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Cardiac Response to Carbon Monoxide in the Natural Environment

CARDIAC RESPONSE TO CARBON MONOXIDE IN THE NATURAL ENVIRONMENT

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ABSTRACT

Carbon monoxide (CO) is a toxic air pollutant normally encountered in low concentrations by people living in urban areas. This gas is a by-product of the combustion of carbon-based fuels such as gasoline and natural gas. CO disperses in air, but activities such as commuting, living near traffic, cooking, heating, working near internal combustion engines, and smoking create high exposure situations that may last minutes to hours. These exposures are usually far below those that cause acute poisoning; however, the exposures are still high enough to adversely affect the blood, heart, and nervous system. CO is toxic because it binds strongly to blood, decreasing its oxygen carrying capacity. People with ischemic heart disease (IHD) are believed to be especially susceptible to CO. The narrowing of their coronary arteries restricts blood flow to the heart tissue and prevents compensation for the low blood oxygen due to CO. Low oxygen conditions disturb the normal beating of the heart and could potentially lead to a heart attack.

Thirty-six subjects with IHD were selected from approximately 2800 medical records of cardiac patients and were continuously monitored as they went about their normal day-to-day activities. Each subject wore a personal CO monitor recording one-minute average exposures in an electronic memory and a portable heart monitor for twenty-four hour periods. All subjects maintained a written diary of activities, locations, symptoms, and psychologic tension during sampling periods. Each subject provided end-expired samples at intervals throughout the monitoring day to assess levels of CO in the blood. Blood CO levels as measured by breath samples were compared with levels predicted from the CO exposure profiles. The association between exposures to CO and predicted blood CO levels and cardiac changes indicative of insufficient oxygen supply were tested.

The sample of subjects in this study indicates that the daily activities of ischemic heart disease subjects lead them to experience variable and sometimes elevated exposures to CO. Over half of these subjects were estimated to spend approximately 2% of their time in exposure conditions leading to blood CO levels shown in laboratory studies to affect IHD subjects. Highest personal exposures were experienced in activities associated with gasoline engines, including passenger automobiles and small gasoline appliances.

To examine whether myocardial ischemia associated with exposure to CO, ST-segment depression on the ECG was used as a marker of ischemia, and an episode was defined as depression of at least 1-mm and lasting for at least one minute. ST-segment analysis was performed on the recordings of 20 men (40 person-days) whose ECG was not confounded by digitalis medication or conduction defects. A total of 340 episodes of ST-segment depression occurred in 8 subjects, with a mean duration of 5.7 minutes. Using multivariate logistic regression, the probability of an episode of ST-segment depression within a 15-minute follow-up interval was significantly associated with level of metabolic activity (uniform odds ratio = 3.22, $p < 0.001$) and COHb estimated from the subject's

personal exposure profile (uniform odds ratio = 1.34, $p < 0.001$). The multiple logistic regression model predicted 15 percent of the incident ST-segment episodes as attributable to ambient CO exposures. Methodological considerations precluded the use of psychological tension as an independent variable in the multivariate model. These results are consistent with the results of controlled clinical studies and suggest that urban CO exposures contribute to the total burden of myocardial ischemia experienced by men with IHD.

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DISCLAIMER

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

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CABG	Coronary artery bypass graft surgery
CARB	California Air Resources Board
CO	Carbon monoxide
COHb	Carboxyhemoglobin
D_L	Lung diffusing capacity for carbon monoxide
ECG	Electrocardiogram
FEV	Forced expiratory volume
FRC	Functional residual capacity
FVC	Forced vital capacity
GC	Gas chromatograph
HEI	Health Effects Institute
Holter monitor	Ambulatory electrocardiograph recorder
IHD	Ischemic heart disease
kcal	kilocalorie
LBVAMC	Long Beach Veterans Administration Medical Center
MI	Myocardial infarction
MET	Metabolic equivalent unit, multiples of basal metabolic rate
MetHb	Methemoglobin
MVV	Maximum ventilatory volume
O_2Hb	Oxyhemoglobin
P-wave	ECG waveform corresponding to depolarization of atria
PTCA	Percutaneous transluminal coronary angioplasty
PEM	Personal exposure monitor
ppm	Parts per million by volume, concentration units
PR-interval	ECG interval corresponding to spread of depolarization from sinoatrial node to ventricles
QRS	ECG waveform corresponding to depolarization of ventricles of the heart
RAM	Random access memory
ST-segment	Segment of ECG waveform lying between QRS and the T-wave
T-wave	ECG waveform corresponding to repolarization of ventricles
UCIMC	UC Irvine Medical Center
U.S. EPA	Environmenal Protection Agency

V_A	Alveolar ventilation per minute
VO_2max	Maximum oxygen consumption

SUMMARY OF CONCLUSIONS AND RESULTS

The following major findings are organized around the original hypotheses:

1. IHD subjects are at risk of developing levels of carboxyhemoglobin reported in clinical studies to cause ischemia and shorten the time to onset of angina.

This study has shown that IHD subjects may experience CO concentrations of sufficient duration and concentration to lead to COHb levels associated in clinical studies with ischemia. Support for this finding comes from measured personal CO exposures and modeled COHb levels.

Carbon Monoxide Exposures

- Highest CO exposures occur while commuting and when near internal combustion engines.
- Average personal CO exposure for all time spent in automobiles was 8.6 ppm; maximum auto exposure was 239 ppm (one-minute average).
- CO exposures on freeways averaged 10-12 ppm.
- Elevated CO concentrations were observed in parking lots and parking structures. Average exposure in these microenvironments was 7.9 ppm.
- The time spent at service stations and motor vehicle repair facilities was associated with average exposures of 7.9 ppm CO.
- Residential CO exposures were generally low, averaging 2.0 ppm. These low residential concentrations allow for washout, from the body, of CO absorbed in other locations.
- Heart disease subjects spend less time in the ambient (outdoor) environment than members of the general population but the time spent in transit is similar to that reported for the general population.

Modeled COHb

- With the measured PEM distributions of CO, most IHD subjects (56%) are calculated to have experienced COHb levels in excess of 2.5% during the 142 person days of monitoring. Modeling results indicate that this level of COHb occurs 1.8% of the monitoring time.

- Based on PEM data, one subject is estimated to have attained 5% COHb (without cigarette use exposure).

2. The normal activities of IHD subjects at times involve increased myocardial oxygen demand (thereby decreasing angina thresholds).

   - This sample of heart disease subjects tend to engage in less strenuous activities than reported for healthy individuals of the same age. On average, exertional aspects of leisure and occupational activities are avoided by this group. The highest metabolic demands in this group tend to be associated with obligatory activities such as home and garden maintenance.

3. Periods of high activity at times coincide with elevated CO exposure and resulting elevations in carboxyhemoglobin.

   - Highest short-term exposures were found in proximity to small gas-powered garden equipment. Transient peaks as high as 134 ppm were observed with use of a gasoline powered chain saw and 226 ppm with use of a gasoline lawn edger. These activities involve relatively high metabolic demands for this group of IHD subjects.

   - Occupational exposures to CO were highly variable. Persons working in warehouses, assembly lines, and garages had an average CO exposure of 6.0 ppm. Proximity to internal combustion engines provides the greatest potential for elevated CO exposures. Occupational activity levels are also variable and may involve short periods of high metabolic rate.

4. Elevated COHb levels are associated with ischemic episodes measurable by electrocardiographic instrumentation.

   - Metabolic activity and estimated COHb levels were significantly associated with the incidence of ST-segment depression on the electrocardiogram. ST-segment depression is a medically recognized indicator of myocardial ischemia.

   - Taking into account the effect of metabolic activity, the risk of ST-segment depression was 1.5 and 2.1 times higher at moderate COHb levels ($1 > \text{COHb} \leq 2$ %) and high (COHb > 2 %), respectively, relative to periods of time when COHb levels were less or equal to 1 %.

   - The multiple logistic regression model predicted 15 percent of the incident ST-segment episodes as attributable to ambient CO exposures.

RECOMMENDATIONS FOR FURTHER RESEARCH

- Further characterize the CO exposures occurring during motor vehicle use.

  Although commuting to work was an infrequent activity amongst the IHD subjects studied, routine motor vehicle use, by virtue of its duration and elevated CO concentrations, was a major determinant of total exposure. In separate studies on the general population, a similar observation has been made. In-transit exposures are increasingly recognized as a potentially high CO exposure environment distinct from indoor and outdoor settings.

- Further characterize the exposures associated with small internal combustion engines used to power yard equipment (e.g., lawn mowers, chain saws, weed-eaters).

  CO exposures as high as 226 ppm were observed during yard work activity using small internal combustion engines. High exposures appeared to be caused by close user proximity rather than malfunctioning engines or extraordinary user behavior.

- Identify the environmental factors (e.g., appliance type, ventilation) that lead to elevated indoor CO exposures amongst IHD subjects.

  Relatively higher CO exposure was observed in the indoor residences of several research subjects. Given the large amount of time spent indoors at home by IHD subjects even small elevations of indoor CO concentrations may have a significant effect on total exposure.

- Validation studies of the standard breathhold method to estimate blood carboxyhemoglobin (COHb) should be performed for subsequent application in community health studies. Breathhold maneuver parameters should be varied, and contrasts made between non-diseased persons and those with IHD or chronic obstructive pulmonary disease. Artificial dosing of subjects could be used to extend the range of observations.*

  Considerable interpersonal variability in the breath CO-blood carboxyhemoglobin relationship was observed amongst IHD subjects. Sources of variability were identified and include physiologic differences, ability to perform breathhold and breath sample collection maneuver, and ambient CO levels at the time of sampling.

- Concurrent with breathhold method studies, analytic techniques to directly measure COHb in blood should be systematically evaluated. IL282 performance should be

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* These recommendations were partially addressed in another report to the Air Resources Board entitled: "A Coordinated Multidisciplinary Research Program on Carbon Monoxide Health Effects", ARB Contract #A5-190-33

compared against reference methods including gas chromatography and manometric (Van Slyke) methods. Interfering constituents in blood should be examined for each respective method.*

The IL282, commonly used for COHb determinations in clinical and research applications, may be subject to interferences or reliability problems at low COHb levels as encountered in community exposure assessment studies.

- Using personal CO exposure and electrocardiographic monitoring methods, community studies should be conducted on heart disease subjects prone to arrhythmias.

Arrhythmias and electrical instability are serious cardiac problems and potentially may lead to sudden death. Early research on the health effects of CO has focused on the aggravation of angina pain. One publisched study suggests that the frequency of ventricular arrhythmics may be increased at COHb levels of 6 % (Scheps et al. 1990). It may now be appropriate to consider initiation of research on arrhythmia outcomes. Because of the difficulties associated with clinical exercise testing of the arrhythmic subject, ambulatory studies in the community environment may be the most appropriate means of research on this question.

- The research methodology developed in this study should be applied to other groups suspected of being at risk for CO exposure. Although cardiac monitoring would not be relevant, personal exposure, activity diary, and blood and breath sampling methods might be used to document community exposures in persons with intermittent claudication or hemolytic anemia, or pregnant women. Perceived symptoms (e.g., leg pain) might be reported in the diary format.

- The ambulatory ECG reading which showed significant ST-segment depression should be reviewed by an independent cardiologist.

The significant and provocative association found between moderate environmental CO exposure and significant ambulatory ECG changes has direct implications for regulatory programs. Due to the potential importance of these results we recommend that an outside, independent review of those ECG tapes with significant ST-segment changes be conducted by a Board Certified Cardiologist. This QA review should be blinded to the CO exposures and to the previous ECG analyses. These QA efforts were not originally incorporated into the program budget due to the limited financial resources allocated to this study.

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* These recommendations were partially addressed in another report to the Air Resources Board entitled: "A Coordinated Multidisciplinary Research Program on Carbon Monoxide Health Effects", ARB Contract #A5-190-33

1. INTRODUCTION

1.1 STATEMENT OF THE PROBLEM

Carbon monoxide (CO) is a toxic air pollutant normally encountered in low concentrations by people living in urban areas. This gas is a by-product of the combustion of carbon-based fuels such as gasoline and natural gas. CO disperses in air, but activities such as commuting, living near traffic, cooking, heating, working near internal combustion engines, and smoking create high exposure situations that may last minutes to hours. These exposures are usually far below those that cause acute poisoning; however, the exposures are still high enough to adversely affect the blood, heart, and nervous system. CO is toxic because it binds strongly to hemoglobin and decreases the oxygen carrying capacity of the blood. People with ischemic heart disease (IHD) are believed to be especially susceptible to CO. The narrowing of their coronary arteries restricts blood flow to the heart tissue and prevents compensation for the low blood oxygen due to CO. Low oxygen conditions disturb the normal beating of the heart and could potentially lead to a heart attack.

1.2 CONCEPTUAL FRAMEWORK FOR STUDY

1.2.1 Limitations of Current Understanding

Clinical studies that expose exercising IHD patients to CO report decreased exercise tolerance and aggravation of angina pectoris at exposure levels typical of city life. This closely controlled exercise-exposure research has provided valuable insights into defining the carboxyhemoglobin (COHb) and activity levels at which health effects are likely to be observed in the ischemic heart disease population exposed to carbon monoxide. However, there has been no direct validation of these models in the urban setting. Recent advances in personal exposure monitoring and ambulatory electrocardiography (ECG) provide the capability to perform the simultaneous surveillance of exposure and cardiac function necessary for field research. These technologies were successfully used in the research described herein, to identify exposure environments, quantify carbon monoxide exposure and predict carboxyhemoglobin response, and estimate the likelihood of cardiac response in IHD subjects under the natural conditions of free-ranging activities.

Historically, the results of exercise-exposure studies in IHD patients have been extrapolated to the general symptomatic IHD population without knowledge of the group's likelihood of encountering the exposure conditions required to elevated their carboxyhemoglobin concentration into the range where laboratory health effects were observed. The lack of exposure and activity level data for IHD subjects has prevented effective evaluation of their risk from CO exposure.

This report presents the results of a community-based study which tested the hypothesis that there are members of the IHD population that are at risk of developing levels of carboxyhemoglobin sufficient to cause ischemia. Furthermore, the normal urban activities undertaken by these individuals do require increased myocardial oxygenation, and that at times, periods of high activity coincide with increased levels of carboxyhemoglobin, and are related to ischemic episodes measurable by ECG.

This ecological research, when viewed with the results of the traditional exercise testing approach, extends the predictive capability of controlled laboratory data and provides essential information on the validity of its extrapolation to the "normal" exposure-activity environment.

1.2.2 Research Background

Coronary artery disease patients are theorized to experience adverse health effects of CO exposure significantly before the general population because of their decreased ability to oxygenate myocardial tissue (Ayres & Grace, 1969; Ayres et al., 1969; Ayres. Gianelli, & Muehler, 1970; DeBias et al., 1973). Myocardial oxygen demands are directly related to heart rate and systolic blood pressure levels, while oxygen supply is determined by coronary artery flow and extraction by cardiac muscle of oxygen supplied to it. However, myocardial metabolism extracts nearly the maximal amount of oxygen possible under normal conditions, thus there is little room for augmentation of oxygen delivery through this mechanism of extraction. Therefore, increased myocardial oxygen requirements are normally satisfied by adjustments in artery caliber (and thus flow). In IHD, however, this compensatory mechanism is impaired by atherosclerotic narrowing of the coronary vessels, with consequent loss of vessel reactivity to changing metabolic demands. In individuals with IHD, certain heart rate and blood pressure requirements exceed available supply (e.g., with exercise), and myocardial ischemia ensues. This "setpoint" of heart rate and blood pressure presumes the availability of normal oxygen concentrations, and normal binding to hemoglobin. In the case of CO exposure, both the amount of oxygen available and oxyhemoglobin binding characteristics are altered, resulting in a lowering of the setpoint at which ischemia occurs.

