.

than 0.40 (Table 7). There were no significant differences between room air and CO exposure days for the different intervals measured regardless of a relatively low ejection fraction (0.40) or a normal or mild impairment of left ventricular function (ejection fraction greater than 0.40).

EXERCISE TEST ANALYSIS

There was no impact of CO exposure on the frequency of exercise-induced VEBs at either level of CO exposure (Tables 4 through 7). The levels of COHb used in this study had no effect on the heart rate or systolic blood pressure response to the exercise test (Table 8).

The end point of time to onset of horizontal or downsloping ST-segment depression of at least 1 mm or 0.1 mV (the depth of ST-segment depression that was analyzed in the Health Effects Institute Multicenter CO Study [Allred et al. 1989a,b]) and the number of abnormal electrocardiographic leads were not analyzed in the present study according to CO exposure levels. This was because the number of patients with exercise-induced electrocardiographic changes who were not on digitalis therapy was too small to permit satisfactory analysis.

Table 6. Effect of Carbon Monoxide Exposure on the Number of Ventricular Ectopic Beats per Hour by Activity Period and Stratified by Presence or Absence of Abnormal Exercise-Induced ST-Segment Depression or Angina

	Events per Hour by %COHb[a]		
Activity Period	0.7%	3.2%	5.1%
Subjects with Exercise-Induced Ischemia (n = 11)			
Baseline	82.0 ± 71.2	102.1 ± 121.5	84.2 ± 73.2
CO uptake	78.5 ± 77.4	92.4 ± 76.4	73.8 ± 81.6
COHb steady state	79.8 ± 73.6	99.4 ± 74.7	66.3 ± 63.05
Exercise test	177.2 ± 267.6	187.8 ± 201.7	276.3 ± 405.3
Exercise recovery	372.8 ± 423.4*	314.4 ± 503.2	247.4 ± 293.8
CO unload	169.0 ± 164.2	119.5 ± 86.0	169.2 ± 173.4
Remainder	78.3 ± 61.7	82.2 ± 86.6	92.2 ± 98.8
Subjects without Exercise-Induced Ischemia (n = 19)			
Baseline	135.7 ± 231.0	127.2 ± 202.6	120.2 ± 215.1
CO uptake	128.7 ± 236.6	113.2 ± 169.1	94.5 ± 122.5
COHb steady state	136.0 ± 182.3	133.8 ± 208.5	109.8 ± 153.9
Exercise test	222.3 ± 407.6	295.4 ± 447.3	102.6 ± 114.8
Exercise recovery	375.7 ± 535.3	374.8 ± 626.2	329.0 ± 426.5
CO unload	192.5 ± 298.9	236.4 ± 315.7	162.9 ± 207.8
Remainder	162.3 ± 318.7	168.3 ± 269.3	150.3 ± 288.8

[a] Values are expressed as means ± SD. All row p values for comparing 0.7% with 3.2% COHb and 0.7% with 5.1% COHb exceed 0.05. All column p values for comparing baseline with activity periods exceed 0.05, except those marked by an *.

PAIRED VENTRICULAR ECTOPIC BEATS AND NONSUSTAINED VENTRICULAR TACHYCARDIA

The frequencies of ventricular couplets and nonsustained ventricular tachycardia were similar in patients exposed to room air, and low and high levels of CO (Table 9). There was a trend toward less frequent repetitive VEB forms at baseline on the 5.1% COHb day. To adjust for the difference in baseline incidence of repetitive forms, the baseline measurements were subtracted from each of the subsequent

Table 7. Effect of Carbon Monoxide Exposure on the Number of Ventricular Ectopic Beats per Hour by Activity Period and Stratified by Baseline Left Ventricular Ejection Fraction

	Events per Hour by %COHb[a]		
Activity Period	0.7%	3.2%	5.1%
Subjects with Ejection Fraction < 40% (n = 13)			
Baseline	188.6 ± 263.4	173.5 ± 231.4	156.8 ± 252.2
CO uptake	182.1 ± 273.9	160.3 ± 194.7	118.5 ± 136.4
COHb steady state	180.4 ± 205.9	170.0 ± 236.2	137.9 ± 177.1
Exercise test	287.8 ± 460.1	222.8 ± 297.4	161.8 ± 221.4
Exercise recovery	318.3 ± 310.1	193.8 ± 211.3	284.6 ± 343.2
CO unload	265.7 ± 352.5	241.8 ± 357.2	219.2 ± 261.8
Remainder	240.8 ± 367.2	210.9 ± 316.7	228.4 ± 337.1
Subjects with Ejection Fraction ≥ 40% (n = 17)			
Baseline	60.5 ± 69.6	75.5 ± 105.1	69.6 ± 69.31
CO uptake	55.5 ± 64.4	63.7 ± 57.2	62.7 ± 76.55
COHb steady state	65.7 ± 65.7	83.9 ± 87.4	60.1 ± 60.3
Exercise test	142.9 ± 253.1	281.2 ± 433.2	169.6 ± 306.3
Exercise recovery	417.8 ± 598.1	474.1 ± 729.0*	310.1 ± 415.8
CO unload	121.4 ± 121.6	156.6 ± 153.8	123.9 ± 108.6
Remainder	47.9 ± 38.2	80.0 ± 79.9	53.0 ± 44.6

[a] Values are expressed as means ± SD. All row p values for comparing 0.7% with 3.2% COHb and 0.7% with 5.1% COHb exceed 0.05. All column p values for comparing baseline with activity periods exceed 0.05, except those marked by an *.

Table 8. Group Average Heart Rates and Systolic Blood Pressures During the Exercise Period of the Arrhythmia Monitoring[a]

		Room Air (0.7% COHb)		Low COHb (3.2%)		High COHb (5.1%)	
Activity Period	Condition	Heart Rate (beats/min)	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/min)	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/min)	Systolic Blood Pressure (mm Hg)
COHb steady state	Rest	90.0 ± 14.8	131.7 ± 19.7	91.6 ± 15.9	129.5 ± 21.9	92.6 ± 16.4	127.6 ± 19.5
Exercise test	Maximal exercise	126.3 ± 20.8	171.7 ± 23.5	130.1 ± 23.0	169.5 ± 26.0	129.6 ± 24.1	168.3 ± 27.5

[a] Values are expressed as means ± SD.

phases (Appendix Table B.4). There were no significant differences in the frequency of repetitive ventricular forms before or after adjustment for baseline frequency.

DISCUSSION

The main finding in this study is that CO exposures producing 3% and 5% COHb levels, as measured by gas chromatography, do not result in a proarrhythmic effect during normal daily activity, as measured by both ambulatory and exercise electrocardiography. The National Ambient Air Quality Standard for CO, published by the U.S. Environmental Protection Agency (EPA) in 1971, is 9 ppm for an eight-hour averaging time and 35 ppm for a one-hour averaging time. According to estimates by the EPA, a typical adult involved in moderate activity would have a COHb level of approximately 2.0% after a one-hour exposure to CO at 35 ppm (U.S. Environmental Protection Agency 1984). Results from exposure models estimate that 60% of individuals with cardiovascular disease would exceed these levels of COHb (U.S. Environmental Protection Agency 1984). The offset in measurement of COHb is approximately 0.7% to 1% greater with CO-oximetry than with gas chromatography. In a study of 63 men with documented coronary artery disease, exertional angina, and exercise-induced myocardial ischemia, the time to development of ischemic ST-segment depression after exposure to CO at 2.0% and 3.9% COHb levels was significantly decreased by 5.1% and 12.1%, respectively, compared with the control day (Allred et al. 1989a,b). Thus, low levels of CO have an adverse effect on patients with active exertional angina and documented coronary artery disease.

The subjects selected for the present study had well-documented coronary artery disease and were included on the basis of having chronic ventricular arrhythmias with at least 30 VEBs per hour. Patients with recent myocardial infarction or unstable angina were excluded because in the early post-infarction phase, high-density VEBs and nonsustained ventricular tachycardia on ambulatory ECGs before hospital discharge have been associated with an increased incidence of cardiac events (Pandis and Morganroth 1983). We also excluded patients with sustained ventricular tachycardia and patients with ventricular ectopy who were hemodynamically unstable. Thus, the clinical patient subset selected for this study consisted of those patients with well-documented chronic ischemic heart disease and frequent ventricular ectopy. Of the 30 subjects in the study, 10 had

Table 9. Effect of Carbon Monoxide Exposure on the Number of Paired Beats and Nonsustained Ventricular Tachycardia Episodes per Hour by Activity Period

	Events per Hour by %COHb[a]		
Activity Period	0.7%	3.2%	5.1%
Baseline	14.3 ± 31.6	10.0 ± 24.4	5.7 ± 14.7
CO uptake	10.8 ± 26.1	12.2 ± 25.4	7.4 ± 16.4
COHb steady state	10.8 ± 21.0	13.5 ± 29.4	10.8 ± 22.3
Exercise test	45.1 ± 134.0	31.6 ± 74.0	17.9 ± 41.3
Exercise recovery	62.2 ± 126.5	32.8 ± 65.8	52.9 ± 130.6
CO unload	24.2 ± 51.2	19.4 ± 14.6	14.4 ± 30.4
Remainder	10.6 ± 26.9	11.7 ± 28.5	9.0 ± 20.4

[a] Values are expressed as means ± SD (n = 30). All row p values for comparing 0.7% with 3.2% COHb and 0.7% with 5.1% COHb exceed 0.05. All column p values for comparing baseline with activity periods exceed 0.05.

a history of myocardial infarction; seven of these had an ejection fraction of less than 40%. Of the 30 subjects, 12 (40%) had nonsustained ventricular tachycardia at baseline. Clearly, patients with ventricular ectopy are a heterogeneous population ranging from healthy individuals with structurally normal hearts, to patients with markedly impaired left ventricular function and hemodynamically unstable ventricular arrhythmias (Moss et al. 1979; Bigger et al. 1984). The patients in the current protocol represent a prognostic intermediate group (Bigger et al. 1984) in whom low-level CO exposure did not worsen their ventricular arrhythmias. Patients with more significant diseases, such as those with life-threatening ventricular ectopy admitted to a hospital for hemodynamic events, and patients with sustained ventricular tachycardia in the early post-infarction phase are clearly not suitable as experimental subjects for the current type of protocol.