Ischemia is manifested by decreased contractibility of the heart muscle, followed by electrocardiographic (ST-segment) alterations. Next, chronologically, some persons will sense chest pain (angina pectoris), while others will be predisposed to electrical instability of the myocardium, leading to the appearance of arrhythmias. Arrhythmias may also reflect episodic ischemia in certain patients (Ryan, Lown, & Horn, 1975; Bodenheimer, Banka, & Helfant, 1977; Kennedy et al., 1980; Moss, 1980; Calvert, Lown, & Gorlin, 1977). Spontaneous depolarization can occur in myocardial cells (foci) irritated by hypoxic conditions (Ayres & Grace, 1969). Thus ischemia can be detected by ECG changes before angina onset or in the absence of angina, and serves as an objective endpoint.

From the perspective of regulatory decision-making, the strongest supporting evidence for the identification of people with IHD as a high risk group has come from exercise-exposure studies of Aronow and Isbell (1973), Anderson et al. (1973), and Aronow (1981). Statistically significant decreases in exercise duration to the onset of angina pectoris were reported for COHb concentrations ranging from 2.02 to 4.50 per cent. Table 1.1 summarizes results of exercise tolerance studies in patients with symptoms of ischemia (angina pectoris). These exercise studies also examined electrophysiologic changes in cardiac performance which under stress testing conditions are considered indicative of ischemia by the clinical medicine community (Redwood et al., 1971; Ekblom & Hout, 1972). ST-segment depression, T-wave inversion, and arrhythmias were observed but not quantitatively assessed. In general, earlier onset (and therefore occurring at lower work levels) and longer duration of ST-segment depression were observed after CO inhalation. Despite minor differences in experimental protocol, and the need for replicate studies, these results would suggest cardiac health effects occur in the IHD subpopulation at COHb concentrations of less than 3%.

While this research has provided valuable insights into defining the approximate carboxyhemoglobin and activity levels in which health effects are likely to be observed, there has been no validation of these models amongst the IHD population in their natural urban setting. Ecologic studies that would validate these hypotheses have been indicated (Health Effects Institute CO Workshop transcript, 12 July 1983). This is the basis for this research project.

2. STUDY DESIGN

Subjects with ischemic heart disease (IHD) were continuously monitored as they went about their normal day-to-day activities. Each subject wore a personal CO monitor recording one-minute average exposures in an electronic memory and a Holter ambulatory electrocardiographic monitor for twenty-four hour periods. All subjects maintained a diary of activities, locations, and symptoms during sampling periods. Each subject provided end-expired breath samples at intervals throughout the monitoring day to assess carboxyhemoglobin levels. Carboxyhemoglobin levels as measured by breath samples were compared with levels predicted from the CO exposure profiles. Exposures to CO and predicted COHb levels will be correlated in later work with cardiac electrophysiologic changes indicative of ischemia.

2.1 EXPERIMENTAL SUBJECT SELECTION

Experimental subjects were selected from the patient populations of the Cardiology Division at the University of California, Irvine, Medical Center in Orange and the Veteran's Administration Medical Center in Long Beach. Medical records provided health history data and allowed selection of patients with ischemic heart disease as documented by coronary angiography, treadmill exercise testing, and/or radionuclide method. Patients were preferentially selected who had IHD and displayed reasonably frequent angina (reproducible with a given effort) or arrhythmia symptoms, yet were believed to be free of confounding conditions. All subjects had at least 50% occlusion of one or more of their coronary arteries and displayed electrocardiographic changes indicative of ischemia during treadmill stress testing.

Patients were contacted by phone and letter to solicit their interest in participation. At that time, they were briefly interviewed to ascertain their occupation (location and characteristics), home (location and characteristics), commuting habits, smoking behavior, passive exposure to cigarette smoke, physical activity level and recent health history. The subjects were briefed as to the plan for personal CO exposure monitoring and ambulatory ECG monitoring and asked if they would like to continue in the study.

Given the relatively high cost associated with clinically-performed ambulatory electrocardiography we anticipated a high rate of participation in this population which generally recognizes its vulnerability. We have provided results of the electrocardiography to the volunteers' private physicians.

Prior to proposing this project we considered the elements that are required to estimate the statistical power of the study design (i.e., likelihood of detecting a real effect). Because of the uniqueness of this research we were not able through our own experience, nor reference in the literature, to formally conduct an analysis of statistical power. The necessary elements for such an estimate would include: 1) knowledge of CO exposure profiles experienced by IHD subjects, 2) uptake and elimination of CO and resulting levels of COHb in IHD subjects under ambient exposure conditions, 3) the joint distribution of CO exposure with oxygen-demanding activities in IHD subjects, and 4) the likelihood of angina pain or electrocardiographic abnormality under different combinations of CO exposure and activity level. [Prior to this research we have only had quantitative information on uptake and elimination of CO in healthy young adults.] Because of this situation we decided that the best plan was to work with as large a sample as could be assembled with the resources available to the project.

2.2 STUDY AREA AND SURVEY TIME

Subjects for the study reside in eastern Los Angeles County, Orange and Riverside counties. Figure 2.1 illustrates that subjects from this study reside across much of the South Coast Air Quality Management District (SCAQMD) and therefore experience a wide range of ambient CO conditions. The original plans were to have sampling activities completed during the winter of 1984-85 so that all monitoring would be done during the time of year with the greatest likelihood of having elevated ambient CO levels. However, the recruitment and assembly of project instrumentation and facilities effort took longer than initially anticipated and sampling extended into early June 1985 (Table 2.1). As it turned out, the Los Angeles Basin was well ventilated during the winter of 1984-85 and CO levels at many stations were lower than typical. Therefore, the ambient microenvironmental exposures may be lower than those experienced during years with stronger inversion patterns.

2.3 DATA COLLECTION INSTRUMENTS

This study required the use and/or development of several instruments for collection of information on subjects, environmental CO levels, and physiologic factors. In this section we describe each of the items used.

2.3.1 Activity Diary

Subjects participating in this study were asked to maintain a diary of their daily activities. Time-activity diaries used for estimating exposure to air pollutants are conventionally designed to provide detailed information on the subject's surroundings and proximity to potential pollution sources. In addition, this study required detailed information on the physical state of the individual: activity level, health symptoms, and medication taken. These data are needed to infer the myocardial oxygenation demands, identify periods of perceived ischemia as manifested in angina pectoris or palpitations, and corrective actions.

An example of pages from the activity diary that was developed is contained in Appendix 4. To use the diary, subjects record environmental setting, noting location, describing activity, identifying proximal CO sources (only in the activity assessment phase), and describing perceived symptoms. Each diary consists of a set of these pages. The first part of each diary contains a set of instructions and sample pages to guide the subject.

The use of formatted pages, as opposed to an "open-ended" diary, is necessary to standardize records, ensure a complete and accurate recording of data, and provide a quick nominally demanding method for the subjects. Superfluous and unnecessary data recording is minimized to the benefit of subject and researcher. Of course the standardized format greatly eases encoding of the data for analysis.

All diary entries were coded, entered into a computer file, and synchronized to CO measurements from personal exposure monitors, and in the case of the final subject group, electrocardiographic data. Location data was collected in order to characterize average level and general distribution of minute-by-minute CO by microenvironments. Activity levels were coded in order to estimate metabolic rates during CO exposure since this factor will influence uptake and elimination of CO. Stress levels were recorded to account for psychological tension unrelated to CO exposure which may affect heart rate and rhythm.

2.3.2 Questionnaire Data

In order to characterize the individuals enrolled in the study and their residential environments, two questionnaires were administered. One inventory (Appendix 3A) is a health and lifestyle questionnaire. We were particularly interested in whether the subjects considered themselves to be active or sedentary. We reasoned that many IHD subjects would, as a consequence of their heart health, lead less active lives. A more sedentary lifestyle would have implications for myocardial oxygen demand and possibly for the distribution of CO exposures.

In a second questionnaire (Appendix 3B) we asked a series of questions about their residences. Of particular interest were factors that might influence CO exposures. Subjects provided information on proximity to roadways, location of garage, potential indoor sources of CO (e.g., space heaters, gas ranges and ovens), and physical characteristics associated with levels of building ventilation.

2.3.3 Interscan 5140 CO Monitor

The personal exposure monitors (PEM) used in this study, the Interscan Series 5140, store data in a random access memory for continuous periods up to 34 hours. The dosimeter record provides one-minute time weighted averages integrated from four measurements per second. Non-destructive readout of the data is accomplished through a software interface to an IBM personal computer. Ten monitors were used in this study.

The Interscan Series 5140 monitors are stable (the diffusion head sensor can measure equally well in any attitude), have good sensitivity (± 1 ppm), are accurate (± 2 % of reading when calibrated daily), and are relatively unaffected by interference (Wallace & Ott, 1982; Interscan, 1983). These instruments proved to be capable of providing the minute-to-minute monitoring required for this study.

Our major instrument concern was sensitivity of the electrochemical cell to large temperature shifts. Because of this concern, the baseline voltage was set to the equivalent of 10 ppm in order to observe any drift in the negative direction. Further, every exposure profile was examined and evaluated against a set of criteria. Laboratory tests were also conducted to test for performance characteristics such as sensitivity to temperature and humidity. These tests were run in parallel with General Electric CO-PEM's which were used by the EPA in the Denver and Washington, DC studies on personal CO exposure.

2.3.4 DelMar Avionics 445b ECG Recorder

Ambulatory recording systems are capable of providing a continuous tracing for a 24-hour period during which time the subject was free to pursue his normal activities. A recent evaluation of ambulatory ECG systems has demonstrated that particular recorder-scanner systems provide very accurate reproductions of the ST-segment and T-wave (Bragg-Remschel, Anderson, & Winkle, 1982). Because ischemia is manifested in the ECG as ST-segment depression and T-wave inversion (Stern & Tzivoni, 1973; Stern & Tzivoni, 1974; Stern, Tzivoni, & Stern, 1975; Crawford et al., 1978), good low frequency response is absolutely necessary. Arrhythmias may also reflect episodic ischemia in certain patients (Ryan, Lown, & Horn, 1975; Bodenheimer, Banka, & Helfant, 1977; Kennedy et al., 1980; Moss, 1980; Calvert, Lown, & Gorlin, 1977). Spontaneous depolarization can occur in myocardial cells (foci) irritated by hypoxic conditions (Ayres & Grace, 1969). Although accurate low frequency response recorders do display

decreased QRS-complex sensitivity, the minor amplitude distortions would not prevent the assignment of arrhythmias to gross severity grading categories as used by Lown and Wolf (1974). This grading system for ventricular premature depolarizations (VPD) distinguishes the severity of ectopic activity by frequency of occurrence, run length, and gross morphology. In summary, ambulatory ECG monitor systems are available which reproduce accurate and reliable tracings suitable for research measurement of ischemic changes.

Criteria for the choice of ambulatory ECG (Holter) monitoring systems in this study included a need for reliable and accurate recording of ST-segments, while at the same time retaining reasonable sensitivity towards families of QRS waveform. Because the major clinical use of Holter monitors is the detection of arrhythmias, most recording systems presently on the market are designed to give good high frequency response and reproducible QRS waveform. This is done at the expense of low frequency or flat response necessary to sense and reproduce the ST-segment of the ECG. Conversely, those systems which faithfully reproduce flat segments distort (over amplify) high frequency signals (Bjerregaard, 1980). Despite this trade-off, two "all around" recording systems have been identified by Bragg-Remschel, Anderson and Winkle (1982) and Deborah Bragg-Remschel (personal communication, September, 1983): the DelMar Avionics Model 445 and ICR Recorder Model 7201. These two systems demonstrated excellent ST-segment reproduction with minimal distortion of typical QRS waveforms and thus we selected the DelMar Avionics system as suitable for the needs of our research application. Stern and Tzivoni (1973) found the Avionics system to satisfactorily reproduce the ST-segment in patient field studies.

Balasubramanian et al. (1980) point out that careful electrode attachment and system set-up can substantially improve the stability of recordings. Artifacts due to poor electrode skin interface can be avoided by the shaving of the application site, abrasion by brisk rubbing of the site with a gauze pad soaked in isopropyl alcohol (or alternatively a burring instrument), and careful immobilization of electrode leads and cable with adhesive tape. These procedures were followed in this study.

A bipolar lead system was used in this monitoring effort. The exploring lead for one channel was a modified precordial V_5, located on the left anterior axillary line over the fifth rib. In subjects with a history of frequent arrhythmias, the other channel lead was a modified V_1, located in the fourth intercostal space adjacent to the sternum. If subjects were relatively free of arrhythmias, the second channel lead was a modified V_3, located over the fourth rib to left of the sternum. The ground lead was attached over the base of the sternum.

The Avionics Model 445b recorder also has an event marker feature that allows the subject to insert time markers for synchronization and indicate when a breath sample is being collected.

2.3.5 Breath Sampling and Breath CO Measurement

The human body's level of COHb is the ultimate measure of CO dose. Although COHb may be predicted via the Coburn equation and exposure data (Coburn, Forster, & Kane, 1965), it is possible to directly and reliably estimate COHb with a simple non-invasive technique: the measurement of CO in a sample of end-expired breath. This method has proved successful in surveying COHb levels across large numbers of subjects (McIlvaine, Nelson, & Bartlett, 1969; Stewart et al., 1976; Smith, 1977; Ayres, Evans, & Buehler, 1979; Jabara et al., 1980). It is ideally suited for this field study application where subjects are free-ranging and unsupervised. Subjects may easily collect several

samples throughout their day's activities and retain them for later laboratory measurement by an electrochemical analyzer.

In sample collection, subjects were instructed to inhale and exhale fully two times, then expire fully, inhale and hold their breath for 20 seconds, and then expire, wasting about half the breath to the room and blowing the other half into a sample collection bag. The inlet tube to the bag was immediately pinched closed by hand and then clamped shut with a pinchcock-style clamp. Subjects were trained on proper sealing of the collection bag, labeling, recording of the exact sample collection time, and storage. If samples could not be immediately analyzed they were stored in a cool place away from CO sources.

A further precaution was necessary to ensure meaningful sample collection. If subjects entered a highly fluctuating CO exposure area, such as a parking garage or high tobacco smoking area, they were instructed to go outdoors or to a well ventilated room, wait 2 minutes, then take the sample. This procedure has been successfully used to improve COHb estimation by Smith (1977).