The 3% and 5% target COHb levels assessed in the present study are similar to the levels studied in a previous HEI-supported study on patients with chronic ventricular arrhythmia (Sheps et al. 1990, 1991) in which levels of COHb also were measured by CO-oximetry. Our findings contrast with the findings of Sheps (1990), in which the frequency of isolated and multiple VEBs per hour during exercise was significantly greater at 6% COHb (measured by IL-282 CO-Oximeter) than at 4% COHb or in room air. In the Sheps study, the frequency of total and multiple VEBs was not significantly different from that for room air in the preexercise phase, or for the post-exercise phase for up to six hours after CO exposure. The only statistically significant difference found in the Sheps study was during brief (less than 20 minutes) bouts of exercise. Ventricular arrhythmias are, to some extent, randomly occurring events, and the shorter the measurement interval, the larger the measurement variability. Exercise is a known stressor that can increase ventricular arrhythmia frequency, particularly in the immediate post-exercise phase. In the Sheps study, the duration of time that ventricular arrhythmias were monitored at baseline is not stated, and the subject's activity level when the baseline measurements were obtained also is not given. In the present study, we designed the protocol to balance the need for sufficiently long recording intervals with the limitation of subject compliance over a prolonged visit. We monitored the subjects for two hours at rest before CO exposure, and allowed at least a one-hour CO uptake phase and a one-hour constant COHb level phase to compare with the baseline measurements (Figure 4).

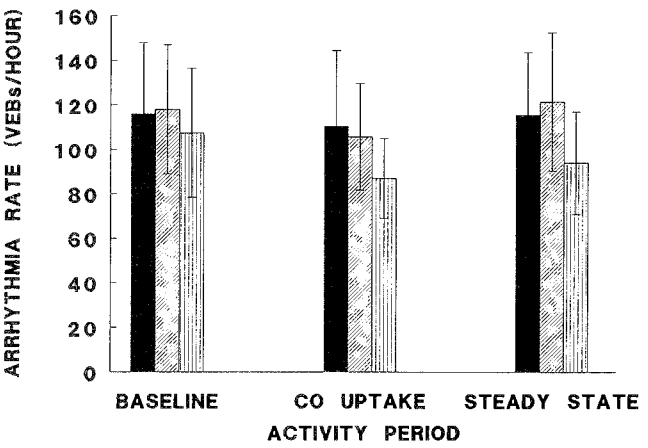

Figure 4. Effect of CO exposure on VEBs per hour at rest for the monitoring periods during baseline before exposure (two hours), during CO uptake (one hour), and the steady-state or maintenance of COHb (one hour). Group mean ± SEM values (n = 30) are presented for all three randomized exposure conditions: room air (solid bars), 3.2% COHb (diagonally hatched bars), and 5.1% COHb (vertically hatched bars).

There are also important clinical differences in subject selection between the Sheps study and the present one (Ta-

Table 10. Similarities and Differences in the Effect of Carbon Monoxide on Ventricular Arrhythmias in Subjects with Coronary Artery Disease[a]: Present Study versus Study by Sheps and Colleagues (1990)

Parameter	Present Study	Sheps et al.
Number of subjects	30	41
% Subjects with ≥ 50 VEBs/hour at baseline	70% (21)	49% (20)
Exercise position	Upright	Supine
Observation frequency	4 Days within 30 days	4 Consecutive days
Beta blocker use	30% (9)	56% (23)
% Subjects with angina or increase in ST-segment depression ≥ 1 mm	37% (11)	54% (22)
Subjects with ejection fraction < 40%	43% (13)	14% (6)
Preexposure %COHb	0.7%[b]	1.8%[c]

[a] Coronary artery disease is defined as arterial stenosis with at least 70% narrowing.

[b] Measured by gas chromatography.

[c] Measured by CO-oximetry.

ble 10). In the present study, the percentage of subjects who had at least 50 VEBs per hour was significantly greater than in the Sheps study, and ventricular function was significantly worse. The percentage of subjects who had myocardial ischemia, as evidenced by exercise-induced angina or ischemic ST-segment depression, was greater in the Sheps study, and a greater percentage of subjects were taking beta-adrenergic blocking drugs. In the HEI Multicenter CO Study (Allred et al. 1989a), low levels of COHb in patients with exercise-induced angina and myocardial ischemia decreased the length of time to onset of angina and the length of time to the onset of ST-segment depression. Myocardial ischemia is a well-known cause of ventricular arrhythmias and can result in a proarrhythmic effect. We analyzed our own data stratifying patients by presence or absence of exercise-induced angina or exercise-induced ST-segment depression of at least 1 mm. We did not find a significant increase in ventricular arrhythmia frequency, regardless of whether or not the patient had exercise-induced angina or ischemia at baseline (Table 6).

Other protocol differences between the two studies also preclude direct comparison of the results. In the Sheps study, COHb levels were determined with an IL-282 CO-Oximeter, an instrument that is inaccurate at low levels of COHb (Allred et al. 1989a). The inaccuracy of the CO-Oximeter measurements raises a concern that there may be variability in the COHb determination itself. This may account for an average value of 1.8% COHb at rest, a level that might be expected in a moderate smoker. In the present report, COHb levels were determined by gas chromatography.

ACCURACY OF AMBULATORY VENTRICULAR ECTOPIC MEASUREMENTS

Spontaneous variability of ventricular ectopic activity as a function of time is well documented in patients with chronic ventricular arrhythmias. In a study by Anastasiou-Nana and colleagues (1988), 47 consecutive patients with at least 30 chronic ventricular arrhythmias per hour were studied in intervals of one day, weekly for four weeks, and one year or longer to determine VEB variability rate. The percentage of increases in total VEBs and repetitive beats required to establish arrhythmia aggravation with a 95% confidence limit were calculated at 124% and 303%, respectively, for one-day interval measurements, 583% and 1,730% for 4- to 10-day interval measurements, and 2,159% and 1,692% for the ambulatory ECG recording intervals separated by as much as 25 to 31 days. Intrapatient hour-to-hour variability in exercise-induced ventricular arrhythmia frequency is also a well-known phenomenon (Anastasiou-Nana et al. 1988). The variability in exercise-induced ventricular arrhythmias becomes particularly relevant when one considers that the total recording interval for an exercise test is usually less than 30 minutes. The ambulatory ECG recording during normal daily activities provides multiple episodes of exercise and other forms of stress during daily activities and may provide a more complete estimate of the impact of CO on ventricular arrhythmia frequency. To adjust for ventricular arrhythmia variability, we performed a two-way ANOVA comparing the same patient at baseline on each test day (two-hour preexposure phase) to results obtained during subsequent phases of the protocol. Furthermore, we compared across-time intervals for CO exposure days to the room air day to detect any significant differences. We were unable to demonstrate a significant difference in total VEB counts or complex ventricular ectopy at 3.2% and 5.1% COHb levels during normal daily activities and during and immediately after symptom-limited exercise.

POWER CALCULATIONS

The statistical power necessary to ascertain differences between the measurement periods and between conditions was determined for simple pair-wise comparisons for the primary hypotheses. These comparisons showed differences between baseline and steady-state exposures, and between baseline and exercise exposures for each condition. In addition, pair-wise comparisons for steady-state and exercise values between the three conditions were made. The power calculations were made using a paired t test with a correction in the alpha level for multiple comparisons. The number of subjects used provided approximately 80% power to detect a change from the baseline level in the magnitude of 50 VEBs per hour. Thus, small but significant differences in the impact of ventricular ectopic activity may have been missed in the present series because of the relatively small sample size.

RELEVANCE OF STUDY TO POPULATION EXPOSURE CONDITIONS

To maintain constant COHb levels (3% and 5% targets) during the steady-state and exercise phases of the protocol, we used 19 ppm and 31 ppm CO, respectively. Both levels are within the recommended one-hour exposure limit of 35 ppm CO. However, the levels of COHb in the subjects during this steady-state exposure were elevated to levels that exceed the upper level of 2% COHb that most individuals would reach during either an eight-hour exposure to 9 ppm or a one-hour exposure to 35 ppm (U.S. Environmental Protection Agency 1984). We assumed that if no effects were observed at these low levels of COHb, the CO probably would not have a proarrhythmic effect at slightly lower levels.

CONCLUSIONS

Carbon monoxide exposure resulting in 3% and 5% COHb levels, as measured by gas chromatography, does not result in a proarrhythmic effect during normal daily activity, as measured by ambulatory and exercise electrocardiography. The findings confirm the study by Hinderliter and colleagues (1989) of patients with ischemic heart disease and no ventricular ectopy, and the data of Sheps and coworkers (1990) for the nonexercise phase of their protocol. Our data differ from those of Sheps and associates, who report that during the approximately 14 minutes of exercise activity, ventricular ectopy appeared to worsen at higher levels of CO exposure. This did not happen in the present study. An explanation as to why this difference may have occurred is presented.

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APPENDIX A. Additional Descriptive Information

Table A.1. Carboxyhemoglobin Levels Measured By IL-282 CO-Oximeter During Exposure[a]

	CO Uptake Period				COHb Steady State: Maintenance CO Exposure			
	Baseline	30 Minutes	40 Minutes	End Uptake	90 Minutes	120 Minutes	1 Minute After Exercise	5 Minutes After Exercise
Room air exposure	1.34 ± 0.29	1.31 ± 0.25	1.31 ± 0.25	1.30 ± 0.24	1.29 ± 0.23	1.27 ± 0.22	1.06 ± 0.29	1.13 ± 0.29
Low-level CO exposure	1.28 ± 0.27	2.72 ± 0.19	3.12 ± 0.19	3.89 ± 0.13	4.04 ± 0.15	3.98 ± 0.17	3.56 ± 0.20	3.70 ± 0.76
High-level CO exposure	1.27 ± 0.26	3.84 ± 0.28	4.59 ± 0.38	5.93 ± 0.27	6.13 ± 0.29	6.06 ± 0.33	5.47 ± 0.28	5.82 ± 0.21

[a] Values are expressed as means ± SD.

Table A.2. Length of Activity Periods[a] Used for the Analysis of the Arrhythmia Data in Response to Exposure to Room Air or to Different Levels of Carbon Monoxide

	0.7% COHb		3.2% COHb		5.1% COHb	
Activity Period	Mean	Range	Mean	Range	Mean	Range
Baseline	133	120–153	132	120–145	135	120–150
CO uptake	60	—	60	—	60	—
COHb steady state	60	—	60	—	60	—
Exercise test	8.9	3–17	9.2	3–16	9.3	3–16
Exercise recovery	6.8	1–11	6.9	5–16	6.9	5–15
CO unload	360	—	360	—	360	—
Remainder	646	539–830	615	453–833	646	523–858

[a] Lengths of activity periods are given in minutes.

Table A.3. Total Number of Arrhythmias in Response to Exposure to Room Air, to Different Levels of Carbon Monoxide, and to Exercise[a]

	Total Ventricular Ectopic Beats		
Activity Period	0.7% COHb	3.2% COHb	5.1% COHb
Baseline	258 ± 435	253 ± 386	229 ± 394
Exercise test	32 ± 50	37 ± 58.2	32 ± 41
Exercise recovery	39 ± 48	40 ± 58	32 ± 41
CO unload	1,059 ± 1,516	1,125 ± 1,559	965 ± 1,139
Remainder	1,337 ± 2,500	1,217 ± 1,714	1,334 ± 2,254

[a] Values are group means ± SD (n = 30).

Table A.4. Summary Description of the Subjects Studied

Number of subjects randomized	33
Males	28
Females	5
Number of subjects employed	5
Number of subjects in the analyzed data set	30
Reasons for removal of subjects from study	
Did not complete series	1
Loss of Holter data	1
Did not meet COHb criterion	1
Evidence of ischemic disease	
Angiographic evidence	31
Prior myocardial infarction	12
Positive stress thallium	17
Positive stress test	2

APPENDIX B. Alternative Analyses

Table B.1. Effect of Carbon Monoxide Exposure on the Number of Ventricular Ectopic Beats per Hour by Activity Period and Stratified by Baseline Ventricular Ectopic Beat Frequency

	Ventricular Ectopic Beats per Hour[a]		
Activity Period	0.7% COHb	3.2% COHb	5.1% COHb
Subjects with ⩽ 30 VEBs per Hour (n = 12)			
Baseline	13.2 ± 10.3	24.0 ± 23.1	25.1 ± 26.4
COHb steady state	22.3 ± 17.0	33.8 ± 30.7	30.6 ± 29.9
Exercise test	114.3 ± 207.1	263.8 ± 522.6	57.3 ± 117.7
Exercise recovery	310.0 ± 535.1	332.1 ± 647.3	307.3 ± 498.0
CO unload	58.9 ± 53.4	113.0 ± 153.0	73.3 ± 67.2
Remainder	36.3 ± 29.8	56.5 ± 71.7	30.6 ± 29.4
Subjects with > 30 VEBs per Hour (n = 18)			
Baseline	184.6 ± 219.4	180.6 ± 204.1	162.2 ± 210.5
COHb steady state	177.5 ± 171.1	179.5 ± 200.4	136.0 ± 151.3
Exercise test	266.7 ± 425.7	250.7 ± 252.4	238.9 ± 316.2
Exercise recovery	417.8 ± 467.6	366.4 ± 542.3	293.6 ± 292.6
CO unload	267.2 ± 300.8	247.2 ± 304.5	226.5 ± 224.8
Remainder	194.9 ± 318.5	190.2 ± 270.8	294.6 ± 288.9

[a] Values represent means ± SD. All row p values for comparing 0.7% with 3.2% COHb and 0.7% with 5.1% COHb exceed 0.05. All column p values for comparing baseline with activity periods exceed 0.05.

Table B.2. Effect of Carbon Monoxide Exposure on the Number of Ventricular Ectopic Beats per Hour by Activity Period and Corrected for Daily Baseline Ventricular Ectopic Beat Frequency

	Ventricular Ectopic Beats per Hour[a]		
Activity Period	0.7% COHb	3.2% COHb	5.1% COHb
CO uptake	−5.7 ± 55.9	−12.4 ± 60.6	−20.5 ± 107.9
COHb steady state	−0.6 ± 138.9	3.2 ± 66.4	−13.5 ± 63.0
Exercise test	89.7 ± 309.9	138.0 ± 362.8	58.9 ± 287.7
Exercise recovery	258.6 ± 459.5	234.7 ± 554.4	191.7 ± 367.4
CO unload	67.9 ± 107.6	75.6 ± 152.0	57.8 ± 105.7
Remainder	15.4 ± 99.9	18.8 ± 114.4	21.6 ± 95.6

[a] Values represent means ± SD (n = 30).

Table B.3. Effect of Carbon Monoxide Exposure on the Number of Ventricular Ectopic Beats per Hour by Activity Period and Corrected for the Corresponding Values Obtained on the Randomized Room Air Exposure Day

	Ventricular Ectopic Beats per Hour[a]	
Activity Period	3.2% COHb–Room Air	5.1% COHb–Room Air
Baseline	1.9 ± 84.6	−8.7 ± 82.3
CO uptake	−4.7 ± 102.3	−23.4 ± 120.4
COHb steady state	5.8 ± 123.4	−21.6 ± 111.4
Exercise test	50.2 ± 382.6	−39.5 ± 334.8
Exercise recovery	−22.0 ± 235.2	−75.6 ± 380.2
CO unload	9.6 ± 142.0	−18.7 ± 105.3
Remainder	5.3 ± 94.2	−2.5 ± 55.4

[a] Values represent means ± SD (n = 30). All p values for the row comparisons exceed 0.05.

Table B.4. Effect of Carbon Monoxide Exposure on the Number of Paired Ventricular Ectopic Beats per Hour by Activity Period and Corrected for Daily Baseline Frequency

	Ventricular Ectopic Beats per Hour[a]		
Activity Period	0.7% COHb	3.2% COHb	5.1% COHb
CO uptake	−0.7 ± 4.1	0.7 ± 9.6	0.8 ± 6.1
COHb steady state	−0.7 ± 6.0	1.6 ± 9.9	2.5 ± 7.9
Exercise test	10.0 ± 34.8	11.2 ± 34.1	6.1 ± 20.3
Exercise recovery	17.1 ± 25.5	11.8 ± 32.7	12.8 ± 25.2
CO unload	4.5 ± 12.8	4.4 ± 15.8	4.0 ± 13.5
Remainder	−0.7 ± 5.1	1.0 ± 11.5	1.3 ± 3.2

[a] Values represent means ± SD (n = 30). All row p values for comparing 0.7% with 3.2% COHb and 0.7% with 5.1% COHb exceed 0.05.

Table B.5. Effect of Carbon Monoxide Exposure on the Number of Paired Ventricular Ectopic Beats and Nonsustained Ventricular Tachycardia by Activity Period Corrected for Daily Baseline Frequency

	Ventricular Ectopic Beats per Hour[a]		
Activity Period	0.7% COHb	3.2% COHB	5.1% COHb
CO uptake	−3.5 ± 14.1	2.2 ± 22.0	1.7 ± 12.1
COHb steady state	−3.6 ± 16.4	3.5 ± 19.4	5.0 ± 15.9
Exercise test	30.7 ± 118.0	21.6 ± 68.0	12.2 ± 40.6
Exercise recovery	47.8 ± 110.5	22.7 ± 65.5	47.2 ± 125.6
CO unload	9.8 ± 27.0	9.5 ± 30.6*	8.7 ± 27.0
Remainder	−3.7 ± 14.9	1.7 ± 23.1	3.3 ± 7.6

[a] Values represent means ± SD (n = 30). All row p values for comparing 0.7% with 3.2% COHb and 0.7% with 5.1% COHb exceed 0.05. All column p values for comparing activity periods with the steady-state period exceed 0.05, except those marked with an *.

Table B.6. Effect of Carbon Monoxide Exposure on the Sum of Paired Ventricular Beats and Ventricular Tachycardia Events per Hour by Activity Period[a]

	Ventricular Ectopic Beats per Hour[a]			p Values for Group Comparisons	
Activity Period	0.7% COHb	3.2% COHb	5.1% COHb	0.7% COHb vs. 3.2% COHb	0.7% COHb vs. 5.1% COHb
Baseline	14.3 ± 31.6	10.0 ± 24.4	5.7 ± 14.7	0.25	0.04
CO uptake	10.8 ± 26.1	12.2 ± 25.4	7.4 ± 16.4	0.52	0.17
COHb steady state	10.8 ± 21.0	13.5 ± 29.4	10.8 ± 22.3	0.31	0.99
Exercise test	45.1 ± 134.0	31.6 ± 74.0	17.9 ± 41.3	0.55	0.28
Exercise recovery	62.2 ± 126.5	32.8 ± 65.8	52.9 ± 130.6	0.14	0.75
CO unload	24.2 ± 51.2	19.4 ± 41.6	14.4 ± 30.4	0.19	0.23
Remainder	10.6 ± 26.9	11.7 ± 28.5	9.0 ± 20.4	0.65	0.31

[a] Events were weighted by × 2 for couplets and × 5 for ventricular tachycardia. Values are means ± SD (n = 30).