Examination of the temporal variation of bi-hourly COHb measurements made by McIlvaine, Nelson, and Bartlett (1969) on Cincinnati urban dwellers supports that three samples per 24-hour period closely characterizes diurnal COHb variation. In this study, each subject was sampled six times each day for expired breath. The sampling schedule was:

Breath Sample	Time	Description
1	3-4 pm	Initial sample and training at clinic
2	6-7 pm	Early evening
3	10-11 pm	Before retiring for night
4	6-7 am	Upon arising
5	8-9 am	Mid-morning
6	12-1 pm	Noon
7	extra	After angina episode if experienced
8	3-4 pm	Ending sample upon return to clinic

One liter capacity polyvinyl bags (Fenwal Laboratories) were used to collect and hold breath samples. Originally manufactured for holding whole blood donations, these bags displayed insignificant losses over 24-hour period (losses were undetectable over 24 hours and averaged less than 0.1% hr^{-1} over 72 hours). Mouthpieces for the bags were fashioned from disposable plastic autopipet tips.

CO concentration was measured on an Ecolyzer 2000 monitor (Energetics Sciences) equipped with an inline Purafil/charcoal prefilter to scrub alcohol and aldehyde interferences (see Hartwell et al., 1984). Instrument zero and span was checked before each use and at intervals during sample analysis runs. Standards were humidified to simulate the moisture content of breath samples. Monthly calibrations were performed using NBS primary standards. All measurements were transformed according to the standard curve. The majority of breath samples were analyzed within a few hours of collection; no sample was held more than 24 hours before analysis.

2.3.6 Blood Sampling and COHb Measurement

Within 15 minutes of breath sampling at the clinic, a 5 cc antecubital blood sample was drawn in a gas-tight plastic syringe rinsed with sodium heparin. Special care was

taken to avoid drawing air into the syringe; any air bubbles were removed immediately and the syringe capped. If blood samples could not be immediately analyzed, they were refrigerated or stored on ice.

COHb was spectrophotometrically measured on an IL282 CO-Oximeter (Instrumentation Laboratories, Lexington, MA). The IL282 aspirates a 0.35 ml aliquot of whole blood and mixes the aliquot with phosphate buffer and octyphenoxydecaethanol detergent for hemolysis. The aliquot is then stabilized at 37°C in the cuvette and light absorbence is measured at four wavelengths: 535, 585.2, 594.5, and 626.6 nm. In turn, a dedicated microcomputer calculates total hemoglobin (THb), oxyhemoglobin, COHb, and methemoglobin. The calculations are performed using absorptivity coefficients stored in the permanent memory and a THb scaler constant. The calibration of the IL282 was regularly checked as part of a monthly interlaboratory quality control program in which UCI participated along with other research laboratories funded by the Health Effects Institute. Samples in the critical range of 1, 3, 5 and 7% COHb were analyzed and compared to determination by other IL282 and gas chromatography (GC) instruments at Dr. T.E. Dahm's laboratory, St. Louis University Medical School. Reported COHb measurements were transformed according to the UCI IL282-GC standard curve ($\%COHb_{GC} = 0.1569 + 0.8956\ \%COHb_{IL282}$, $r^2 = 0.98$). The IL282 is reported to have an accuracy of 1% COHb and a precision (1 S.D.) of 0.5% COHb (Brown, 1980; Dennis and Valeri, 1980).

2.4 MONITORING PROTOCOL

In Figure 2.2 a record of subject recruitment efforts and movement is presented. A total of 2800 medical records of cardiology patients were screened in order to identify 217 subjects that met the entry criteria established for the study. These subjects were invited by letter to participate in the study. The following sections describe the monitoring protocol used in this project.

2.4.1 Activity Assessment

The subjects were asked to carry activity diaries for three separate 24-hour periods. The diaries were mailed to participants with instructions to record their normal activities on days pre-selected by the research team. Two weekdays and one weekend day were monitored. The research team called each subject to check if the diary package was received and to answer questions that arose. Subjects recorded activities and locations, proximity to sources of CO, health symptoms, emotional excitement, and medication taken (Appendix 4). Upon completion of the three one-day diary records, the subjects returned activity diaries via a stamped return envelope that was provided.

Activity data were used to characterize environments by a potential of CO exposure and to characterize the metabolic rates of participants. These data may be used in subsequent risk assessments that require information on microenvironments and oxygen-demanding activities in order to estimate the probability that persons with IHD will encounter CO exposure and activity conditions that increase the probability of cardiac complications.

Sixty-three (63) subjects participated in this phase of the monitoring contributing 128 person-days of activity data.

2.4.2 CO Exposure Assessment

Subjects completing the paper and pencil task of activity diary assessment were asked to participate in the CO exposure phase of the study if they were available and denied smoking cigarettes. These subjects were asked to wear CO personal exposure monitors (PEM) for three 24-hour periods: 2 separate weekdays and 1 weekend day. While wearing the monitor, subjects again kept a written personal activity diary. Subjects were asked to provide end-expired breath samples at six specified intervals during sampling days. These samples were used to calculate COHb. This monitoring served several purposes: further characterization of the time-activity schedules of IHD subjects for comparison against data for the normal population; characterization of the CO exposure pattern encountered in normal urban activities and the resulting COHb experienced by an IHD subgroup; a recent self-quantitation of perceived cardiac symptoms; and a demonstration of the subject's compliance with experimental protocol before more extensive CO and cardiac monitoring began.

To minimize inconvenience to the subject, PEM's were delivered by the research team to each subject at their residence or job site. Upon delivery, subjects were trained in the use of the PEM, diary instructions were reviewed, and the breath sample maneuver and collection technique was taught and practiced. The first breath sample was taken. These tasks required 15-20 minutes.

At the end of the twenty-four hour monitoring period, a member of the research team again met the subject at an appointed location of convenience. The CO monitor was retrieved and switched to standby mode; the diary record was reviewed by the technician and the subject was debriefed. Special inquiries were made about activities to assess levels of exertion, CO exposure, and perceived symptoms. The final breath sample was collected. The subject's ability to properly perform the breathhold maneuver without coaching was observed and recorded. Although rarely necessary, subjects using improper technique were retrained and a second correctly performed breath sample was collected. The visit to retrieve the monitoring instrumentation generally lasted 15-20 minutes.

Forty-three (43) subjects participated in CO monitoring contributing 91 person-days of personal exposure data.

2.4.3 Joint Assessment of CO Exposure and ECG Activity

In this phase of the study, subjects were monitored for two separate 24-hour periods. As during the first measurement series, subjects kept activity diaries, wore the continuously recording CO personal exposure monitor, and took end-expired breath samples at intervals throughout the waking day. Additionally, the subjects wore an ECG (Holter) monitor system to obtain a continuous, simultaneous electrocardiographic record.

Subjects were asked to come to the cardiovascular clinic (e.g., Long Beach V.A. Medical Center, U.C.I. Medical Center, or U.C. Southern Occupational Health Center) at the beginning of each monitoring period. At that time, present health status was quickly assessed by oral interview, pulse, blood pressure, standard 12-lead electrocardiogram, and measurement of height and weight. Each individual was instructed as to the use of the CO monitor and told or reminded how to keep an activity diary. The ambulatory ECG system was attached to the subject (see Appendix 2). The subject was also reviewed in the self-sampling technique for end-expired breath collection, and the first breath sample was collected. A venous blood sample was drawn. These tasks took 30-45 minutes to complete per subject.

At the end of the monitoring period, patients returned to the clinic. CO PEM and ECG monitors were detached. Vital signs were assessed, a 12-lead ECG performed, and final breath and blood samples were taken. Patient diary entries were reviewed for completeness by the technician.

Additionally, psychological factors may influence ischemic changes in the ECG (Bellet et al., 1968; Gazes, Sovell, & Dellastatious, 1969; Taggart, Gibbons, & Somerville, 1969; Taggart, Parkinson, & Carruthers, 1972; Golding et al., 1973; Allen et al., 1976; Brodsky et al., 1977; Schang & Pepine, 1977; Ivanova et al., 1980; Armstrong et al., 1982). To assess emotional stress and its influence on the autonomic nervous system, the Speilburger State-Trait Anxiety Test was filled out by subjects at the beginning and end of the monitoring day. The questionnaire has proven reliability and validity in self-administered field applications (Speilburger, Gorsuch, & Lushene, 1970). The 20 question state test takes approximately 5 minutes to complete. (To measure anxiety "proneness," the 20 question trait test was administered once during the study.)

A total of 34 individuals participated in 68 person-days of joint CO exposure and ambulatory ECG monitoring.

2.5 CODING AND DATA ANALYTIC PROCEDURES

The activities logged in subject diaries were coded according to a standardized system used in the analysis of human activity patterns (Szalai, 1966; Stone, 1972). The assignment categories of this system allow calculation of simple duration and frequencies of primary activities (i.e., the larger classes of related sub-activities such as working time, travel, meals and sleep, and housework), average durations and frequency for combinations of activities, and analysis of the sequence of activities. These activities were combined with the CO exposure information to characterize types of exposure-activity environments encountered by the IHD patients. This information is useful in evaluating the risk of IHD patients developing particular levels of COHb in their urban movements.

The CO exposure record, recorded in one-minute averages and stored in the electronic memory of the PEM, was transferred directly to an IBM Personal Computer. These exposure profiles were coded, "backed up," and a separate file transferred to the University mainframe computer (CP-6). The 1440 individual minute averages making up the 24-hour monitoring period were input into uptake-elimination model algorithms (initially the Ott and Mage (1978) model; later the Coburn, Forster, and Kane (1965) model will be used) to predict the individual's COHb response to exposure. The end-expired breath samples allow comparison of the model prediction with actual measures.

The ECG records were played back and recorded to hard copy using a full disclosure electrocardioscanner. The UCI Medical Center made their American Edwards Eliminator Electrocardioscanner available for this transcription. The tape, completely transcribed to paper, yielded 1440 lines of one-minute ECG tracings. For each one-minute duration, heart rate, ventricular premature depolarization (VPD) rate, VPD run length, and arrhythmia grade (see Lown & Wolf classification scheme 1974) were quantified. The full disclosure tracing generated by the "Eliminator" is too compressed to allow interpretation of ST-segment and T-wave changes. Therefore, the ECG tapes were played back on a DelMar Avionics Model 655A Electrocardioscanner (Long Beach Veterans Administration Medical Center) to get a high resolution tracing upon which ST-wave changes could be measured. T-wave inversion, and significant ST-segment depression (2 mm for 5 consecutive beats) and duration were measured. These minute-by-minute electrophysiologic features were, in turn, related to exposure-activity data.

2.6 QUALITY CONTROL

Ecological studies of the physiologic response to CO exposure involve an experimental design in which critical attention is focused upon the reliable quantification of the personal exposure and the electrocardiogram. Unlike the data derived from laboratory studies, PEM, activity diary, and ambulatory ECG data are complex and somewhat cumbersome. These characteristics necessitate careful quality control. Aerometic instrumentation was subjected to redundant cross-instrument comparison; activity diary and ECG data was checked at several levels of data coding, entry, and analysis.

The Interscan 5140 was the primary instrument used to measure personal CO exposure. Immediately before every monitoring use each PEM was checked and adjusted for zero and span using primary gas standards at concentrations of 0, 2, and 50 ppm. After each deployment, zero and span was checked for drift. An a priori level of 5% drift was acceptable over the 0-50 ppm range of calibration.

The Interscan 5140 PEMs were spanned with the zero point set at 10 ppm. This offset allowed convenient tracking of negative zero drift should it have occurred during the monitoring day. Negative zero drift was typically observed during cold overnight temperatures. A correction factor was applied to compensate for this downward drift; concentrations were additively corrected to zero. We believe the electrochemical sensor cell of the Interscan 5140 is negatively influenced by the cold temperatures existing in unheated homes during the wintertime overnight hours. It should be noted that the correction applied assumes a default CO concentration of zero and this may cause a downward bias in the reported night sleep and bedroom CO measurements.

When monitors were exchanged on field location in back-to-back monitoring day sequences, overlapping periods of measurement were examined to ensure that PEMs performed within the 5% drift criteria (3 ppm). At several points during the research period, the Interscan PEMs were deployed as a group in a variety of typical field conditions (e.g., indoor residential, outdoors, automobile passenger compartment). Performance was compared to that of another portable instrument, the Ecolyzer 2000, deployed as a continuous monitor with a strip chart recorder.

The Ecolyzer 2000 served as primary measurement instrument for the analysis of CO in breath samples and as a reference instrument to evaluate calibration and field performance of the Interscan 5140 PEMs. The Ecolyzer was calibrated using National Bureau of Standards (NBS) reference gases at concentrations representative of the full range of use: 9.7, 17.9, and 43.1 ppm. Calibrations were performed by the UCI research team and independently by Mr. Jack Horrocks of the Air Resources Board Haagen-Smit Laboratory. Humidified samples of the NBS reference standards were used to construct the standard calibration curve for the analysis of breath samples.

The Dasibi 3003 Gas Filter Cell CO monitor was used as the primary instrument standard. This instrument was loaned to UCI by the ARB and provided a cross-instrument comparison against an EPA approved reference method. The Dasibi 3003 was calibrated on a monthly basis by Mr. Horrocks using the NBS reference gases.

The concentrations of all purchased primary gas standards were independently certified by the ARB laboratory. These standards were used to check the zero and span of the Interscan, Ecolyzer, and Dasibi instruments.

Because data transfer from the Interscan 5140 PEM to the computer is direct without a human transcription step, there was minimal need for quality control at this step. However, cumulative frequency distributions, time trend plots, and the diary records were used to identify spurious measurements and intervals of suspected zero or span drift. Linear corrections for drift were applied if the maximum drift did not exceed the 5% acceptable drift criteria.

During the course of the research study there were 12 person-days of CO data lost due to PEM instrument failure. Over the 168 monitoring day attempts, nine (9) monitoring days were lost due to excessive zero and/or span drift, corresponding to a failure rate of 5.3%; four (4) monitoring days were lost due to apparent data logger failures, corresponding to a failure rate of 2.4%. An additional person-day of CO monitoring was lost due to a lack of diary record by a research subject who had difficulty completing writing tasks.

After the activity diary data was coded and entered into the computer, the entire computer record was examined for coding accuracy against the original diary records. During descriptive and summary statistic analysis, all outliers were again verified against the original diary record.

Ambulatory electrocardiographic data was collected using a calibrated recording system. Before each monitor deployment, the system was attached to a one-millivolt signal generator and a series of calibration signals were recorded onto tape. After placement of the ECG monitoring system on the subject, each lead and electrode was examined for artifact. Upon the subject's return to the clinic at the end of the monitoring day, all leads and electrodes were visually inspected; the occurrence of leads which had pulled loose was noted. In sixty-eight person-days of ECG monitoring, loose electrodes were observed on only two occasions. In both cases, the alternate channel of the two-channel system remained viable and continued to record data. One person-day of ECG data was lost due to monitor failure: a recording tape jam occurred 2.5 hours into a monitoring run destroying the tape. The one person-day of ECG data lost corresponds to a failure rate of 1.4%. The joint PEM and ECG instrumentation failure rate was three person-days out of 68 or 4.4%.

A two-stage method of analysis was used to review the ambulatory ECG data. The ambulatory ECG tape was played back on a DelMar Avionics Trendsetter II system (Model 9000A DCG VII) with Model 9021 Arrhythmia Analyzer. Using a scanning speed of 60X real time, the technician taught each subject's normal, ventricular ectopic and supraventricular ectopic beats, and unknown waveforms to the processor's template memory. The 60X real time playback ensured maximal processing accuracy. High frequency ectopic beats were better detected by the human observer at this replay speed; faster playback would have increased the chances of artifactual classification errors by the technician. QRS complexes were superimposed on the oscilloscope display. When an unknown or premature complex was encountered by the analyzer, the abnormal beat was classified by the technician according to ectopy class or rejected as artifact. Real time ECG strips were produced for any of the following:

1. changes in the morphology of the P-waves, QRS complexes, T-waves, or ST-segment;
2. arrhythmias with onset and termination shown;
3. patient perceived symptom periods;
4. high activity periods;
5. normal base electrocardiogram for various times of the day.

The technician traced to hardcopy examples of arrhythmia waveform, recording the classification which was taught to the arrhythmia processor. This record was available to the cardiologist reviewing the analysis for quality control.

The semi-automated ECG system software is programmed to produce hourly summary statistics of ventricular and supraventricular ectopy, tachy- and bradycardia, and the number of minutes of ST-depression and elevation. These data were used to identify periods of the monitoring day in which intensive minute-by-minute analysis was necessary. This was the second stage of the minute-by-minute occurrence of ST-T wave changes or arrhythmias.

Arrhythmia grades were assigned according to the scheme of Lown and Wolf (1974) and Lown et al. (1975):

0 = no ventricular ectopic depolarization
1 = occasional isolated ventricular premature depolarization (VPD); less than 1 per minute;
2 = frequent VPD; more than 1 per minute or 30 per hour;
3 = multiform VPD;
4 = repetitive VPD
  a) couplets
  b) salvos or ventricular tachycardia;
5 = early VPD (abutting or interrupting the T-wave; this class was to be detected by visual scanning and less reliably by the arrhythmia analyzer's prematurity algorithm.

It should be noted that data reduction using a similar procedure of semi-automated processing by the Lown group at Harvard demonstrated a combined false-positive and false-negative rate of less than 5% (Lown et al., 1975).

This ECG analysis approach was technician intensive and therefore required careful review by the research team cardiologist. Within each 24-hour tape, three hours were randomly chosen for separate and additional analysis by the cardiologist. If a greater than 10% error rate was discovered in two of the three hours the entire tape was reanalyzed by the technician. The tape was then reanalyzed a second time for quality by the cardiologist. If the error rate was greater that 10% in only one of the three hours, then only the hour in question was reanalyzed by the technician. The hour in question was then reviewed for corrections by the cardiologist.

In addition to the quality control procedures followed for aerometric, activity diary, and ECG data, UC Irvine participated in an interlaboratory comparison of blood COHb analysis by the IL282 CO-Oximeter. This comparison was sponsored by the Health Effects Institute in an effort to standardize blood gas analysis amongst its various research centers. On a monthly basis, Dr. T. E. Dahms of the St. Louis University School of Medicine prepared blood samples of approximately 0.8, 3.0, and 7.0 %COHb which were air mailed to the laboratories for analysis. The samples were not presented in a blinded manner to the participating labs. Measurement of COHb by the UC Irvine CO-

Oximeter compared well to the St. Louis IL282 (UCI-IL282 = 0.0254 + 0.9937 SLS-IL282, r^2 = 0.9941) and gas chromatograph measurements (UCI-IL282 = -0.1569 + 0.8956 SL-GC, r^2 = 0.9765).

3. STUDY RESULTS AND DATA ANALYSIS

3.1 DESCRIPTION OF STUDY GROUP

Several personal factors have been demonstrated to be significant determinants of activity patterns and behavior. The major factors as identified by Chapin (1974) and Robinson (1977) are: age, employment status and occupation, life stage, and health status. In this section we present relevant characteristics of the subject population which are hypothesized to influence activity patterns and hence, CO exposure and cardiac response.

3.1.1 Health Status

The sample of individuals used in this study were pre-selected from medical records at the UCI Medical Center and the Long Beach Veteran's Administration Medical Center. As identified from coronary angiogram data, each individual invited to participate in the study had at least 50% occlusion of one of the three major coronary arteries. A further criteria for selection was "objective" electrocardiographic evidence of ischemia during exercise stress testing. Angina is a "subjective" indicator of ischemia and may or may not reproducibly occur during exercise tests. Thus, the presence of angina during clinical stress testing was not a prerequisite for participation in the research program.

A basic assumption underlying this research design is that the selected cases are representative of men with ischemic heart disease. This assumption is threatened by several factors:

(1) Subject selection was limited to those individuals who are in the clinical phase of illness and those whose symptomatology was deemed serious enough to warrant coronary catheterization and angiography procedures. Many potential subjects with significant disease which is silent may not have had cause to seek medical attention (e.g., angina or decreased work capacity) and therefore remain unidentified in the medical records used to selected subjects. Further, this group remains statistically undescribed in the medical literature so as to preclude a comparison.

(2) The selection process did not canvas all medical facilities of the region to identify the total pool of eligible IHD subjects. Within the research budget it was not practical to attempt this, since there exists no "registry" of heart disease patients.

This research design intended to identify and select for inclusion those individuals with severe IHD. Because of the advanced stage of disease in this population, we believe that most individuals are beyond the developmental stage where symptoms appear and have therefore sought medical care. However, this sampling strategy omits those individuals with silent disease, a subgroup believed to comprise twenty-five percent of all individuals with ischemic heart disease.

The electrocardiographic methodology of the research forced yet another selection bias into the design. Subjects with conditions which confounded the study's

electrocardiographic endpoints were excluded. Thus, individuals whose resting ECG displayed ST-T wave changes due to cardiac medications such as digitalis were not selected for participation. Similarly excluded were individuals with conduction defects and/or mitral valve prolapse.

Cognizant of the above discussed possibilities of selection bias, we have no reason to believe that the frequency of disease characteristics in the sample population differs substantially from that of the general population of men with severe IHD.

The characteristics of research subjects who wore PEM and/or the electrocardiographic monitors are presented in Table 3.1. By self assessment, most individuals considered themselves to be of average general health and heart health. Typically a subject's evaluation of his general health reflected his perception about his heart health condition.

Angina presence and frequency was ascertained during the medical history using a Rose-type line of inquiry (Heyden et al., 1971). Angina, defined as chest pain associated with exertion, was present in 71% of the subject group. Among the angina sufferers, 35% experienced angina episodes at least once each day and 28% experienced angina approximately 2-3 times per week.

No research subject had suffered a myocardial infarction in the four months preceding enrollment in the study. No subject suffered a myocardial infarction during the CO monitoring phase of the study, although several subjects were hospitalized for heart-related illnesses during the course of the study.

The various medications used by the research subjects are listed in Table 3.1. Most prevalent were the nitrates, including nitroglycerine, isosorbide dinitrate and nitroglycerine skin patches. Beta-blockers and calcium channel antagonists were also commonly prescribed medications. Twenty of the 42 subjects were hypertensive and took anti-hypertensives or diuretics. Six of the subjects were diabetic and took insulin.

Body height ranged from 160 to 188 cm; mean height was 174.4 cm. Body weight ranged from 60 to 120 kg; mean weight was 84.6 kg. Subjects typically exceeded their ideal weight as predicted from their height.

3.1.2 Age, Occupation, and Life Stage Status

The ages of subjects ranged from 39 to 74 years; mean age was 60 years old.

The research subject group displayed a diverse cross-section of employment status (Table 3.1.). Thirty-five percent worked full or part-time jobs. Occupations included but not restricted to security guard, theater projectionist, electrician, housekeeper, construction worker, accountant, salesman, and auto repair garage manager. Twenty-eight percent of subjects were unemployed and thirty-five percent were retired or were supported by state disability. The severity of the ischemic heart disease condition restricted the employment opportunities available to this group and forced early retirement in several cases.

The majority of the research group was married and lived with their spouse. Nine of the forty-two subjects had children who lived at home. Three subjects lived alone. All subjects may be considered to be a head-of-household.

3.1.3 Home Characteristics

When assessing an individual's total exposure to air pollution, residential characteristics become important due to the large proportion of time typically spent in these surroundings. By questionnaire survey, we assessed the CO sources present in the homes of our subjects. The majority of subjects participating in the CO monitoring phases of the project lived in homes which had gas appliances (Table 3.1); only two subjects lived in "all-electric" homes. Seventy-four percent of homes had gas-fueled ranges and ninety-five percent of homes had gas-fueled furnaces. Two of the 42 subjects used kerosene space heaters in the living areas or workshop areas of their homes. Forty percent of the homes surveyed had attached garages, however inquiry was not made as to whether or not the garage was used to park a motor vehicle.

3.1.4 Proximity to CO Sources

The potential for high daily CO exposure is also influenced by occupational exposures to gas fumes or exhausts. Two subjects indicated having moderate to high exposure to running auto exhaust (Table 3.1).

Transportation behavior was expected to influence CO exposure. However, within this sample population, little opportunity for contrasting modes of transportation was available: 95% of subjects travelled by personal auto. Commuting behavior varied widely throughout the subject population. Forty percent of the group did not report any commuting behavior, while twenty-five percent reported one-way travel times of 0.5 to 1 hour's duration occurring on at least three days per week (Table 3.1).

Passive exposure to cigarette smoke may affect CO exposure. Sixty percent of subjects characterized themselves as rarely being around others who smoke. Three subjects were frequently exposed to cigarette smoke of others while on the job and twelve subjects were frequently exposed to the cigarette smoke in their home (Table 3.1).

3.2 DAILY ACTIVITY PATTERNS OF AGGREGATE

Behavioral patterns of activity and location determine air pollution exposure in the absolute sense: time spent in activities and/or settings define the time-weighting of pollutant concentration required to calculate compartmentalized exposure. An individual's pursuance of activity schedules is believed to be determined by their life stage role, person characteristics, and their motivations and attitudes (Chapin, 1974; Robinson, 1977). In the case of the person with IHD, activity choice may also be influenced by their angina pain experience and their knowledge and beliefs about angina pain and heart health. Presumably some activity choices will be constrained by anginal pain, while other choices in which angina pain is associated are pursued because of energizing factors which outweigh angina considerations. It is probably overly simplistic to view angina as consistently constraining activity. Little data exists on the influence of health status on time-activity patterns, and no data has been published for persons with IHD.

It is possible that the physical constraints imposed by IHD and angina may alter the CO exposures experienced by this subgroup as compared to the general population. While exposures could be indirectly estimated using an extension of exposure models for the general population, it is possible that CO exposures could in reality be higher for this subgroup. This uncertainty in exposure estimation spurred the direct monitoring of activity and CO exposure undertaken in this study. Activity data not only provides

complete description of physical settings involved with CO encounters, but also potentially allows identification of high risk, or protective behaviors (e.g., averting behaviors). Importantly, data on activities allows characterization of myocardial oxygen demand and examination of its joint distribution with elevated CO exposure. The uptake and elimination of CO from the body is regulated by physiological parameters which vary with activity level, such as minute alveolar ventilation volume and lung diffusing capacity.

3.2.1 Frequency of Time Spent in Activities and Microenvironments

Occupancy periods, defined as the time a subject spends in a "microenvironment" or location on a single visit, vary from activity to activity. Mean occupancy times for each day of monitoring can be calculated for each activity class and microenvironment. Similarly, microenvironment CO concentrations may be calculated and are defined as the average concentration level measured in a setting on a single visit. (The time-weighted mean CO concentrations will be presented in Section 3.4.) Maximum occupancy periods (assume minimum = 0) and arithmetic and geometric means and standard deviations are presented for activities pursued by non-smoking subjects while wearing the PEM (Tables 3.2 and 3.3). Discussion of activities will be limited to data collected on non-smoking subjects wearing the PEM; tabulation of smoking subject data is provided in Appendix 1 for reader comparison.

In Tables 3.2 and 3.3, "doers" are defined as the number of different subjects attempting the activity or occupying the microenvironment. "Occurrences" are the number of unique engagements in a particular activity or separate occupancies of that specific microenvironment.

Time spent in indoor residential microenvironments dominates the time-weighted classification of daily activities (Figure 3.1, Tables 3.2 and 3.3). The IHD subjects in this sample spent 79% of their monitoring day inside their residences. This aggregate statistic represents the combined activity patterns of the several full and part-time working status subjects with those of the larger group who were unemployed or retired. Nevertheless, the 79% time spent in indoor residential microenvironments is comparable to the 87% value reported for unemployed or retired men and women of Kingston/ Harriman, Tennessee (Spengler et al., 1983). In the Tennessee study, working individuals spent less time, 63-70%, indoors at home. Although that distinction is expected to be true of the working IHD subjects, it was not calculated for comparison. Unfortunately, national time-activity databases (e.g., Chapin, 1974) are not organized in a manner that allows estimation of time spent indoors at home.

Night sleep (Code 45) and bedroom (Code 115) are the single longest duration activity and microenvironment each day; or with ninety-five percent of night sleep occurred between 10 pm and 6 am. Arithmetic mean occupancy at sleep activity was 476 minutes (66 minutes S.D.) and bedroom occupancy was 515 minutes (134 minutes S.D.). These data compare well with national mean of 450 minutes for the average weekday sleep (Chapin, 1974).

Television viewing (Code 91) averaged 167 minutes (143 minutes S.D.) each day across the IHD subject group as compared to the national average of 147 minutes (Chapin, 1974). Television viewing and other passive leisure activities largely take place in living room (Code 114) and family room (Code 111) locations where average occupancies were 234 minutes (206 minutes S.D.) and 76 minutes (131 minutes S.D.) respectively.

Mean values of 99 minutes per day for maintenance of home, yard, and/or auto in the national sample (Chapin, 1974) are comparable to IHD subject data: 7 minutes per

day for house cleaning (Code 12), 12 minutes for outdoor chores (Code 13), 15 minutes for gardening (Code 17), and 28 minutes for other duties including auto maintenance (Code 19). The mean proportion of time spent in outdoor environments was, at 4%, the least frequently visited major microenvironmental class (Figure 3.1).

Relaxation, rest, and napping classes of activity as a group averaged 107 minutes per weekday in the national survey of general population by Chapin (1974). These activities were generally associated with the indoor resident environment. Resting (Code 47) averaged 33 minutes (41 S.D.), and relaxing (Code 98) averaged 90 minutes (88 S.D.). Daytime sleep was infrequently reported in the IHD subjects. These values are believed to be comparable to those published for the general population.

Walking for exercise (Code 82) averaged 28 minutes per day (31 minutes S.D.), a lower value than published for the national sample of the general adult population for the combined activity class of walking and cycling: 57 minutes. Participation in active sports (Code 80) was also lower for IHD subjects, averaging 22 minutes (45 minutes S.D.) as compared to the national average of 90 minutes per day (Chapin, 1974).

Time in personal auto accounted for most of the 10% of daily time spent in transit microenvironments (Figure 3.1). Time spent in personal automobile microenvironments (travel and waiting for travel) average 97 minutes per day (64 minutes S.D.) across the IHD subjects, as compared to national travel and waiting for travel time at 84 minutes (Chapin, 1974). In a pilot field study of Los Angeles subjects, Ziskind, Fite, and Mage (1982) observed that subjects spent 12% of their daily time in the "commute" microenvironment.