APPENDIX C. Individual Data

Table C.1. Mean Ventricular Ectopic Beats per Hour During Room Air Exposure

Subject Number	Baseline	CO Uptake	COHb Steady State	Exercise Test	Exercise Recovery	CO Unload	Remainder
1	32	53	58	167	231	69	7
2	70	99	136	50	120	97	100
3	0	0	1	0	0	43	1
4	96	205	194	35	338	201	42
5	23	38	49	44	26	40	53
7	271	336	295	138	188	356	366
9	1	11	6	0	0	31	62
10	18	7	13	0	100	48	52
11	1	3	5	78	40	7	15
12	209	217	211	500	593	82	142
13	25	19	36	706	1,840	194	95
14	35	18	19	0	1	37	20
15	50	40	54	133	94	51	22
16	1	0	0	0	34	51	4
17	252	185	184	40	1,450	254	70
18	110	18	33	175	430	455	202
19	54	99	544	138	70	113	67
20	51	56	158	100	40	43	36
21	14	12	38	0	25	28	52
22	41	31	99	45	94	25	38
23	9	17	20	4	500	128	12
25	247	223	109	280	440	330	273
26	185	64	4	33	250	438	145
27	245	15	33	300	670	80	13
28	545	362	552	1,740	990	534	505
29	25	21	40	160	450	49	16
30	132	142	91	860	1,510	325	50
31	175	7	26	80	35	8	61
32	895	988	423	365	680	1,280	1,353
33	48	24	31	1	1	120	70

Table C.2. Mean Ventricular Ectopic Beats per Hour During Carbon Monoxide Exposure Resulting in 3.2% Carboxyhemoglobin

Subject Number	Baseline	CO Uptake	COHb Steady State	Exercise Test	Exercise Recovery	CO Unload	Remainder
1	51	57	67	69	350	95	10
2	44	124	169	54	50	82	66
3	0	0	0	0	156	436	144
4	24	109	106	87	190	222	156
5	27	34	40	46	60	53	67
7	309	329	268	100	110	292	415
9	0	0	2	0	0	7	20
10	60	36	56	13	80	39	51
11	0	7	4	10	10	9	8
12	254	239	271	561	440	147	205
13	64	77	74	1,831	2,270	408	250
14	56	54	67	17	75	49	27
15	36	32	57	153	161	85	24
16	3	0	13	370	140	179	31
17	264	133	374	210	1,850	476	115
18	65	36	66	50	0	193	44
19	63	69	9	131	80	116	70
20	6	13	39	500	0	10	13
21	33	55	45	6	0	11	26
22	20	21	41	500	500	9	20
23	47	62	99	115	69	115	1
25	96	196	118	40	100	88	114
26	226	127	140	295	129	231	257
27	14	19	19	255	600	55	13
28	695	560	740	470	470	863	667
29	14	15	22	520	600	31	35
30	366	204	101	335	1,730	201	93
31	26	38	31	0	0	13	32
32	604	509	571	930	310	1,164	1,046
33	72	12	27	10	50	127	82

Table C.3. Mean Ventricular Ectopic Beats per Hour During Carbon Monoxide Exposure Resulting in 5.1% Carboxyhemoglobin

Subject Number	Baseline	CO Uptake	COHb Steady State	Exercise Test	Exercise Recovery	CO Unload	Remainder
1	26	36	18	4	86	17	5
2	159	95	101	90	92	99	76
3	0	0	0	0	34	74	15
4	22	251	216	55	653	230	119
5	17	10	19	30	20	39	57
7	368	393	333	193	747	433	385
9	0	0	0	0	10	9	5
10	49	18	33	0	160	78	44
11	3	1	1	19	0	6	6
12	108	96	119	729	510	105	95
13	72	28	45	406	1,470	208	56
14	30	14	24	67	61	34	10
15	31	43	22	92	52	40	13
16	0	0	0	10	50	75	4
17	173	187	160	260	600	249	123
18	30	14	37	482	50	539	356
19	143	66	144	169	17	159	111
20	30	77	126	40	0	26	13
21	28	57	91	18	60	25	100
22	34	29	59	60	810	21	68
23	69	54	76	4	83	200	39
25	87	193	122	10	30	140	204
26	114	25	3	320	17	204	118
27	19	23	38	155	760	92	13
28	238	249	180	130	360	320	377
29	37	34	37	15	1,040	46	18
30	156	198	73	1,265	410	410	123
31	7	14	27	30	0	27	10
32	919	362	644	280	630	883	1,244
33	51	40	67	55	160	168	63

Table C.4. Atmospheric Carbon Monoxide Levels During Uptake Period[a]

Subject Number	Low-Exposure Uptake (ppm)	Low-Exposure Steady State (ppm)	High-Exposure Uptake (ppm)	High-Exposure Steady State (ppm)
1	132	19	237	29
2	154	18	260	30
3	180	20	298	32
4	151	20	271	31
5	161	20	275	28
7	153	20	327	31
9	174	19	414	29
10	213	21	364	31
11	213	20	390	31
12	159	20	286	32
13	178	20	337	29
14	133	19	246	31
15	140	18	212	30
16	193	19	335	30
17	149	19	272	31
18	131	19	243	31
19	137	21	244	32
20	131	20	275	29
21	129	19	227	31
22	137	19	227	31
23	165	19	280	31
25	148	19	267	31
26	203	19	238	31
27	182	19	302	28
28	166	19	313	29
29	202	19	336	31
30	155	19	270	31
31	126	19	229	31
32	174	18	299	33
33	136	20	254	31
Mean ± SD	159.5 ± 25.2	19.3 ± 0.7	287.9 ± 47.2	30.5 ± 1.2

[a] Low exposure means the level of CO to produce 3.2% blood COHb, and high exposure means the level of CO to produce 5.1% blood COHb.

Table C.5. Percent Carboxyhemoglobin Data on Room Air Exposure Day

Subject Number	Baseline		End of Exposure	30 Minutes Steady State	60 Minutes Steady State		End of Exercise	
	Gas Chromatography	CO-Oximeter	CO-Oximeter	CO-Oximeter	Gas Chromatography	CO-Oximeter	Gas Chromatography	CO-Oximeter
1	0.8	1.6	1.4	1.4	0.7	1.3	0.5	1.1
2	0.6	1.2	1.3	1.2	0.6	1.2	0.6	1.0
3	1.1	1.6	1.3	1.4	0.8	1.4	0.8	1.2
4	0.6	1.3	1.4	1.3	0.7	1.3	0.6	1.2
5	0.7	1.2	1.3	1.3	0.6	1.3	0.6	1.1
7	0.8	1.7	1.6	1.6	0.7	1.6	0.7	1.4
9	0.5	0.9	1.1	1.0	0.6	1.0	0.6	0.7
10	0.7	1.3	1.2	1.4	0.7	1.3	0.6	1.2
11	0.7	1.3	1.4	1.3	0.7	1.3	0.7	1.0
12	0.6	1.2	1.2	1.3	0.6	1.2	0.5	1.0
13	0.6	1.1	1.1	1.2	0.6	1.1	0.5	0.9
14	0.9	1.4	1.3	1.3	0.6	1.3	0.6	1.2
15	0.7	1.3	1.2	1.3	0.5	1.2	0.5	1.0
16	0.8	0.9	1.1	1.0	0.7	1.0	0.7	0.9
17	0.9	1.4	1.4	1.5	0.8	1.4	0.7	1.3
18	0.7	1.6	1.8	1.6	0.6	1.6	0.5	1.3
19	0.9	1.6	1.6	1.7	0.9	1.6	0.8	1.5
20	1.0	1.7	1.6	1.5	0.9	1.6	0.8	1.4
21	0.5	1.2	1.2	1.1	0.5	1.1	0.4	1.0
22	0.7	1.3	1.2	1.2	0.6	1.3	0.5	1.2
23	0.5	1.1	1.2	1.2	0.5	1.2	0.5	0.8
25	0.5	1.1	1.0	1.0	0.5	0.9	0.5	1.0
26	0.8	0.9	0.9	0.8	0.8	0.9	0.7	0.7
27	0.6	1.4	1.3	1.0	0.6	1.2	0.5	0.8
28	0.7	1.6	1.4	1.5	0.7	1.4	0.6	1.1
29	0.6	1.1	1.1	1.1	0.6	1.1	0.5	1.1
30	1.4	2.1	2.0	1.8	1.1	1.8	1.0	1.5
31	0.9	1.8	1.5	1.4	0.7	1.5	0.7	1.2
32	0.5	0.9	0.9	1.0	0.5	1.0	0.4	0.7
33	0.7	1.3	1.1	1.2	0.7	1.1	0.5	0.9

Table C.6. Percent Carboxyhemoglobin Data on the 3% Carboxyhemoglobin Target Exposure Day

	Baseline				60 Minutes Steady State		End of Exercise	
Subject Number	Gas Chromatography	CO-Oximeter	End of Exposure CO-Oximeter	30 Minutes Steady State CO-Oximeter	Gas Chromatography	CO-Oximeter	Gas Chromatography	CO-Oximeter
1	0.9	1.6	4.1	4.2	3.3	4.0	2.9	3.4
2	0.7	1.2	3.9	4.2	3.4	4.0	3.1	3.6
3	0.7	1.3	4.0	4.0	3.5	4.1	3.4	3.6
4	0.7	1.3	3.9	4.0	3.3	3.9	3.0	3.6
5	0.6	1.2	3.9	4.1	3.4	4.2	3.2	3.6
7	0.8	1.8	4.1	4.3	3.2	4.2	2.9	3.8
9	0.6	0.9	3.7	3.8	3.2	3.8	2.8	3.0
10	0.7	1.2	3.8	3.9	2.9	3.9	2.6	3.7
11	0.7	1.3	4.2	4.4	3.7	4.5	3.2	3.8
12	0.6	1.2	3.9	4.1	3.2	4.0	3.1	3.7
13	0.8	1.4	4.2	4.1	3.4	4.1	3.2	3.6
14	0.9	1.6	4.0	4.1	3.3	4.1	2.8	3.8
15	0.6	1.2	4.0	3.9	3.2	3.9	3.1	3.2
16	0.9	1.1	4.0	4.2	3.7	3.8	3.3	3.5
17	0.7	1.3	3.8	3.8	3.1	3.8	3.0	3.5
18	0.6	1.5	3.7	3.9	2.7	3.8	2.3	3.3
19	0.8	1.5	3.8	4.0	3.1	3.8	2.9	3.7
20	0.8	1.8	3.9	4.1	3.0	4.0	2.9	3.7
21	0.6	1.3	3.8	3.9	3.1	3.8	2.7	3.3
22	0.8	1.5	3.8	3.9	3.0	4.0	2.7	3.6
23	0.5	0.9	3.7	4.0	3.2	3.9	2.8	3.6
25	0.5	0.9	3.9	4.1	3.4	4.0	3.2	3.9
26	0.7	0.8	3.9	4.1	4.0	4.1	3.7	3.8
27	0.5	0.7	3.9	4.1	3.5	4.2	3.2	3.6
28	0.7	1.3	3.9	4.0	3.2	3.9	2.9	3.6
29	0.5	1.1	3.8	3.9	3.4	4.0	3.1	3.7
30	0.8	1.4	3.7	3.8	2.8	3.8	2.7	3.4
31	0.6	1.6	4.0	4.3	3.1	4.2	2.8	3.6
32	0.6	1.0	3.7	4.0	3.0	3.7	2.4	3.2
33	0.9	1.5	3.9	4.0	2.9	3.8	2.8	3.4