3.2.2 Implications of Time-Activity Patterns for CO Exposure and Uptake

The uptake end elimination of CO from the body may be conceptualized as a differential equation of mass balance. Coburn, Forster, and Kane (1965) have determined that several physiologic and environmental factors regulate CO flux: ambient CO concentration, endogenous CO production, barometric pressure, diffusing capacity for CO, alveolar ventilation, blood volume, mean capillary pO_2 and O_2Hb concentration. As will be demonstrated in the next section, CO concentrations are unique between microenvironment settings and activities. Duration of occupancy in microenvironments will determine uptake and washout, and the degree to which blood COHb attains steady state with the settings CO concentration. Increased levels of physical activity within a microenvironment will speed the rate at which uptake or elimination to steady state COHb is achieved. Strenuous activity such as exercise or yardwork is associated with increased minute alveolar ventilation and increased diffusing capacity for CO. An increase in either or both of these physiologic factors increases CO flux. Strenuous levels of activity were relatively infrequent across the IHD sample group. In general, the subjects' highest level of exertion would still be considered moderately light for individuals free of coronary disease (see Section 3.2.3). For these reasons, the requirements of uptake and elimination modeling become simplified; linear models can be applied. These models assume light physical activity and do not incorporate the input of individual physiologic parameters as the Coburn equation does.

"Clusters" of high CO concentration activity may recur with regularity in the activity schedules of particular individuals, allowing the buildup of COHb levels over 2.5%. Evening, cross-town commuting, followed by cooking activities, and then nighttime, indoor residential wall furnace emissions, are believed to contribute to the elevated COHb levels observed in one research subject on two separate monitoring days. Other such "clusters" or runs of high CO exposure seem to exist in the data base. Further analysis will be directed towards identifying these runs and the reasons for their grouping as a string in the exposure time series.

3.2.3 Implications of Time-Activity Patterns for Myocardial Oxygen Demand

Work intensity may be described in multiples of the resting metabolic rate. When body weight is taken into account, there is a direct relationship between work intensity and energy expenditure by the body's metabolic processes. Energy expenditure is described by an index called the MET, which is calculated as: work metabolic rate/resting metabolic rate. The resting rate is slightly higher than basal and equivalent to inactive sitting. Caloric expenditure is estimated on the basis of 1 MET = 1 kcal kg^{-1} hr^{-1} and oxygen consumption is estimated by 1 MET = 3.5 ml 0_2/min/kg body weight (Passmore and Durnin, 1955; Consolazio, Johnson, & Pecora, 1963; Astrand and Rodahl, 1970). Acheson et al. (1980), Bouchard et al. (1983), and Christensen et al. (1983) report that heart rate is of limited use in estimating energy expenditure and oxygen consumption; variations in heart rate, caused by factors independent of oxygen consumption, is great at low levels of physical activity. Posture, emotion, food, temperature, time of day, fatigue, previous exertion, and physical fitness will all influence the heart rate to energy expenditure relationship. The relationship is best described for activities involving the legs and is less accurate for activities involving the upper body. For studies of individuals whose average 24-hour heart rate is only slightly higher than their resting heart rate, such as heart patients, more precise estimates of oxygen consumption can be made from accurate diary reports of activities. Therefore in this research, whole body oxygen consumption and myocardial oxygen demand is evaluated using activity diary data. Approximate metabolic costs of activities derived from literature reports (Table 3.4) were assigned to each of the activity classes (Table 3.5).

Several classes of activity are associated with very high myocardial oxygen demands. These include regular work at a job site (Code 00) or at home (Code 01), outdoor chores at home (Code 13), lifting work at home such as carrying in firewood (Code 18) or moving furniture (Code 16), exercise and outdoor recreation (Codes 25, 80), sexual activity (Code 48), and travel such as bicycling or walking and driving in stressful situations (Codes ending with 9). However, in the IHD subpopulation sampled, the occurrence of these strenuous activities was relatively infrequent, not only in terms of the number of occurrences but also in terms of the number of individuals choosing to engage in such activities. As indicated by the low geometric means, sustained intervals of heavy activity were uncommon across the aggregate. Yet certain individuals who were inclined to do heavy work did undertake such activity on a regular routine, and at times, maintained high levels of exertion for as long as two hour periods. Yesterday interviews revealed that though these individuals were prone to exertional angina, they were able to undertake heavy activity if they paced themselves. These activities included heavy carpentry, auto repair, and cutting firewood. During the interval very high levels of exertion were achieved.

Walking for exercise represents the upper level of daily exertion for the majority of the IHD patients studied in this effort (98 separate occurrences by 25 unique subjects). For most individuals it is a walk at a pace that is just slightly below their personal threshold of angina. It was not unusual for angina symptoms to be reported during walking exercise. During separate graded exercise testing on a treadmill using a modified Naughton-Balke protocol, the majority of the subjects identified a workload of 3-4 METs as subjectively equivalent to their personal level of perceived exertion during walking. Thus, a low functional capacity was characteristic of the IHD group selected for study.

This low functional capacity identifies the importance of considering activities in the 4 MET range as increasing myocardial oxygen demand to a level where angina onset

may be expected. Further, if the exertion is coincident with or preceded by prolonged CO exposure, earlier onset (aggravation) of angina might be expected to occur.

3.3 EXPOSURE PATTERNS OF THE AGGREGATE STUDY GROUP

A primary objective of this research was to estimate CO exposure in the variety of settings and activities comprising the daily routin of subjects with ischemic heart disease. This section presents the CO data collected by the personal exposure monitors over two classification schemes: by activity type and by microenvironment type. As explained previously (see Section 3.2) activities may be coded according to an international classification system, and integrated or mean CO exposures may be calculated over the interval of the activity regardless of the location of the individual which may change over the duration of the activity. Pollutant exposure may also be integrated over the time spent in a particular location, or what has come to be called a "microenvironment." By the most strict definition, a microenvironment is the parcel of air surrounding the individual of interest which is of uniform pollutant concentration over the time interval occupied (Duan, 1982; Aklund et al., 1984). The intent of the microenvironment concept is to allow the calculation of the day's integrated exposure by summing the individual products of the concentration encountered by the person in each environment and the respective time that person spent in that location. The pragmatic limitations of data recording have changed the modeler's definition of microenvironment to that of a simple locational class. In the course of a day's self reporting, it is possible to record locations, activities, and movement without great intrusion or burden on the research subject. It is not reasonable to expect the research subject to record each change in environmental factors which might influence air pollutant concentrations during the occupancy of that location. Hence the modeler's assumption of uniform exposure at a particular location is not always met.

Therefore, it is important to consider the CO exposure associated with both activity and location. A simple example will illustrate this point. A subject may spend forty minutes at "cooking, eating breakfast, and reading the morning newspaper" in the kitchen. During the first half of that interval, the gas surface range may have been used for cooking activities in close proximity to the person being monitored. However, during the second half of the interval the source was not active and CO levels rapidly decayed in the kitchen as the person ate breakfast and read the paper. Here, two separate diary entries are ideally desired to allow distinction of two microenvironments: one in which cooking is going on in the kitchen and one in which cooking is not. Despite the most careful instructions and training, only some of the research subjects will report this difference in activity; the more common diary entry is the general description of kitchen location, lumping several activities together over the entire kitchen occupancy interval. Therefore, this research reports CO concentrations by the complementary description schemes of activity type and location type. To be consistent with the published literature, location type is called "microenvironment." Either scheme will allow computation of the integrated exposrue over a day's profile by summation of the time-weighted concentrations associated with each activity or location component.

The COED-1 data loggers used in the EPA Denver-Washington study were specially constructed to compute and record arithmetic mean concentrations integrated over the time spent in each microenvironment (Ott, 1984; Ott et al., 1986). The research subject carrying the monitor pressed a switch to signal the end of an activity or location change, and recorded pertinent data in their diary. The Interscan data loggers used in the present study recorded minute average CO concentrations. The continuous minute-by-minute exposure record allowed computation of arithmetic and geometric mean and standard deviations, and minimum and maximum measured minute averages for each activity and

microenvironment class. The microenvironment measurements can be compared to those of the EPA Denver study (Johnson, 1984) and Washington, D.C. study (Hartwell et al., 1984), the only published reports of CO by microenvironment concentrations. Less useful comparisons may be made to a coarser level of classification by Ziskind, Fife, and Mage (1982) in Los Angeles during pilot testing of research protocols for the later EPA Denver-Washington field studies. Mean CO exposure by activity and microenvironment class is presented in Tables 3.6 and 3.7 for nonsmoking IHD subjects; data for smoking IHD subjects may be found in Appendix 1. Arithmetic means and standard deviations are presented to allow comparison to EPA and other published data. However, geometric means provide a more accurate index of centrality in these highly skewed data.

3.3.1 Variation in Exposure by Microenvironment

The 24-hour report profiles of the nonsmoking sample of IHD subjects produced measurements of CO concentrations in hundreds of activities and locations. The survey data was reduced according to the classification scheme of activity and microenvironment location described previously (see Section 2.5).

Activities and microenvironments associated with gasoline powered engines displayed the highest CO concentrations in terms of observed maximum minute average, and arithmetic and geometric mean. Motor vehicle use activites include the travel activity categories (e.g., Codes ending with 9) and transit microenvironment categories (e.g., Code 300 series). Personal auto use, an activity with high daily occurrence and relatively long occupancy time, was associated with mean levels of 8.6 ppm. A maximum level of 239 ppm was observed in one subject's vehicle driven in heavy traffic conditions. Another subject was notified of abruptly higher than usual measurements for his personal auto, up to 84 ppm, and he immediately was able to correct exhaust and carburetor problems lowering subsequent CO measurements. Freeway measurements typically averaged 10-12 ppm under normal traffic flow conditions. Of the 34 IHD patients studied, only 2 individuals made regular freeway commutes lasting approximately one hour's time (one way). Typically, the duration of regular freeway driving was less than 15 minutes (one way).

The majority of reported personal auto use was on city streets. Arithmetic mean concentration measured for IHD subject's personal auto use was 8.6 ppm (9.6 ppm S.D.). An arithmetic mean of 8.1 ppm (9.9 ppm S.D.) is reported for the "in car" transit class of the general population studied in Denver by the EPA (Johnson, 1984).

The close proximity of running autos is believed to be responsible for the elevated CO measurements in parking lots or parking structures (Code 213) and service stations or motor vehicle repair service areas (Code 214). The respective arithmetic means of 7.9 ppm (10.0 ppm S.D.) and 7.9 ppm (5.9 ppm S.D.) are generally higher than the Denver study arithmetic mean measurements of 8.2 ppm (5.3 ppm S.D.) for outdoor public garages, 3.5 ppm (4.2 ppm S.D.) for outdoor parking lots, and 3.7 ppm (3.8 ppm S.D.) for outdoor service stations or motor vehicle repair facilities (Johnson, 1984).

Indoor residential microenvironments (Codes 100-119) and activities (e.g., Codes 12, 45, 90-98) were generally associated with low arithemtic and geometric mean, and relatively low maximum CO concentrations. Arithmetic and geometric means and standard deviations approximated 2.0 and 2.0 ppm respectively. These data compare well with those with unspecified indoor residential exposures of 2.0 ppm (4.1 ppm S.D.) reported for Denver (Johnson, 1984). Given the high proportion of total time spent in the home indoor microenvironment, the low residential concentrations dominate the computation of the daily integrated exposure.

The microenvironmental measurements of CO near running motor vehicles and the indoor residential environment represent the extremes in CO exposure. Taking into account maximum observations, CO exposures can vary over two orders of magnitude in adjacent microenvironments or sequential activities in the same location. The variability in CO exposures measured for IHD subjects in the South Coast Air Basin compare well with those reported for the general population residing in Denver, Colorado. In the following section specific major classes of microenvironmental CO exposures will be discussed.

3.3.2 Ambient (Outdoor) Exposures

Outdoor microenvironments displayed a wide range of CO concentrations (Codes 200-231, Table 3.7). For brief periods, generally less than 2-3 minutes, CO concentrations may exceed 100 ppm. These peaks were often characterized by extremely close proximity to gasoline engine exhaust from running autos or gasoline powered lawn equipment. Transient peaks to as high as 134 ppm were observed for wood cutting activities with a gasoline powered chain saw and 226 ppm for gardening activities where 2-stroke gasoline engine powered lawn care equipment was used. In both examples, the monitored user held the source and/or walked in its exhaust plume. Integrated geometric mean CO concentration over the course of the reported total gardening or outdoor chore interval was much lower, typically near 2 ppm for most individuals.

Neighborhood residential street CO concentrations (Code 211) are the most representative class of measurement for neighborhood background levels. This microenvironment class includes measurements taken while subjects walked, cycled, or visited with neighbors on residential streets near their home. In contrast, around the house measurements (Code 210) are slightly higher due to the influence of source activities such as use of barbecue, auto or yard equipment. An arithmetic mean concentration of 3.1 ppm (3.4 ppm S.D.) was observed for neighborhood residential streets. This measurement can be compared to EPA's Denver study concentrations of 1.33 ppm (2.24 ppm S.D.) for outdoor residential grounds (Johnson, 1984).

Ambient measurements at outdoor locations within 10 yards of an active roadway were described by arithmetic mean CO concentrations of 4.0 ppm (3.8 ppm S.D.). These measurements compare well to those for the general population in Denver: 4.0 ppm (5.4 ppm S.D.).

Measurements taken during outdoor activities at locations away from running autos were substantially lower. Bike path measurements averaged 1.5 ppm (1.5 ppm S.D.). These measurements were made during routine early morning (6 a.m.) bike rides by one research subject along the Los Angeles riverbed bike trail. Park or golf course measurements in the EPA Denver study (Johnson, 1984) averaged 0.7 ppm (1.0 ppm S.D.) and are probably more comparable to our bike path measurements than outdoor recreation area (Code 215) class, which may have been influenced by nearby motor vehicle activity (mean, 5.4 ppm; S.D., 6.5 ppm).

The outdoor (ambient) setting CO measurements for the IHD study group are comparable to reported values for the general population of Denver, Colorado (Johnson, 1984). The IHD study group in aggregate did not spend a large portion of time in outdoor activities (other than transit) consistent with the results of other time-activity studies (Szalai, 1972; Chapin, 1974). Therefore, the calculation of integrated daily exposure were not be greatly influenced by ambient exposures. However, activities in certain outdoor settings may have significant acute CO exposures if proximal to running automobiles or small gasoline engines.

3.3.3 Indoor Residential Exposures

The EPA Denver study compared indoor microenvironmental CO concentrations to simultaneous measurements taken at the nearest fixed station monitor for ambient CO (Johnson, 1984). When indoor location CO measurements were regressed on local fixed site ambient measurements, low correlations were observed, as well as non-zero intercepts and slopes other than 1. These results suggest that fixed-site measurements are of very limited usefulness in representing personal exposures, particularly those of the indoor microenvironments. Indoor residential exposures expected to be influenced by types and proximity of sources and ventilation characteristics.

CO concentrations encountered in indoor residential microenvironments become an important consideration when total time-weighted exposures are calculated. In the IHD subpopulation studied, the majority of individuals spent 16-18 hours each day at home, indoors. The CO concentrations measured for this subgroup in indoor home locations were slightly higher than those measured in the EPA study of the general population living in Denver. The Denver exposure assessment reported indoor residential arithmetic mean concentration of 2.0 (4.1 S.D.) (Johnson, 1984). For the IHD subpopulation studied, arithmetic mean concentrations by room of the house ranged from 2.1-4.0 ppm (see Codes 111-116). Transient peaks of greater than 100 ppm were observed in homes but these were of infrequent occurrence and short duration.

Kitchen activities such as preparing food and meal cleanup (means ranged from 3.7-6.1 ppm, standard deviations ranged from 4.0-7.3 ppm) were associated with elevated CO concentrations relative to long term mean levels for the home. This is attributed to combustion appliance activity during these intervals. Higher exposures were also observed during clothes upkeep activities (mean 4.6 ppm, standard deviation 3.8 ppm), possibly due to gas dryer emissions. Exposures during TV watching (mean 3.5 ppm, standard deviation 3.3 ppm) are representative of mean indoor living area exposures and present, as daily activity class, an important time-weighted contribution to total exposure.

3.3.4 Occupational Microenvironment Exposures

The occupational microenvironment class is comprised of a more diverse set of locations and activities than is observed in outdoor, residential, or transit classes. As such, the aggregate statistics for occupational exposures (Codes 00-09, 120-124, and 230) represent a wide range of situations, and are associated with high degree of variation about the mean. Clerical or administrative office areas demonstrated arithmetic mean CO concentrations of 3.4 ppm (3.1 ppm S.D.). Work areas such as assembly lines, shop, warehouse or garage settings displayed relatively higher CO concentrations, averaging 6.0 ppm (13.7 ppm S.D.). The two individuals working in outdoor locations were exposed to concentrations averaging 3.8 ppm (7.1 ppm S.D.).

The wide range of locations and activities included in the occupational class necessitates consideration of individual examples. A carpenter's exposures at a construction site averaged 2.5 ppm (2.4 ppm S.D.) in outdoor settings with peak exposure of 26 ppm. Indoor work by the same subject at the same jobsite was associated with an arithmetic mean of 3.6 ppm (3.9 ppm S.D.) and peaks to 27 ppm. Mean CO concentrations of 9.7 ppm (6.5 ppm S.D.) and peaks to 47 ppm were measured during travel by personal truck to pick up job materials.

Another individual managed a motor vehicle repair facility. During personal monitoring, office measurements averaged 3.9 ppm (3.4 ppm S.D.) with peaks to 50 ppm,

while mean garage area exposures were higher, 6.6 ppm (3.5 ppm S.D.) with peaks to 22 ppm.

A third individual's personal exposure averaged 4.8 ppm (2.6 ppm S.D.) during workhours in a basement file room adjacent to food preparation areas with cooking activity occurring throughout the day.

3.3.5 Transit Microenvironment Exposures

The most common mode of travel for the monitored IHD subjects was by personal auto. The arithmetic mean CO concentration was 8.6 ppm (9.6 ppm S.D.) with peak exposures to 239 ppm. Personal exposures in pickup trucks and vans averaged 9.9 ppm (7.7 ppm S.D.), and a more limited number of measurements for bus and motorcycle averaged 5.7 ppm (2.5 ppm S.D.) and 8.7 ppm (8.8 ppm S.D.) respectively. Diesel truck driving, monitored mainly on interstate roads outside of city limits, was associated with arithmetic mean exposure of 2.6 ppm (2.3 ppm S.D.). Motorcycle, bus, and car exposure measured in the Denver study similarly ranged in mean concentration from 7.0 ppm to 9.8 ppm (Johnson, 1984).

3.3.6 Time-Weighted Daily CO Exposure

Activity pattern and CO concentration data may be combined to produce time-weighted CO exposures by activity and microenvironment class. Tables 3.8 and 3.9 present rankings of activities and microenvironments in order of contribution to total daily CO exposure. The highest time-weighted exposures are generally associated with long duration activities or frequently occupied locations rather than high CO concentrations. These tabulations must be carefully interpreted. While providing insight into the respective contributions to total daily exposure, the biological significance of the temporal sequence of activities or microenvironments is lost. The uptake and washout of CO from the body is largely dependent on recurring strings or cycles of activities. Activities and geographical locations are temporally coupled and these links may act to produce elevated carboxyhemoglobin levels, or allow washout of CO. Night sleep and occupancy of the bedroom microenvironment have the highest time-weighted CO exposure by virtue of the 8 hour duration of the activity. CO exposure during night sleep was generally low, representing a time of CO washout during the daily exposure profile of the IHD subject.

Travel related to goods and services and the personal auto microenvironment are major contributors to total CO exposure. As compared to other activities, the mean CO concentration and the daily proportion of time spent in the automobile is high. Other transit activities are less frequently performed (e.g., travel related to personal care of child care) and, although usually involving motor vehicle use, make a much smaller contribution to total exposure. Outdoor and indoor service station and motor vehicle repair areas are associated with very high CO exposures but are not frequently visited. However, when a motor vehicle repair facility was visited, the event was often of long duration because of waiting for services to be performed. By using mean time weighting for the aggregate, the qualitative aspect of long duration is obscured for infrequently occurring activities like auto repair services.

A large proportion of wakeful time is spent indoors, at home in the living room or kitchen areas. Activities commonly associated with these locations include television viewing, relaxing, and eating and preparing meals. The five hours spent in the living room and kitchen during the course of daily activity drive the relatively high time-weighted ranking of these locations.

Frequently occupied public indoor locations include stores, restaurants, shopping malls, and meeting halls. These locations, and their associated activities, are described by moderately high mean CO concentrations which, when time weighted, make high ranking contributions to total exposure.

The "outdoors, around the house" microenvironment is host to a variety of activities. The most frequently performed activities do not involve close proximity to CO sources and therefore only low to moderate mean CO levels are calculated. Comprising part of the "around the house" class of activities are several high exposure situations including gardening and lawnmowing with small gasoline powered engines, and auto repair. These activities occurred infrequently during the monitoring study but were associated with very high CO exposures for durations approaching one hour. These important exposures are not clearly represented in these time-weighted calculations using mean statistics.

Other outdoor locations such as golf courses, bike paths, and neighborhood residential streets host the high metabolic demand activities of exercise. These microenvironments are described by low CO concentrations, and the associated activities were infrequently engaged in, thus leading to relatively low time-weighted exposures.

Two artifactual results appear in the time-weighted presentations. The "occupational health center van" represents exposures measured during freeway to return research subjects to their homes after physiological testing at the clinic. Similarly, time-weighted hospital exposures are overestimated due to a large amount of daily time (30 minutes of the 24-hour monitoring day) for monitor attachment and experimental procedures.

3.4 ESTIMATION AND DISTRIBUTION OF CARBOXYHEMOGLOBIN LEVELS

3.4.1 Introduction to Breath Sampling Technique to Estimate COHb

A person's exposure to CO varies as a function of time spent within microenvironments. In turn, the dose or body burden of CO is largely dependent on a person's time-weighted CO concentration in microenvironments that they occupy. Dose is further dependent on respiration rate which is a function of metabolic activity level.[1] Carbon monoxide only enters the body via the respiratory system; obviously, a single route of administration greatly simplifies determination of dose. Because of its high affinity for heme-containing proteins, the distribution of CO within the body is believed to be predominantly confined to one compartment, hemoglobin, and to a much smaller degree myoglobin. COHb is generally regarded as the single most representative measurement of absorbed dose.

An increasingly important aspect of the comprehensive framework for CO epidemiology, is the accurate estimation of carboxyhemoglobin. For it is only by our measurement of COHb that we are able to evaluate the success of ambient CO personal exposure monitoring efforts and the predictive capabilities of simulation models. As part of our study of community exposure of persons with IHD, we evaluated the efficacy of the end-expired breath sampling method in predicting venous carboxyhemoglobin levels. Before reporting these findings, we present a brief literature survey as a basis for the

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[1] Other physiological variables enter into this relationship, i.e., endogenous production of CO, blood volume, hemoglobin content, lung transfer factor (D_L) for CO. The rates determining factors of CO uptake and elimination are described by Coburn, Forster, and Kane (1965).

discussion of methodological and physiological aspects of the end-expired breath method which may lead to discrepant results.

3.4.2 Previous Findings

The measurement of CO concentration, [CO], in end-expired breath after breathhold permits estimation of COHb levels. The method was developed by Jones et al. (1958) to overcome the invasive and tedious methods inherent in the direct determination of COHb in blood samples. This pioneering work built upon that of Sjostrand (1948) who realized that during breathholding the lungs functioned as "aerotonometers". After a sufficient period of breathholding, the gas pressures of the pulmonary blood and alveoli approach equilibrium. The concentration of CO in end-expired breath, assumed to be most representative of alveolar air, is related to blood COHb by Haldane's first equation (Douglas, Haldane, & Haldane, 1912):

$$\frac{M \cdot P_{CO}}{P_{O_2}} = \frac{COHb}{O_2Hb} \tag{1}$$

where: M = Haldane constant of proportionality
P_{CO} = alveolar pressure of CO
P_{O2} = mean capillary pressure of oxygen
O_2Hb = concentration of oxyhemoglobin
COHb = concentration of carboxyhemoglobin

Solving for COHb in percent units, and CO concentration in ppm units, and factoring in the effect of barometric (P_B) and water vapor pressure yields:

$$COHb = \frac{M\,(P_B - 47) \cdot 10^{-6}\,[CO_{ppm}] \cdot 100\%}{P_{O_2} + M\,(P_B - 47)\,10^{-6}\,[CO_{ppm}]} \tag{2}$$

Assuming M to equal 245, P_{02} to equal 85 mmHg, and a sea level barometric pressure (P_B) of 760 mmHg:

$$\%COHb = \frac{0.206\,[CO_{ppm}]}{1 + 0.00206\,[CO_{ppm}]} \tag{3}$$

This relationship was demonstrated by Jones et al. to provide a relatively good fit over the larger range of COHb levels, 0.7-26%, when end-expired breath samples were collected in a specific fashion using a 20-second breathhold. Jones et al. evaluated several types of inspiration maneuvers and breathhold duration, recommending a procedure which has come to be regarded as standard:

1. expiration to residual volume (RV);
2. inspiration to total lung capacity (TLC) and a 20-second breathhold;
3. breathhold is followed by smooth expiration; discarding the first 500 ml of expired breath and collecting the remainder of the volume of the expired breath for analysis. (The discarded 500 ml volume represents gas from the conducting and non-gas exchange regions of the lungs.)

Ringold and Goldsmith et al. (1962) verified the Jones et al. method reporting a regression relationship which agreed closely with the prediction made by Haldane's first

equation (see Table 1). Confident in the method, Ringold and Goldsmith et al. (1962) applied it to the first large-scale urban exposure assessment: 168 persons visiting a medical clinic. The breathhold technique was quickly embraced by epidemiologists conducting community, occupational, and tobacco smoking research, reporting blood-breath regressions with slopes approximating 0.14-0.22 and intercepts of 0.0-1.0% of COHb (Table 3.10).

Despite years of use, limited published data are available on the precision of the breathhold method when COHb levels are less than 3%, the expected range for nonsmoking persons living in an urban area. It is possible that the data for measurements made at higher COHb levels are disproportionately influencing the derived regression describing the relationship of CO in end-expired breath to %COHb; thereby reducing the accuracy of predictions at low COHb levels. Often, the fitted line has been extended into the low %COHb range where there are no or few observations. Haldane's first equation provides a good fit over the larger range of COHb levels and theoretically should predict [CO] in end-expired breath at low %COHb; however, precision at low levels remains empirically undemonstrated.

Considerable variability in end-expired samples for COHb levels less than 3% is observed in the published bivariate blood-breath plots (Ringold et al., 1962; Goldsmith, 1965; Peterson, 1970; Rea et al., 1973; Stewart et al., 1976; Rawbone, Coppin, & Guz, 1976; Smith, 1977; Rees, Chilvers, & Clark, 1980; Wald et al., 1981). Two studies in particular show high variability. Peterson (1970) attributes observed variation to inter- and intra-person differences in the breath collection technique and specifically notes "none of the subjects had a breath CO level that was consistently higher or lower than the average [regression]." Interestingly, Peterson also observes without elaboration that the method is accurate "provided the ambient concentration is near zero". Goldsmith (1965) published blood-breath data for a group of longshoremen, some of whom had cardiorespiratory disease. The linear regression for subjects with cardiorespiratory conditions was found to differ from that of the normal population (see Table 3.10). Although no regression for normals as an exclusive group was presented, the combined cardiorespiratory and normal regression line plot displayed a shift towards the origin and slope increased. Substantial variability was observed in both groups. Similarly, Jarvis, Russell and Saloojee (1980) observe higher slopes in subjects with emphysema as compared to normal smokers. This difference was attributed to impaired diffusion of CO from blood into the alveoli.

Smith (1977) and Wallace (1983) have reported [CO] increases or decreases in sequential end-expired breath samples which occur too rapidly to be plausibly explained by the known dynamics of CO uptake and elimination. These researchers suggest that the rapid changes in breath [CO] are caused by ambient [CO] influencing the delivered end-expired breath. Because end-expired breath samples are, depending on the health of the individual, diluted to a greater or lesser degree with air from non-active gas exchange regions of the lung, ambient [CO] which diverge from the true alveolar [CO] may dilute or increase the [CO] measured in the end-expired breath sample.

The design of our study incorporated a blood-breath comparison to validate the use of the breathhold technique on a population subgroup that might be expected to perform differently from literature values for the general healthy population. We were aware that inter- and intraperson variability would probably be observed, and that ambient [CO] at the time of breath sampling might affect end-expired [CO]. We expected, theoretically, Haldane's first equation to hold although the literature was unclear on the end-expired [CO] and COHb relationship at blood levels less than 3%. The large portion of this section is devoted to evaluating the end-expired breath sampling technique for the special case of the subject with ischemic heart disease (IHD).

3.4.3 Results of Blood-Breath Comparison Studies

End-expired breath samples were correlated against %COHb as directly measured in blood samples for 112 cases. These data were collected from 28 male subjects, ages 39-72. Two of these subjects were smokers. CO concentration ranged from 2.0 to 13.3 ppm in nonsmokers ($\bar{x}$ = 5.3, S.D. = 2.2) and 6.1 to 36.7 ppm in smokers ($\bar{x}$ = 24.1, S.D. = 10.4). Blood COHb ranged from 0.4 to 3.2 % in nonsmokers ($\bar{x}$ = 1.5, S.D. = 0.6) and 2.5 to 6.7% in smokers ($\bar{x}$ = 4.4, S.D. = 1.5). Thus for all subjects combined end-expired [CO] ranged from 2.0 to 36.7 ppm ($\bar{x}$ = 6.7, S.D. = 5.9) and COHb ranged from 0.4 to 6.7% ($\bar{x}$ = 1.7, S.D. = 1.0).

The data for smokers and all subjects combined were relatively well fit by a straight line (Figure 3.2; Table 3.11). Compared with the regression for nonsmokers, the proportion of variance explained, r^2, and standard error of the estimate are improved for the smokers' regression and all-subjects-combined regression. However, the data for high levels of COHb (i.e., smokers) does not appear to be driving the regression: The null hypothesis of no difference in slope and intercept estimates for nonsmokers and smokers was accepted. Further, the intercepts of any of the aggregate regressions are not significantly different from zero.

To consider the effect of measurement error in the end-expired breath [CO] variable, a geometric mean functional regression method was used (Halfon, 1985); no difference was observed in slope and intercept as compared to coefficients estimated by ordinary least squares.