Table C.7. Percent Carboxyhemoglobin Data on the 5% Carboxyhemoglobin Target Exposure Day

Subject Number	Baseline Gas Chromatography	Baseline CO-Oximeter	End of Exposure CO-Oximeter	30 Minutes Steady State CO-Oximeter	60 Minutes Steady State Gas Chromatography	60 Minutes Steady State CO-Oximeter	End of Exercise Gas Chromatography	End of Exercise CO-Oximeter
1	1.1	1.7	6.1	6.2	5.7	6.1	4.7	4.9
2	0.7	1.1	5.5	5.6	4.8	5.6	4.5	5.4
3	1.0	1.5	6.0	6.2	5.6	6.1	5.3	5.6
4	0.6	1.4	6.4	6.5	5.6	6.5	5.1	5.8
5	0.7	1.2	5.7	5.7	4.9	5.6	4.5	5.2
7	0.6	1.4	5.8	6.1	4.6	5.8	4.2	5.3
9	0.6	0.9	6.8	7.0	6.1	7.0	5.4	5.7
10	0.9	1.3	5.6	6.0	4.5	5.8	4.0	5.4
11	0.7	1.2	6.1	6.2	5.2	5.9	5.0	5.6
12		1.2	5.9	6.1	5.2	5.9	5.0	5.7
13	0.6	1.1	5.8	6.5	5.4	6.3	5.0	5.5
14	0.9	1.5	6.4	6.4	5.9	6.6	5.3	5.8
15	0.5	1.3	5.8	5.9	5.0	5.6	4.8	5.3
16	0.8	1.1	5.9	6.2	5.3	6.2	4.3	5.3
17	0.8	1.3	5.6	5.9	5.0	5.9	4.6	5.5
18	0.7	1.5	5.6	5.7	4.6	5.7	3.8	4.6
19	0.7	1.6	6.1	6.3	4.6	6.4	3.9	5.7
20	0.9	1.5	5.7	5.9	4.7	5.7	4.8	5.6
21	0.6	1.3	5.8	6.0	4.8	6.0	4.1	5.3
22	0.6	1.2	5.9	6.3	5.1	5.9	4.5	5.4
23	0.4	0.9	5.6	5.8	4.9	5.6	4.7	5.5
25	0.4	0.9	5.7	6.0	4.8	6.0	5.1	5.6
26	0.8	0.7	5.9	6.1	5.8	6.2	5.7	5.9
27	0.5	0.8	6.0	6.3	5.3	6.2	4.9	5.7
28	0.7	1.3	5.9	6.3	5.5	6.2	5.0	5.6
29	0.5	1.2	6.1	6.3	5.2	6.0	4.8	5.7
30	1.1	1.7	6.2	6.3	5.3	6.4	5.1	5.7
31	0.7	1.6	6.0	5.7	4.6	6.0	4.1	5.2
32	0.6	1.2	6.2	6.4	5.3	6.4	4.3	5.1
33	0.8	1.5	6.0	6.1	4.9	6.1	4.7	5.4

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PUBLICATIONS RESULTING FROM THIS RESEARCH

Younis LT, Dahms TE, Byers SL, Carroll LM, Wiens RD, Chaitman BR. 1991. Does low level carbon monoxide exposure have a proarrhythmic effect in patients with coronary artery disease and ventricular arrhythmia (abstract). J Am Coll Cardiol 17:80A.

Dahms TE, Younis LT, Wiens RD, Zarnegar S, Byers SL, Chaitman BR. Effects of carbon monoxide exposure in patients with documented cardiac arrhythmias. J Am Coll Cardiol (in press).

ABBREVIATIONS

ANOVA	analysis of variance
CO	carbon monoxide
COHb	carboxyhemoglobin
ECG	electrocardiogram
ppm	parts per million
psig	pounds per square inch gauge
VEB	ventricular ectopic beat

INTRODUCTION

In the summer of 1984, the Health Effects Institute (HEI) issued a Request for Applications (RFA 84–2) soliciting proposals for studies of "Acute Effects of Carbon Monoxide on Cardiac Rhythm." In response to this RFA, Dr. Bernard R. Chaitman of St. Louis University School of Medicine, St. Louis, Missouri, submitted a proposal entitled "Carbon Monoxide Exposure to Patients with Documented Cardiac Arrhythmias." A revised proposal was submitted in April 1986, and the approved project began on August 1, 1987 and was completed in December 1989. Total expenditures were $491,923. The Investigators' Report was received at HEI in November 1990 and accepted by the Health Review Committee in July 1991.

During the review of the Investigators' Report, the Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in the Investigators' Report and in the Review Committee's Commentary. The following Commentary is intended to serve as an aid to the sponsors of HEI and to the public by highlighting both the strengths and limitations of the study and by placing the Investigators' Report into scientific and regulatory perspective.

REGULATORY BACKGROUND

Section 109 of the Clean Air Act, as amended in 1990, mandates that the U.S. Environmental Protection Agency (EPA) establish primary and secondary National Ambient Air Quality Standards (NAAQS) for air pollutants based on their health effects at levels "requisite to protect the public health . . . allowing an adequate margin of safety." The Senate Report on the 1970 Clean Air Act Amendments states that "[a]n ambient air quality standard . . . should be the maximum permissible air level of an air pollution agent or class of such agents (related to a period of time) which will protect the health of any group of the population" (U.S. Senate 1970).

Although this reference to "the health of any group of the population" is not clearly defined in the Clean Air Act itself or in the Senate Report, the Senate Report does specify that: "Included among those persons whose health should be protected by the ambient standard are particularly sensitive citizens (such as bronchial asthmatics and emphysematics) who in the normal course of daily activity are exposed to the ambient environment."

The Senate Report also states that "in establishing an ambient standard necessary to protect the health of these persons, reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group."

The current primary NAAQS for carbon monoxide (CO)* is 9 parts per million (ppm), averaged over eight hours, and 35 ppm, averaged over one hour, both not to be exceeded more than once a year (U.S. Environmental Protection Agency 1985). This standard was established in 1971; since that time, there have been proposals to lower the one-hour standard from 35 ppm to 25 ppm. In 1985, the EPA decided not to implement the lower standard, in part, because of controversy related to the reports regarding the effects of CO exposure on the cardiovascular system (Anderson et al. 1973; Aronow and Isbell 1973; Aronow et al. 1974).

As part of the periodic reevaluation of the criteria pollutant standards mandated by Section 109(d)(1), the EPA is now (July 1992) in the process of reviewing several recent studies of the effects of exposure to CO on the human cardiovascular system. The agency released an external review copy of its draft "Carbon Monoxide Air Quality Criteria" document on March 29, 1990 to solicit public comment. The draft Staff Paper of the Office of Air Quality Planning and Standards was circulated for technical review and comment in April 1992.

SCIENTIFIC BACKGROUND

The question being addressed by Chaitman and coworkers is important. Does exposure to CO at levels present in polluted air produce adverse effects on the cardiovascular system? In particular, will exposure to CO exacerbate ventricular arrhythmias in subjects with coronary artery disease? The following section reviews the cardiovascular effects of exposure to CO, focusing on the possible relationship between CO and cardiac arrhythmias. It also presents background information on the clinical significance of cardiac arrhythmias and describes how they are identified and evaluated.

CARBON MONOXIDE

Sources

Carbon monoxide, an imperceptible poisonous gas, is produced by the incomplete combustion of organic sub-

* A list of abbreviations appears at the end of the Investigators' Report for your reference.

stances such as gasoline, wood, kerosene, natural gas, and other fuels. Exposures may come from indoor and outdoor sources. Outdoor exposures occur largely from motor vehicle exhaust, but fires, industrial processes, and other combustion operations also contribute. In rural areas, background levels of CO are usually less than 1 ppm. Urban CO levels can vary from 2 to 4 ppm near roadways (Akland et al. 1985) to levels in excess of 40 ppm in highway tunnels (Stern et al. 1988). The highest levels of exposure (5 to 30 ppm CO) occur on heavily traveled roads during commuting hours (Akland et al. 1985; Bevan et al. 1991; Chan et al. 1991). Indoor concentrations of CO are usually lower than 2 ppm but can reach dangerous levels, especially in enclosed spaces when appliances or equipment malfunction, or combustion takes place in a poorly ventilated space. Cigarette smoke is an important source of inhaled CO, from either sidestream or mainstream smoke (approximately 400 to 1,000 ppm) or environmental tobacco smoke (1 to 18 ppm) (Wald and Howard 1975; National Research Council 1977; Turino 1981).

Biological Effects

Carbon monoxide exerts its adverse health effects by interfering with the normal oxygen-carrying function of the blood. Because hemoglobin's affinity for CO is approximately 240 times greater than its affinity for oxygen, inhaled CO binds strongly, but reversibly, to hemoglobin to form carboxyhemoglobin (COHb). As a result of this competitive binding, and because hemoglobin releases oxygen more slowly in the presence of CO, the ability of the red blood cells to deliver oxygen to tissues is reduced. The resulting tissue hypoxia (decreased levels of oxygen) may cause transient or permanent damage, especially in those organs that demand high oxygen delivery, such as the brain and heart. Other factors, such as reduced cardiac output and reductions in the partial pressure of oxygen in inspired air, also limit tissue oxygenation. Individuals with heart disease, whose ability to increase cardiac output during exercise is compromised, may be especially susceptible to the hypoxic effects of elevated COHb levels.

Blood COHb concentration serves as a biological measure of the integrated internal dose of CO to which a person recently has been exposed. In fact, blood COHb serves as an excellent biomarker for CO exposure. Venous blood COHb levels are influenced by a number of factors, including the CO concentration in the atmosphere, the duration of exposure, and certain physiological variables, especially pulmonary ventilation (Coburn et al. 1965). Nonsmokers with little or no environmental CO exposure have background levels of venous blood COHb that average between 0.5% and 1.0% due to the endogenous production of CO during normal metabolism (Coburn et al. 1965; Urbanetti 1981; Radford and Drizd 1982). Inhaling CO at the current NAAQS of 35 ppm (one-hour average) produces approximately 2% COHb in nonsmoking male subjects who exercise moderately for one hour (U.S. Environmental Protection Agency 1984). Smokers and workers in certain occupational settings typically have elevated blood COHb levels that range from 3% to 8% (Radford and Drizd 1982).

Public Health Concerns

The health effects of acute CO exposure are usually expressed in relation to blood COHb levels and can be summarized as follows (reviewed by Ilano and Raffin 1990, and by Coultas and Lambert 1991). Blood COHb levels in excess of 70% are fatal within minutes. Patients with severe CO poisoning (blood COHb levels in excess of 40%) have impaired cardiovascular or neurologic function. Moderate poisoning (COHb levels of 30% to 40%) causes severe headaches, nausea, and other neurological symptoms. Mild poisoning (COHb less than 30%) leads to headaches and dyspnea (shortness of breath). Usually there are no symptoms at levels below 10% COHb.

Although the toxic consequences of COHb levels in excess of 10% are well established, there has been considerable concern that exposures to levels of CO that cause only minimal elevations in blood COHb may lead to adverse effects, especially in patients with cardiovascular disease who already have a reduced capacity to deliver oxygen to the heart and other tissues (Turino 1981; Rosenman 1990; Coultas and Lambert 1991). The possible link between CO exposure and the exacerbation of cardiovascular disease is an important public health issue because of the widespread exposure and the size of the population at risk. Approximately 22 million people live in areas of the United States where CO levels exceed the National Ambient Air Quality Standard (U.S. Environmental Protection Agency 1991).

CARDIOVASCULAR EFFECTS OF CARBON MONOXIDE

Current understanding of the effects of CO on the cardiovascular system indicates that exposures to CO either could contribute to the underlying pathology of cardiovascular diseases or provoke the onset of clinical manifestations of these diseases (Turino 1981; Ilano and Raffin 1990; Coultas and Lambert 1991). Both hypotheses have been examined in laboratory studies using human subjects and animal models, as well as in epidemiology investigations. In this section, the cardiovascular effects of exposures to CO are discussed, with an emphasis on the data related to the effects of CO on arrhythmias.

Population and Occupational Studies

Interpretation of the few epidemiologic studies on the re-

lation between CO exposure and mortality from heart disease is limited by the absence of exposure information and the presence of potential confounders, such as smoking and other pollutants. Three studies have shown an association of morbidity (Kurt et al. 1978) or mortality (Cohen et al. 1969; Hexter and Goldsmith 1971) from heart disease and ambient CO concentrations. However, Kuller and coworkers (1975) reported no relationship between CO exposure and myocardial infarction in an urban setting. There are several reports of associations between accidental exposures to moderate levels of CO (blood COHb levels of 10% to 40%) in occupational settings and sudden death from cardiac arrest (Balraj 1984; Atkins and Baker 1985; Rosenman 1990).

Two occupational studies of tunnel workers exposed to high concentrations of motor vehicle exhaust indicate that chronic exposure to CO (and other pollutants) may be associated with an elevated risk of death from arteriosclerotic heart disease (Stern et al. 1981, 1988).

Myocardial Ischemia

In the 1970s, there were reports that CO exposure (50 and 100 ppm for one to four hours) decreased the time to the onset of chest pain (angina) in subjects with coronary artery disease (Anderson et al. 1973; Aronow and Isbell 1973; Aronow et al. 1974). Because the results of these studies were questioned (U.S. Environmental Protection Agency 1984), there have been further investigations of CO effects on symptoms associated with cardiovascular disease using more rigorous protocols and objective measures.

In these more recent studies, three groups of investigators reported a decrease in the time to onset of angina in exercising subjects exposed to levels of CO sufficient to produce COHb levels in the range of 2% to 6% (Adams et al. 1988; Allred et al. 1989, 1991; The HEI Multicenter CO Study Team 1989; Kleinman et al. 1989). The HEI Multicenter CO Study Team also observed dose-related decreases of 5.1% and 12.1% in the length of time to onset of electrocardiographic ST-segment changes after CO exposure (COHb levels of 2.0% and 3.9%, respectively, as measured by gas chromatography) (Allred et al. 1989, 1991; The HEI Multicenter CO Study Team 1989). Another group of investigators reported that the left ventricular ejection fraction, which measures the pump function of the heart, was reduced during submaximal exercise when the subjects were exposed to CO under conditions producing mean COHb levels of 5.9%, as measured by CO-oximetry (Adams et al. 1988). It is uncertain whether these pathologic effects of CO exposure in subjects with angina were caused only by a COHb-mediated reduction in oxygen delivery to the heart or by a direct effect of CO on myocardial tissue.

Arrhythmias

The four chambers of the heart normally contract in a highly organized sequence that is governed by electrical impulses. Under certain pathologic conditions, the well-coordinated activation and contraction system of the heart may be interrupted, thereby leading to abnormal heart beats, or arrhythmias. Some arrhythmias, such as ventricular fibrillation (complete disorganization of contractile activity) affect the pump function of the heart and can lead to sudden death. The relationship between isolated ventricular ectopic beats (VEBs) and cardiac mortality is complex and not completely understood. It has been established that the combination of heart damage and ischemia enhances the risk of ventricular arrhythmias, as do other factors, such as medications, exercise, stress, and alcohol consumption (Velebit et al. 1982; Zipes 1988; The Cardiac Arrhythmia Suppression Trial 1989). Some antiarrhythmic drugs designed to prevent ventricular arrhythmias, although effective in controlling abnormal heart beats, actually have been shown to be associated with increased mortality (The Cardiac Arrhythmia Suppression Trial 1989).

Although there appears to be agreement that exposure to CO, resulting in 2% to 6% blood COHb, exacerbates myocardial ischemia in exercising subjects with coronary artery disease (Anderson et al. 1973; Aronow and Isbell 1973; Adams et al. 1988; Allred et al. 1989, 1991; The HEI Multicenter CO Study Team 1989; Kleinman et al. 1989), there is less information on the potentially life-threatening arrhythmogenic effects of CO.

A limited number of investigations of arrhythmias in laboratory animals, under conditions of acute and chronic CO exposure, have yielded equivocal results. As in studies with human subjects, abnormal electrocardiograms have been reported in studies with dogs (Preziosi et al. 1970; Sekiya et al. 1983) and Cynomolgus monkeys (DeBias et al. 1973) exposed to CO. The threshold for the induction of ventricular fibrillation by electrical challenge to the heart was reduced in monkeys (Debias et al. 1976) and dogs (Aronow et al. 1978, 1979) after acute exposures to CO leading to 6% to 10% COHb. In contrast, other investigators found no effects of CO exposure (leading to 10% to 20% COHb) on spontaneous ventricular arrhythmias (Foster 1981), ischemic conduction delay (Foster 1981), or threshold for ventricular fibrillation (Verrier et al. 1990) in dogs with experimentally-induced acute myocardial ischemia. Acute exposures to CO at concentrations leading to 5%, 10%, and 15% COHb did not alter the frequency of ventricular arrhythmias in dogs with healed myocardial infarctions when these animals were challenged with mild exercise and acute coronary artery occlusion (Vanoli et al. 1989; Farber et al. 1990).

There have been few studies of the potential arrhythmo-

genic effect of CO in human subjects. In one short report, which is lacking in experimental detail, Knelson (1972) reported that seven out of 26 subjects who exercised and were exposed to 100 ppm CO for four hours had abnormal electrocardiograms. Two subjects developed arrhythmias following CO exposure.

Sheps and coworkers examined the arrhythmogenic effects of exposure to CO in subjects with mild coronary artery disease. Acute CO exposures (leading to 4% or 6% blood COHb, as measured by CO-oximetry) had no effect on cardiac arrhythmias in subjects who had no baseline arrhythmias (Hinderliter et al. 1989; Sheps et al. 1991). Subjects with baseline arrhythmias who were exposed to CO leading to 6% COHb exhibited a higher frequency of single and multiple VEBs during exercise than did subjects exposed to air (Sheps et al. 1990, 1991). This effect was significant only for measurements made during a short exercise period; it was not significant when measurements were made at rest, during exposure, or during the postexposure periods. No significant increase in VEBs was observed during exposure to CO that resulted in 4% COHb.

TECHNICAL ISSUES

Carboxyhemoglobin Measurements

The most widely used method for measuring blood COHb is based on spectrophotometric procedures that employ commercially available CO-oximeters. The instruments used for this purpose, although precise and well-suited for obtaining rapid measurements of high levels of blood COHb (10% to 100%), are not sufficiently accurate to measure small changes in COHb under ambient conditions (Guillot et al. 1981; the HEI Multicenter CO Study Team 1989). The error of analysis for CO-oximeters is reported to be 1% (Instrumentation Laboratories 1980), which could lead to errors exceeding 50% in the range of interest (0.5% to 5% COHb). In this range, gas chromatographic techniques are more accurate and less prone to interference (Dahms and Horvath 1974; The HEI Multicenter CO Study Team 1989). In the HEI Multicenter CO Study (1989), gas chromatography values were lower than those measured by CO-oximetry. In normal subjects, mean levels of 1.9%, 3.2%, and 5.5% COHb, measured by CO-oximetry, corresponded to mean levels of 1.0%, 2.2% and 4.4% COHb, measured by gas chromatography. The reader should be alerted that without appropriate reference standards, reported COHb levels in the 0% to 10% range are not directly comparable between studies.