In the aggregate, [CO] in end-expired breath displayed great variability in the range 0-3% COHb. However, the variability was markedly reduced within the individual (Figure 3.3). Rather than relying upon the prediction of %COHb based on aggregate data, more precise estimates were made using regressions derived for each individual subject (Figure 3.4; Table 3.11).

Haldane's first equation was used to calculate alveolar [CO] for the blood COHb levels directly determined by IL282. Measured end-expired [CO] was regressed on predicted alveolar [CO] (Figure 3.6; Table 3.11). This was effectively a transformation of the blood COHb data according to equation 3. This procedure was repeated for the selected individual subjects and is presented in Figure 3.6.

Several uncertainties are involved in estimating the concentration of CO in breath from COHb measurements. In addition to the assumption of accuracy of the blood COHb determination, the values assigned to the Haldane constant and mean pulmonary capillary oxygen pressure represent median values obtained from a review of the literature. With a reported range of 210-250 (Joels and Pugh, 1958; Rodney, O'Neal, & Collison, 1969; Roughton, 1970), the Haldane constant was assigned a value of 245, while the mean pulmonary capillary oxygen pressure was assigned a value of 85 mm-Hg from a range of 70-100 mm-Hg (Lambertsen, 1952). The inherent variance in these parameters is sufficient to produce deviations from the median literature values used. However, the skewed nature of the distributions is such that deviations from the median values are likely to be small, tending to minimize the predicted breath [CO] error to approximately 1 ppm (see Appendix 1). Random deviations around the median values chosen for input into Haldane's first equation are therefore expected to have little effect on the estimate of alveolar [CO], within the 0.5-2.5% COHb range of observed values.

3.4.4 Discussion

Precise estimates of dose are necessary to study the potential effect of low level microenvironmental exposures to CO on the cardiac function of persons with ischemic heart disease. The COHb estimate is not problematic in the laboratory setting where exposure atmospheres are generally controlled and constant. Here the direct measurement of COHb in blood sampled at close time intervals is regarded as practical. In contrast the field setting is complex, for not only do ambient levels of CO fluctuate, but the physiological state of individuals varies depending upon activity, making the prediction of uptake and elimination much more difficult. The most widely used predictive model was developed to fit the steady-state conditions of the laboratory exposure chamber (Coburn, Forster, & Kane, 1965), although very limited data does validate its application to the natural environment (Joumard et al., 1981). When applied to the dynamic situation, assumptions about the assignment of mean physiologic parameters may greatly affect the precision of the COHb estimate.

In community research, the breathhold technique provides discrete estimates of COHb, and thus biological dose, at intervals throughout the subject's day. The measurements serve as frequent checks to validate the accuracy and precision of COHb estimates as extrapolated from personal exposure monitoring data. The breathhold method is noninvasive, and importantly it is simple. Subjects may be trained to be self-sufficient in the performance of the breathhold manuever and end-expired breath sample collection. Samples, once collected have no special storage or handling requirements. The electrochemical analysis is without elaborate protocol.

While offering these advantages, the efficacy of the breathhold technique has not been validated for COHb estimates <3%, the range of interest in cardiac health effect research. We report on results from simultaneous blood COHb and breath [CO] measurements focusing particularly on the relationships ultimate predictive use. The major findings are:

1. Considerable scatter is observed in the aggregate blood COHb to breath [CO] relationship at levels of less than 3% COHb. The variability would introduce substantial uncertainty in estimates of COHb from other discrete breath samples taken during the subjects' monitoring days (SE_{mean} = 0.6 for a COHb of 1.7%).

2. Much less scatter exists and results are more internally consistent when the blood COHb to breath-CO relationship is determined for each individual separately. Where there is sufficient range to observe a trend over several COHb sample points, individual slopes are similar to one another. These slopes compare well to previously reported results. Individual differences appear principally in the intercept values and suggest factors specific to each individual influence the blood-breath relationship. The use of regressions derived for each individual substantially improves the precision of COHb estimates (see decreased SE for selected individuals relative to aggregate, Table 3.11).

These findings may result from person and/or instrumentation factors. We first discuss personal and physiologic aspects of the blood-breath relationship and then evaluate methodologic factors.

Physiologic Factors

Suppose a perfect end-expired breath sample could be obtained after breathhold. In this hypothetical situation the effect of inspired ambient air [CO], conducting airway dead space dilution, and regional differences in alveolar-capillarly CO tension are assumed not to exist. The value M is perfectly known, as is the mean pulmonary capillary O_2 tension. Under these conditions, end-expired breath [CO] is equivalent to alveolar [CO], and alveolar [CO] is related to blood COHb by Haldane's first equation (see equation 3). These assumptions effectively comprise the set of conditions used by early investigators to describe the blood-breath relationship. In the analysis of our data on IHD patients we apply this model with the temporary assumption that IL282 blood measurements are accurate. Considering the aggregate set of data (Figure 3-5, Table 3.11) the end-expired [CO] was less than predicted by a net difference of 12%. Again, note that clinic air was usually very clean (<3 ppm CO). This 12% difference suggests that a dilution has occurred. Alveolar air volumes have reached equilibrium with the blood have, upon expiration, mixed with volumes of air which have not occupied gas exchange areas such as the anatomical dead space (i.e., conducting airways). This dilution occurs despite initial clearing of the conducting airways before the end-expired breath sample is collected. A small amount of conducting airway contamination is expected since perfect piston flow does not occur in reality. However the discard of the first half of the held breath is probably adequate to clear this volume. Mixing of alveolar volumes from separate regions of the lung where different levels of equilibrium have been reached may be partially responsible for the dilution phenomena.

Individual differences in regional diffusing capacity, and physiologic dead space (ventilated but non-perfused alveoli) may explain some of the observed variance between individuals (Figure 3-6). Among the IHD subjects the dilution effect was generally observed. Much less commonly, certain subjects displayed a pattern of higher than predicted end-expired [CO]. This deviation may be attributed to a bias in the blood analysis as ex[redacted]below.

A subject's ability to deliver an end-expired breath sample after breathhold may also explain some of the observed inter-individual differences. The breathhold technique as a trained maneuver is vulnerable to person-to-person performance differences. While breathhold is timed by the clock for 20 seconds, subjects must resist the urge to exhale quickly and gulp a fresh lung full of air. To blow out the first portion of the held breath, pause, and exhale the remainder of the breath to the collection bag requires considerable control. The overall length of the maneuver approaches 30 seconds. While all subjects were capable of performing the maneuver with practice, there was some individual difference in the a amount of air discarded before sample collection. Each subject's self [redacted]erception of the discard volume (one-half a lung full) was noticeably different. But the discard volume, to the training researcher's observation, was at least 500 ml in all subjects. Thus from subject-to-subject, the collection of the end-expired sample took place at different points in the lung emptying cycle. Within a subject, the repetition of practice and

coaching routinized the timing of the sample collection to a constant interval. Importantly, in repetitive maneuvers, [CO] in breath samples rarely differed by more than 0.1 ppm.

The time during the expiration phase of the maneuver at which the sample is collected is important because the contributed volumes from the different regions of the lung changes during expiration (Fowler, 1952). Tsunoda, Young, and Marlin (1972) observed, for tidal breathing subjects, dead space volumes to be virtually cleared after a 400-500 ml expiration. Immediately following conducting airway volumes, expired breath is predominantly comprised (80%) of volumes from poorly ventilated lung compartments. Of course the breathhold maneuver involves maximal inspiration to total lung capacity and emptying patterns may differ somewhat from the tidal breathing case.

Assuming the anatomical dead space has been successfully cleared and discarded, the timing of the sample collection only becomes a concern if there are significant regional differences in gas exchange which affect the attainment of CO equilibrium during breathhold. Preliminary calculations suggest that even in the most under perfused regions of the normal lung more than adequate blood volumes are circulated during the 20-second breathhold to achieve equilibrium. There was no indication of severe ventilation-perfusion mismatching or shunts in any of our research subjects. Unfortunately anatomical and physiologic dead space was not measured in our subjects. No discernible trend in blood-breath CO relationship was observed across age or smoking history of subjects to indicate physiologic dead space, and hence decreased gas exchange area.

The influence of anatomical and physiological dead space on end-expired breath [CO] is a salient factor to consider in light of reports of ambient dilution effects (Smith, 1977; Wallace, 1983). Inspired ambient air, which during the breathhold resides in ineffective gas exchange regions of the lung, will remain at CO gas tensions closer to those of the ambient air. End-expired air will then be a mixture of air containing CO equilibrated with the blood and air containing ambient CO. The largest error in breath [CO] will occur when the proportion of ambient air is high and the difference in ambient and equilibrium blood COHb is great. In the present study ambient [CO] was consistently low during simultaneous blood-breath sampling and no interpretation of the ambient effect's magnitude can be made. Our findings do, to a limited degree, corroborate the presence of a dilution effect; however, it is not possible to identify the source as anatomical or physiological dead space.

Instrumentation Factors

Remarkable consistency in the blood-breath relationship was observed in particular individuals where there was coincidentally a wide range of COHb levels sampled. The regression slopes were very consistent in this group, however intercept values varied considerably. Given the good breath sample reproducibility with a subject and the straightforward nature of the [CO] measurement in breath, the intercept differences suggest that the IL282 is sensitive to an unidentified factor varying between individuals. Inherent in the spectrophotometric operating principle of the IL282 is the danger that

constituents of the blood, other than the hemoglobin species of interest, absorb light near the measurement wavelengths.

None of the research subjects were known to be taking medications identified as interferences (e.g., cardiac dyes used in diagnostic imaging) by Instrumentation Laboratories, the manufacturer of the IL282. Severely lipemic samples are also known to scatter light in the measurement wavelength range of the IL282 increasing COHb measurements. This finding suggests that moderately high levels of triglycerides, a condition expected although not measured in the IHD patients, may influence COHb determinations. Similarly, heme may combine with organic nitrogenous species to form hemochromogens. This class of heme compounds is largely uncharacterized but is known to absorb light in the 550-555 nm wavelength range (Van Assendelft, 1970). Small absolute differences in blood constituents may be expected to be translated to large relative differences in COHb at the low concentrations of interest in health effects studies. Considering the great reliance on the IL282 in laboratory and community research this finding, in itself, suggests further research.

3.4.5 Implications for COHb Estimation in IHD Subjects in the Field

These results have important implications for community research designs relying upon breath sample analysis to estimate blood COHb. In most community studies such as ours on IHD subjects, the observed range of experience with breath [CO] is limited for most individual cases; that is subjects tended to have about the same % COHb, and in turn breath [CO], at the beginning and end of each monitoring period when simultaneous blood and breath sampling was performed. Obstensively this observation reflects a person's routine day-to-day occupancy of exposure conditions, and blood-breath sampling under identical conditions of time of day and clinic location. (For certain subjects participating in experiments involving CO exposure and exercise testing, we took advantage of sampling opportunities after dosing.) Still the subjects were free ranging in their activities while wearing the CO and ECG monitoring instrumentation, and during this time collected end-expired breath samples at intervals of 2 to 3 hours during their wakeful day. Some of these breath samples were substantially outside the range of breath [CO] observations used to construct the individual blood-breath regression models. This presented a dilemma of extending the model or selecting an alternative. Drawing upon on experience with the collective data for all subjects, it was decided to apply the individual model to breath measurements within 2 standard deviations of the individual's mean breath [CO] point. Should breath measurements fall outside these limits, the slope for the all-subjects-combined model was applied in a linear model which passed through the $\overline{XY}$ point of the simultaneous blood-breath data points.

For example, this protocol was applied to Subjects ES whose breath samples ranged from 2.4 to 7.4 ppm, exceeding the 2 S.D. limits. The original linear regression model for Subject ES would over estimate COHb at the 7.4 ppm upper bound measurement and under estimate COHb at the lower bound (Figure 3-4). The decision criteria selecting the

strict linear regression approach produces a counterintuitive result: a negative slope (Table 3.11). Therefore, passing a line of slope 0.15 through $\overline{XY}$ point was the only rational model.

3.4.6 Observed Distribution of COHb Levels

The level of blood carboxyhemoglobin (COHb) may be estimated from continuous CO concentration data via predictive models of uptake and elimination. One model, a differential equation based upon first principles of respiratory physiology was developed by Coburn, Forster, and Kane (1965). This model was validated against equilibrium values experimentally produced in an exposure chamber. Although formulated under conditions of constant CO and constant physiologic state, it has been validated and applied to dynamic settings more representative of the natural community environment (Joumard et al., 1981). More parsimonious models which do not account for changes in physiologic parameters over time or physiologic differences between individuals have been successfully used to predict CO uptake and elimination (Petersen & Stewart, 1970; Petersen & Stewart, 1975; Ott & Mage, 1978; Venkatram & Louch, 1979). In evaluating these alternative models against the Coburn equation, Marcus (1980) found that the more simple linear models produced consistently accurate estimates at CO concentrations less than 50 ppm and when activity levels are low. The implicit assumption of a single set of physiologic parameters across the exposed population was not found to introduce a bias in COHb estimates at low CO exposures. The analysis of Marcus (1980) indicates that the linear model of Ott and Mage (1978) is appropriate to apply to our research group of IHD subjects, a group that is characterized by moderate environmental CO exposures and activity levels. In this report, COHb levels were estimated for the IHD subjects using the Ott and Mage (1978) model.

The linear model of Ott and Mage (1978) assumes that at any particular point in time, COHb levels are a function of the endogenous COHb generated internally by metabolic processes of the body, and exogenous COHb resulting from the inhalation of air containing CO:

$$TAU \frac{d\%\ COHb_{blood}}{dt} + \%COHb_{blood} - BETA = ALPHA\ CO_{ppm}$$

where TAU = 2.49 hr, corresponding to a halflife of 1.73 hr.

$\%COHb_{blood}$ = blood COHb level in percent at time t

BETA = 0.5% COHb baseline level of endogenous CO, and

ALPHA = 0.15, proportionality constant

Numerical solutions of this differential equation can be used to describe reference curves of uptake and elimination for various constant CO concentrations (Figure 3-7). These curves provide estimates of COHb levels for individuals with 0.5 % baseline levels of COHb and engaged in low levels of activity.