Evaluation of Cardiac Arrhythmias

Cardiac arrhythmias may be difficult to identify if they occur sporadically and the individual is not aware of their occurrence. A conventional electrocardiogram (ECG), which records electrical activity in the heart, detects arrhythmias only if they occur during the short recording period. Long-term ambulatory electrocardiography (often referred to as Holter monitoring) provides a continuous recording of the heartbeat for 24 hours or longer, permitting documentation of isolated instances of abnormal cardiac electrical behavior during the course of normal daily activities. As ambulatory ECG instrumentation has improved, its use has expanded to evaluate the therapeutic efficacy of antiarrhythmic and antiischemic drugs (American College of Cardiology/American Heart Association Task Force 1989), and, in experimental settings, to studying the effects of environmental factors on cardiac arrhythmias.

Evaluating the frequency of arrhythmias, even with the most sensitive instrumentation available, is complicated by within-subject variability in the frequency of VEBs (Morganroth et al. 1978; Winkle 1978; Michelson and Morganroth 1980; Pratt et al. 1985; Schmidt et al. 1988). This variability can mimic the effect of agents intended to suppress or enhance cardiac arrhythmias if strict criteria are not applied (American College of Cardiology/American Heart Association Task Force 1989). The degree of change in the frequency of arrhythmias required to establish a treatment effect depends on a number of factors, including: the number of measurements, the length of the ECG recording (shorter duration, increased variability), the subject population, medications (enhanced variability with beta-blocking agents), and the frequency and severity of arrhythmias.

JUSTIFICATION FOR THE STUDY

Although the effects of breathing CO on cardiac function have been examined in a number of experimental models, it is not known whether or not exposure to CO causes or potentiates cardiac arrhythmias. The HEI solicited proposals under RFA 84-2 for studies on "Acute Effects of Carbon Monoxide on Cardiac Electrical Stability" for research on the effects of CO, at or near ambient levels, on myocardial excitability. The HEI was interested in proposals for research in three categories: (1) clinical studies of potentially susceptible individuals; (2) epidemiological studies of potentially susceptible individuals in which heart function and CO exposure were monitored during the course of a normal day; and (3) animal studies directed toward understanding effects of CO on ventricular electrical stability.

After reviewing the proposals submitted in response to RFA 84-2, the Institute decided to support four research projects. Two studies examined the effects of CO exposure

on cardiac electrical stability in animal models (Farber et al. 1990; Verrier et al. 1990). Sheps and associates (1990, 1991) and Chaitman and colleagues conducted clinical studies to evaluate the effects of CO exposure on human subjects with ischemic heart disease and ventricular arrhythmias. By supporting studies using diverse biological models and end points, the Institute's goal was to implement a comprehensive research program to determine the effects of CO exposure on cardiac arrhythmias.

GOALS AND OBJECTIVES

The overall objective of the proposal submitted by Dr. Chaitman and coworkers was to assess the effects of low levels of CO exposure, leading to 3% or 5% COHb, on ventricular arrhythmias in patients who previously had demonstrated arrhythmogenic potential. Such individuals represent a significant portion of patients with cardiovascular disease. The investigators did not address the mechanism by which any proarrhythmogenic effect of CO exposure might be mediated.

The protocol called for 40 nonsmoking subjects with coronary artery disease, who had specifically defined cardiac arrhythmias, to undergo exercise tests and ambulatory electrocardiography with and without exposure to CO. The CO exposure concentrations were calculated to elevate blood COHb levels from background values of less than 1% to either 3% or 5%, as assessed by gas chromatography. The frequency and severity of ventricular arrhythmias during the different phases of the protocol, which included a period of moderate exercise, would be monitored by a 24-hour Holter ambulatory ECG.

STUDY DESIGN

The potential study population was identified from records of patients who had ambulatory ECGs at St. Louis University School of Medicine between January 1986 and December 1989. The patients were all nonsmokers with ischemic heart disease and chronic ventricular arrhythmias, defined as 30 VEBs or more per hour (averaged over 20 hours). An unspecified number of patients in the potential study population were excluded because of a broad range of medical conditions. Of the 68 eligible patients, 35 had less than 30 VEBs per hour on repeat tests and therefore were not included in the study; 33 remaining subjects were enrolled after giving informed consent. Subsequently, three subjects were dropped from the analysis because of missing or uninterpretable data or failure to meet COHb entry criteria.

The average age of the 25 men and 5 women included in the study was 65 years; all had coronary artery disease, identified by angiography in 28 subjects, previous myocardial infarction in one subject, and abnormal exercise ECG and thallium defect in one subject. All but four subjects were taking cardioactive medications including antiischemic and antiarrhythmic drugs. The findings, therefore, refer to a population under medication; however, the dose and time of ingestion were the same on each test day. The left ventricular ejection fractions ranged from 25% to 71%; mean VEBs per hour ranged from 31 to 795; paired beats per hour ranged from 0 to 718; and total episodes of ventricular tachycardia ranged from 0 to 61.

The study design consisted of three nonconsecutive days of randomized experiments, permitting double-blind exposure to control air or one of two levels of CO. During the week preceding the experiments, a complete history and physical examination, standard laboratory tests, 20-hour ambulatory ECG, echocardiogram, and treadmill exercise test were performed on patients meeting the entrance requirements. The investigators also determined individual CO uptake rates for each subject before the actual exposures. These CO uptake rates were used to establish the appropriate CO concentrations required to elevate blood COHb levels to the target values within a one-hour exposure period.

Subjects were exposed for one hour to either air or one of two levels of CO sufficient to produce either 3% or 5% blood COHb, as analyzed by gas chromatography. Following the rapid uptake period, the chamber CO level was lowered to a concentration sufficient to maintain the target blood COHb level for an additional 90 minutes. The mean exposure levels of CO for the one-hour rapid uptake periods were 159 ppm ± 25 ppm and 292 ppm ± 47 ppm CO for the 3% COHb and 5% COHb target concentrations, respectively. During the 90-minute steady-state period, the mean CO exposure levels were 19 ppm ± 1 ppm for the 3% COHb target concentration and 31 ppm ± 1 ppm for the 5% COHb target.

Exercise testing was initiated during the steady-state period. The subjects walked on a treadmill with gradually increasing workloads until they were unable to continue because of fatigue, shortness of breath, or pain. Thus, the length of the exercise period varied among subjects (mean time was nine minutes; range was 3 to 17 minutes).

Subjects were monitored for ventricular arrhythmias by Holter ambulatory electrocardiographic recording. They were monitored for a period of two hours before exposure, throughout the one-hour exposure period, during the steady-state period at rest, during exercise, during a six-hour postexercise phase when subjects still had elevated

COHb levels but assumed their daily routine, and for an additional 10 hours. Other end points included measurements of systolic blood pressure and exercise performance.

TECHNICAL EVALUATION

ATTAINMENT OF STUDY OBJECTIVES

Although studies of this type are very difficult to conduct because the protocol is tedious and demanding for both the subjects and the investigators, this study was carefully planned and generally well executed. A strength of this investigation was the meticulous monitoring of the CO exposures and the careful measurement of blood COHb levels. The investigators successfully achieved the target doses of 3% and 5% COHb. The methodology used to monitor arrhythmias was carefully described and the data collection appears to be precise. The objectives were addressed successfully and the findings were well documented and presented clearly.

STUDY DESIGN AND METHODS

There are a number of features of the CO exposure protocol that are noteworthy. In order to establish the relationship between exposure to CO and the results of that exposure, careful measurements were made of blood COHb levels. CO-oximetry was used to obtain rapid information about subjects' responses to CO exposure, but the final blood COHb values were based on gas chromatography measurements, which are more accurate than CO-oximetry measurements at low concentrations of COHb (Guillot et al. 1981; The HEI Multicenter CO Study Team 1989). CO-oximeter values for blood levels of COHb were approximately 1% higher than values obtained by gas chromatography.

Ventricular arrhythmias (the end point of this study) are known to vary in frequency, both spontaneously and as a result of exercise and medical management. Although potential subjects were identified because their ECG records documented that they had had instances of arrhythmias in which the number of VEBs per hour (averaged over 20 hours) was 30 or more, more than half of the potentially eligible patients (35 out of 68) did not have 30 or more VEBs per hour, averaged over 20 hours during the screening examination. Even the final subject population had variable episodes of spontaneous arrhythmias. The variability in VEBs per hour is apparent in Appendix Tables C.1, C.2, and C.3 of the Investigators' Report, in which data are provided for each subject and each phase of each exposure. Twelve of the 30 participants had fewer than 30 VEBs per hour at baseline on the room air exposure day, and nine of the 30 did not have 30 VEBs per hour averaged over the final 10-hour ambulatory period. On the high CO-exposure day, nine subjects had fewer than 30 VEBs per hour at baseline, and 11 averaged fewer than 30 VEBs per hour during the final 10-hour monitoring period. Thus, with this small sample, inter- and intrasubject variability in frequency of VEBs is a major problem.

STATISTICAL METHODS

The experimental design was a repeated measures design with a factorial design (days by periods) on occasions within subjects. The response variable for most analyses was the change in VEB rate from baseline to a given exposure period. Because the distribution of numbers of VEBs was highly skewed, the authors employed Friedman's nonparametric analysis of variance for the principal analysis of VEBs. They also performed a repeated measures analysis of variance on both the logarithms of the counts and the differences between postexposure and daily preexposure values. Essentially, the same results were obtained using each of the three methods. This property of the results, called robustness by statisticians, should increase the reader's confidence in the validity of the statistical results.

INTERPRETATION OF THE RESULTS

As shown in Table 4 of the Investigators' Report, the study showed no evidence of a CO effect on arrhythmias for the group as a whole. In fact, the VEB rates were consistently lower on the high CO exposure day. The only suggestive finding was a nonsignificant increase in VEB rates during exercise among the 11 subjects with exercise-induced myocardial ischemia at the 5% COHb level (Table 6 of the Investigators' Report). There are a number of factors related to the design and conduct of the study that must be considered in interpreting these results.

Given the variability of exercise-induced VEB rates, a key consideration in interpreting this study is the adequacy of the sample size and duration of observation during exercise. As the investigators note, a study of 30 subjects will inevitably have limited power to detect small increases in the rate of VEBs due to CO exposure. The investigators report that the study had power of 80% to detect an increase of 50 VEBs per hour during any period after CO exposure when compared with room air exposure. Thus, moderate increases in VEB rates due to CO exposure are not precluded by these results. Still, the absence of a trend in the observed mean rates of VEBs during the high exposure regimen makes an effect of this size unlikely. The authors could have provided confidence intervals for the differences in change

from the preexposure to postexposure mean rate of VEBs between each CO regimen and room air to characterize the range of increases that are compatible with the observations. Because this calculation depends on the within-subject variability of VEBs, a quantity that is not provided in the report, this calculation can not be performed with the data as reported.

The study was a randomized double-blind experimental exposure to air or two concentrations of CO. The exposure levels resulted in COHb levels that are routinely found in cigarette smokers and that can be exceeded under conditions known to occur in daily life. The levels of COHb were relevant to practical situations, but the CO exposures were brief, and responses were to the acute situation. Whether or not patients with coronary artery disease and ventricular arrhythmias are likely to engage in brief periods of exercise of the intensity used in this study is not known. It is also not known whether responses to CO exposure under different experimental conditions, such as higher levels of CO, chronic exposure, or prolonged activity would be similar to the subjects' responses in this study.

Although all study subjects had some evidence of coronary artery disease, they were heterogeneous with respect to clinical characteristics. Some subjects had previous myocardial infarctions. The range of ejection fractions was quite large, and the frequency and nature of ventricular arrhythmias varied. Patients with recent myocardial infarctions, unstable angina, sustained ventricular tachycardia, and other serious conditions were excluded. The results may not apply to cigarette smokers, to patients with symptomatic arrhythmias, symptomatic ischemia, or recent myocardial infarction, or to subjects with lung disease. Most subjects were being treated with medications to control their heart disease. Testing patients who are receiving antiarrhythmic or other cardioactive drugs reduces the possibility of finding an arrhythmogenic effect of CO exposure. However, this kind of testing is justified from practical and ethical perspectives. These limitations must be considered in interpreting and generalizing the results of this study, but they should not be construed as weaknesses under the investigators' control.

The extent to which the results of this study can be generalized to patients with coronary artery disease and frequent VEBs is inevitably limited. The clinical significance of ventricular arrhythmias varies substantially, and the prognosis depends on too many factors to allow any broad generalizations. Thus, although this negative study does not support the hypothesis that CO exposure leading to 3% or 5% COHb (as measured by gas chromatography) has a significant impact on the frequency of total or repetitive ventricular arrhythmias, it is not possible to conclude that such exposures would be without effect in other patients with coronary artery disease.

IMPLICATIONS FOR FUTURE RESEARCH

For the last six years, a major focus of HEI's research program has been directed toward determining the acute effects of CO on potentially susceptible individuals -- patients with coronary artery disease. A major component of this program, The HEI Multicenter CO Study Team, investigated the effects of CO exposure on myocardial ischemia in men with documented coronary artery disease. The other component of the CO program was directed toward understanding the effect of CO on cardiac arrhythmias. Four groups of investigators, using different experimental models (two studied human subjects, two utilized laboratory animals), evaluated the arrhythmogenic potential of CO. The publication of the results of Dr. Chaitman and coworkers marks the completion of HEI's program on the effects of CO on cardiac rhythm. A brief discussion of the findings of these studies and the lessons learned may help point toward directions for future research.

As discussed earlier, the two animal studies supported by HEI did not show any effects of acute exposure to CO on cardiac arrhythmias or related end points (Vanoli et al. 1989; Farber et al. 1990; Verrier et al. 1990). These findings suggest that CO exposure does not induce cardiac arrhythmias in dogs. However, the negative findings may be the result of an insensitive or inappropriate model, or there may have been limitations in the experimental preparation or in the study design.

The two human studies funded under RFA 84-2, the present study and the study of Sheps and associates (1990, 1991) had similar objectives and protocols. Both were designed to address the question of whether or not acute exposure of patients with mild coronary artery disease to moderate levels of CO (leading to approximately 3% or 6% blood COHb) enhances the frequency of cardiac arrhythmias.

Sheps and coworkers found no effect of CO exposure in 10 subjects who had coronary artery disease but no baseline arrhythmias (Hinderliter et al. 1989; Sheps et al. 1991). There was, however, a positive finding in the 30 subjects who had baseline ectopy (Sheps et al. 1990, 1991). When these subjects were exposed to CO leading to approximately 6% COHb (as measured by CO-oximetry), they exhibited a higher frequency of both single and multiple VEBs during exercise than did subjects exposed to air. The effect of CO exposure on arrhythmias was significant only for measurements made during the exercise period (approximately 13

minutes); it was not significant in resting subjects or in subjects exposed, either at rest or during exercise, to approximately 4% COHb. The absence of an effect at the lower COHb levels, in addition to the absence of effects of CO exposure on other indices of cardiovascular function (ECG measurements and ejection fraction), raises the possibility that the single statistically significant finding may have been due to chance.

In the present study, Chaitman and coworkers found no increase in the frequency of ventricular arrhythmias after CO exposure leading to either 3% or 5% COHb (as measured by gas chromatography), regardless of the level of activity. The symptom-limited exercise period in both studies (an average of 9 to 13 minutes) was quite short, and the number of subjects was small. In addition to the variability of the end point, these two factors limit the power to detect any possible association and to distinguish between real and chance associations.

Overall, the results of the four HEI arrhythmia studies suggest that a brief exposure to CO is not a major contributor to cardiac arrhythmias. However, the issue of the effects of CO on potentially susceptible subpopulations, particularly patients with myocardial ischemia, has not been completely resolved. As discussed earlier, the results from three independent groups of investigators confirm the hypothesis that exposure to CO that produces relatively small increments in blood COHb levels decreases the time to onset of myocardial ischemia in exercising males with coronary artery disease (Adams et al. 1988; Allred et al. 1989; The HEI Multicenter CO Study Team 1989; Kleinman et al. 1989). The effect of 6% COHb on the frequency of arrhythmias that occurred during exercise was reported in the study of Sheps and associates (1990, 1991). The subject population in that study contained a higher percentage of patients with myocardial ischemia than in the study of Chaitman and coworkers, in which the findings were negative. At the 5% COHb level, the latter group reported a nonsignificant increase in numbers of VEBs per hour during exercise in a subset of 11 subjects with myocardial ischemia. It is unclear whether this is a reproducible finding that would have statistical significance if the study population were larger or whether the result is a chance finding that reflects the spontaneous variability in ventricular arrhythmias (Morganroth et al. 1978; Schmidt et al. 1988; American College of Cardiology/American Heart Association Task Force 1989).

Although both the Chaitman and Sheps studies provide significant new information and advance our understanding of the effects of elevated COHb levels in patients with coronary artery disease, the ability to generalize the results is limited by practical constraints. Studies of this sort are demanding and cannot include a full range of patients. Although they provide new data under carefully controlled experimental conditions, they should be undertaken only when scientific justification is strong and information to satisfy regulators' needs cannot be met by less demanding approaches.

Further research might include studies to optimize and standardize exposure protocols at rest or during exercise. A more important research direction might be to determine optimum methods for monitoring VEBs and ischemic episodes over longer periods of time and during activities of daily living. It is reasonable to expect that measurements made during exercise might be most sensitive to the effects of CO exposure. However, the observations made in the two clinical studies discussed above illustrate the difficulties of trying to measure a highly variable phenomenon during an isolated short exercise period using conventional Holter monitoring.

Questions concerning the prognostic significance of arrhythmias are being addressed in other studies and are relevant to arrhythmias from a variety of causes, including environmental factors. Such questions may require longitudinal epidemiological studies of large numbers of affected and unaffected persons and the ascertainment of morbidity and mortality, with controls for numerous confounding factors. It is unlikely that the prognosis of CO-induced arrhythmias can be determined apart from the prognosis of arrhythmias in general. Finally, the most common cause of increased COHb is smoking, and the effects of smoking on the heart are more complex than the effects of CO alone.

CONCLUSIONS

In this study of 30 subjects with mild coronary artery disease and 30 or more VEBs per hour, a single exposure to CO, sufficient to raise COHb levels to approximately 3% or 5% (as measured by gas chromatography), did not result in any increase in frequency of ventricular arrhythmia at rest, during exercise, during recovery from exercise, or during usual activities. The levels of CO exposure used in this study also had no effect on heart rate or the systolic blood pressure response to the exercise test. Subgroup analyses did not detect any statistically significant effect of CO exposure on ventricular arrhythmias in individuals with more than 60 VEBs per hour, ejection fractions less than 40%, or exercise-induced ischemia.

The findings of this study differ from those of Sheps and coworkers (1990, 1991), who used a similar protocol but a different subject population. The latter group reported that when subjects with mild coronary artery disease were exposed to CO leading to 6% COHb (as measured by CO-oximetry), they exhibited a higher frequency of single and multiple VEBs during exercise than did subjects exposed to

air. No effect of CO exposure on VEBs was observed at rest or during exercise at the 4% COHb level, nor were effects of CO exposure observed on other functional or electrophysiological measurements.

Taken together, the results from both studies do not suggest that acute exposure to CO, leading to small elevations in COHb levels, is a major contributor to cardiac arrhythmias in patients with stable coronary artery disease who are on medication. It is not possible to conclude whether or not such exposures would be without effect in other people, such as subjects with more severe coronary artery disease, subjects who are not on medication, subjects with lung disease, and subjects exposed chronically to CO.

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