The frequency distribution of mean minute CO exposures for the aggregate is presented in Figure 3.8. The distribution is log normal with a arithmetic mean of 3.8 ppm (sd_a = 5.6 ppm), and geometric mean of 2.6 ppm (sd_g = 2.3 ppm). As a point of reference, the National Ambient Air Quality Standard for CO is set at 9 ppm averaged over 8 hours and 35 ppm averaged over 1 hour. These ambient standards were selected to prevent carboxyhemoglobin levels from attaining 2 percent in 99 percent of the population (Federal Register, 1984). For the sample of men with IHD monitored in our study, 6.7 percent of mean minute CO measurements exceeded 9 ppm and 0.3 percent exceeded 35 ppm. Calculating the time course of exposure, the 9 ppm 8-hour standard was exceeded on ten percent of the monitoring days (15 days). Thirty-six percent of the IHD subjects (n = 13) experienced exposures in excess of the 8-hour standard on at least 1 monitoring day. Comparable findings were observed in the U.S. EPA Denver-Washington study where 3-10 percent of the nonsmoking population was estimated to have exceeded the 8-hour standard (Akland et al. 1985; Wallace et al. 1988). Further, in our survey of IHD subjects, one exceedance of the 35 ppm 1-hour standard was observed; this high personal exposure was experienced during freeway driving at mid-day. In comparison, personal exposures exceeded the one-hour standard in 3 percent of the Denver population; no exceedences of the one-hour standard were observed in Washington, D.C. (Akland et al. 1985). The resulting frequency distribution of the modeled minute-by-minute blood COHb concentrations ranged from 0.5 to 9.2 percent (Figure 3-9). The arithmetic mean COHb concentration was 1.1 percent, the mode was 0.8 percent, and the median was 0.9 percent. The distribution of the modeled COHb levels (Table 3.12) indicated that 23 of the 36 men experienced COHb levels which attained or exceeded 2 percent. Nine subjects attained or exceeded 3 percent COHb and 3 subjects attained or exceeded 4 percent. Four subjects never developed COHb levels above 1 percent, while at the other extreme, only one subject exceeded the 5 percent COHb level. The aggregate sample was estimated to have spent 5.2 percent of the total monitoring time at COHb levels of 2 percent or greater.

Table 3.12 also presents the person-hours of time spent at each COHb level and the proportion of total time spent at that particular COHb level by the subjects who attained that level. For example, 23 men developed COHb levels of 2.0 to 2.9 percent during their monitoring, and the average time spent per subject at the 2.0 to 2.9 percent COHb level was 6.8 hours. The average time spent per subject at a COHb level was then converted to the proportion of total time the subjects were monitored. On average, 98 hours (4.1 days) of monitoring data was available for each subject. Thus, for the 23 men who developed COHb levels of 2.0 - 2.9 percent, on average, 7 percent of their total monitoring time was spent at this COHb level.

3.5 CARDIAC RESPONSE TO CO IN THE COMMUNITY SETTING

3.5.1 Introduction

Myocardial ischemia results from the interaction of increased demand for oxygen and a decreased oxygen supply (Miller 1985) and has a wide spectrum of manifestations ranging from asymptomatic episodes, or "silent" ischemia, to angina pectoris on exertion, unstable angina, rhythm disturbances, myocardial infarction, coronary spasm, and sudden death. The inhalation of carbon monoxide has been demonstrated to aggravate the oxygen supply-demand imbalance in exercising heart patients (Anderson et al. 1973; Kleinman et al. 1989; Allred et al. 1989), causing earlier onset of angina pectoris and ST-segment changes on the electrocardiogram (ECG) indicative of ischemia. Additionally, increased ventricular ectopy has been observed during the 24 hours following 100 ppm exposures sufficient to elevate COHb levels to 6 percent (Sheps et al. 1990). The exact mechanism of CO's toxic action is not known, however, most hypotheses implicate impaired oxygen delivery and tissue hypoxia. CO reversibly binds to hemoglobin, out-competing oxygen for the available binding sites, and causing a leftward shift of the oxyhemoglobin dissociation curve (Douglas 1912). Therefore, inhalation of CO decreases the oxygen-carrying capacity of the blood and decreases the ability of the myocardium to extract oxygen at low partial pressures (Ayers, Evans, and Beuhler 1979).

To date, the results of epidemiologic studies (Table 3.13) provide limited support to the hypothesis that exposure to CO increases the frequency and severity of myocardial ischemia and its clinical manifestations (e.g., myocardial infarctions). Most of the investigations have been ecologic studies in which the quantification of personal exposures have been based upon estimates derived from outdoor monitoring stations. Because the spatial and temporal distribution of CO is highly variable, estimates of exposure derived from central site measurements do not provide accurate estimates of personal exposure (Ott and Flachsbart 1982; Akland et al. 1985; Wallace and Ziegenfus 1985), and therefore, causal inferences cannot be made. Additionally, given the multifactorial nature of heart disease and acute cardiac events, the study designs may have been confounded by unknown or uncontrollable factors, such as cigarette smoking and medications. Characterization of the risk posed by exposure to CO in the community setting would be improved by study designs which incorporated methods to obtain precise information on personal exposures and cardiac health effects.

The clinical research (Anderson et al. 1973; Kleinman et al. 1989; Allred et al. 1989) has provided some insights into defining the approximate COHb levels at which health effects are likely to be observed during the activities of daily life. Persons with stable, symptomatic myocardial ischemia which is induced by exercise, and hence by increased oxygen demand, should experience more frequent angina and ST-segment depression when exerting themselves while their COHb levels are elevated. It is also possible that CO could aggravate ischemia associated with reduced oxygen supply caused by coronary vasospasm or obstruction by platelet aggregation, and other hypothesized

causes of myocardial ischemia (Nesto and Kowalchuk 1987), although there have been no animal or human studies to evaluate these latter mechanisms.

The major factors influencing the balance of myocardial oxygen supply and demand, and the hypothesized role of CO, are presented in Figure 3-12. All or a combination of these factors may contribute to the development of ischemic episodes in the ambulatory setting. This complexity makes it difficult to use clinical data to predict the amount of additional myocardial ischemia in susceptible populations caused by exposure to ambient CO. The measurement of ischemia and CO exposure during the activities of everyday life should provide a more complete understanding of the relationship between community exposure to CO and myocardial ischemia.

Therefore, we conducted ambulatory monitoring of personal CO exposure and the ECG on a sample of men with ischemic heart disease (IHD) who lived in Los Angeles. In previous sections of this report, we have described the activity patterns, CO exposures, and resulting COHb levels. We found that the daily activities of men with IHD brought them into frequent contact with CO. High exposure situations included travel by automobile and the use of gasoline-powered engines for lawn care or cutting wood. Some of the sequences of exposure were sufficiently high to allow the development of COHb levels into the range at which clinical studies have demonstrated aggravation of myocardial ischemia. Twenty-three of the 36 men with IHD subjects who participated in the monitoring experienced COHb levels of 2 percent of greater. The total time of elevated COHb levels represented 5.2 percent of the 142 person-days of monitoring, and indicates that men with IHD living in Los Angeles frequently experience COHb levels that could place them at risk for cardiac health effects.

In this section, we use the ambulatory monitoring data to test the hypothesis that elevated CO exposures and the resulting COHb levels are temporally associated with an index of myocardial ischemia measurable by ECG, specifically ST-segment depression. The relation of CO exposure and myocardial ischemia is analyzed within the conceptual framework of Miller (1985), controlling for the influence of dose (carboxyhemoglobin), exertion, psychological tension, and medication.

3.5.2 Subject Characteristics and Methods

Subject Selection: The subjects in this study were patients of the cardiology divisions of the University of California, Irvine Medical Center and the Long Beach Veterans Administration Medical Center. Medical records from coronary angiography and treadmill exercise testing were used to confirm the presence of IHD. Potential subjects had at least 50 percent occlusion of one or more of the Major coronary arteries and displayed ECG ST-segment depression during treadmill testing. The presence of angina pectoris was not a criteria for entry into the study. We excluded patients whose medical records specified conditions which would confound the ECG ST-segment analysis including digitalis and quinidine medication, mitral valve prolapse, left ventricular

hypertrophy, and left bundle branch block. Further, patients with Prinzmetal's or variant angina were excluded to reduce the potential for confounding by coronary vasospasm. The sample population was limited to nonsmoking men.

As has been reported in previous chapters, we monitored the personal CO exposures of 36 men with ischemic heart disease. A total of 142 person-days of exposure data was collected, including 61 person-days on which the ECG monitor was worn in tandem with the CO monitor. Thirty subjects participated in the ambulatory ECG monitoring. Four subjects declined to undergo ECG monitoring because of the "uncomfortable wires" and restriction of movement. One subject was noncompliant and was released from further monitoring, and another subject's CO exposure monitor failed on the one day on which we were able to monitor his ECG (see below).

The characteristics of the subjects who were monitored are presented in Table 3.14. Age ranged from 52 to 71 years (mean =61 years). As presented in Chapter 3, the majority of men were married, unemployed retired or supported by disability insurance. The mean level of education was 14 years. By self assessment, most individuals considered their heart health and general health to be "average". Angina presence and frequency was ascertained during the medical history interview using a modification of Rose's line of inquiry (Friedman et al. 1985). Angina, defined as chest pain associated with exertion, was present in 72 percent of the subject group. Among the angina sufferers, 35 percent reported to experience angina at least once each day and 28 percent experienced angina approximately 2 to 3 times per week. Coronary artery bypass graft surgery had been performed on 14 subjects (39 percent). In four men, the grafts had remained patent and they did not experience angina. No research subject had suffered a myocardial infarction in the four months preceding enrollment or during the five month course of the study, however during the study, five subjects were hospitalized for heart-related illnesses.

Subjects maintained their usual schedule of medications during the study. Long-acting nitrates were taken by 14 of the 30 subjects. Beta-adrenergic blocking agents were taken by 9 subjects, calcium channel blockers were taken by 11 subjects, and anti-hypertensive medications were taken by 13 subjects (Table 3.15). After review of their medical records, and after participation in personal CO monitoring, four subjects were discovered to be taking digitalis and/or quinidine, cardio-active drugs which cause depression of the ECG ST-segment and T-wave changes mimicking ischemia (Marriott 1984). As will be discussed below, ambulatory monitoring was performed on these subjects, however these subjects were excluded from the ST-segment analysis. Quinidine will also suppress ventricular arrhythmias, therefore, the one subject who was taking digoxin and quinidine was excluded from the arrhythmia analysis. Other anti-arrhythmic drugs (e.g., procainamide, disopyramide, amiodarone) were not used by the subjects.

Study Protocol: The ambulatory monitoring was conducted from January to May 1985. In order to observe a sufficient number of ischemic episodes to evaluate the cardiac response to CO, each subject was monitored for two non-consecutive 24-hour periods. The choice of two monitoring days was based on the characterization of day-to-day variability

by Deanfield et al. (1983), which was later confirmed by the findings of Tzivoni et al. (1987). For the attachment of the ambulatory ECG and CO monitoring instrumentation, subject came to one of three clinics (Long Beach Veterans Administration Medical Center, UC Irvine Medical Center, or Southern Occupational Health Center) located nearest to their residence or place of employment. At that time, current health status was assessed by oral interview. pulse, blood pressure, standard 12-lead resting ECG, and measurement of height and weight. To assess emotional stress and its influence on the autonomic nervous system and in turn cardiac activity, the Speilberger State-Trait Anxiety Test (Speilburger, Gorsuch, and Lushene 1970) was completed by the subjects. Each subject was instructed on use of a diary to record their activities and symptoms, the end-expired breath sampling technique was reviewed, and the first breath sample was collected. A venous blood sample was drawn. The ambulatory ECG and CO monitors were attached to the subject.

During the 24-hour monitoring period, subjects were free to pursue their normal range of activities, with the exception of bathing because immersion would damage the monitoring equipment. Subjects maintained their usual regimen of medications prescribed by their physician. For each activity lasting 15 minutes or longer, subjects made an entry in their diaries, recording the activity and their location, any symptoms experienced, the use of medications, and their level of psychological tension. At intervals of 2 to 3 hours during the wakeful portion of their day, subjects collected a sample of end-expired breath.

At the end of the monitoring period, the subjects returned to the clinic where they had been met the previous day. The ECG and CO monitors were removed, vital signs were assessed, a resting 12-lead ECG was performed, and final breath and blood samples were collected. Activity diaries were reviewed for completeness and subjects were questioned about cardiac symptoms experienced during the monitoring period. The Speilberger questionnaire was administered again.

Ambulatory ECG Monitoring: The ambulatory ECG was monitored with a two-channel amplitude-modulated recorder (Del Mar Avionics Model 445b, Irvine, CA). This system has been demonstrated to provide accurate recording and reproduction of ST-segment and T-wave using electronic simulations of the ECG (Bragg-Remschel, Anderson and Winkle, 1982) and patient generated ECG signals obtained during exercise testing (Tzivoni et al 1985; Lambert, Imperi and Pepine 1986; Shook et al. 1987). ST-segment depression was the primary indicator of ischemia in our research design. The fidelity of the high frequency waveform recording was a secondary concern, and this recording system had been demonstrated to adequate recording for the classification of ventricular ectopy into arrhythmia grades (Bragg-Remschel, Anderson, and Winkle 1982).

A bipolar frontal lead system was used with the two-channel ECG recorder. A CM_5 exploring lead was used for channel one; the electrode was located on the left anterior axillary line of the fifth rib. This lead placement had been demonstrated to be most sensitive for the detection of anterior and inferior ischemia (Chaitman 1978; Quyyumi et al. 1986). In subjects with a history of frequent arrhythmias, a CM_1 lead was used for the second channel; the electrode was located in the fourth intercostal space

adjacent to the sternum. If the subjects were known to be relatively free of arrhythmias, the CM_1 lead was replaced by a CM_3 lead, located over the fourth rib to the left of the sternum; this lead placement provided an additional measure of anterior-inferior ischemia (Tzivoni et al. 1985). The ground lead was attached in the right lower thoracic area. The placement site for each silver/silver chloride electrode was abraded and cleansed with isopropyl alcohol. To reduce artifact associated with lead wire movement, loops of adhesive tape were placed on the lead wires approximately 50 cm away from each electrode to prevent pulling on the electrode during changes in posture.

Prior to attachment to the subject, the ECG recording system was calibrated using a 1-mV signal generator. After placement of the chest leads on the subject, each lead and electrode was examined for artifact caused by movement and changes in posture. At the end of the monitoring period, the leads and electrodes were visually inspected, and the occurrence of leads which had pulled loose were noted.

In 61 person-days of ECG monitoring, loose electrodes were observed on only two occasions. In both occasions, the alternate channel remained viable and continued to record the ECG. One day of ECG data was lost due to monitor failure caused by a recording tape jam occurring 5 hours into the monitoring period. The personal CO monitor could also fail to collect acceptable data (see below) and the joint CO and ECG instrumentation failure rate was three days. We were able to perform additional monitoring to replace 2 of the 3 lost or invalid days. Thus, a total of 58 person-days of ambulatory ECG and CO monitoring was successfully obtained from 30 subjects (Figure 3-11). (Data from only 1 24-hour monitoring period were obtained for 2 of the 30 subjects.)

Personal CO Exposure Monitoring: Personal exposure to CO was measured with the Interscan Series 5140 CO monitor (Interscan Inc., Chatsworth, CA). The monitor measures CO electrochemically with a passive diffusion head sensor. The accuracy of the instrument is $\pm$ 1 ppm. An internal data logger integrates four CO signal measurements per second and computes a mean CO concentration for each minute, which is stored in random access memory for later transfer to a desktop computer. The monitors were zeroed and spanned at the beginning and end of each monitoring period using gas standards of 0, 2 and 50 ppm certified against National Institute of Standards and Technology transfer standards. Data were considered invalid if zero or span drift exceeded 3 ppm between the start and end of each 24-hour monitoring period. Two monitoring days were discarded due to excessive zero or span drift in the personal exposure monitors.

COHb levels were estimated from the CO concentration of breath samples collected by the subjects at the beginning and end of each monitoring period, and at 2 to 3 hour intervals during the monitoring day. Using the method of Jones et al. (1958), subjects were trained to collect samples of alveolar air after a 20-second breath hold. The breath samples were stored in polyvinyl bags and analyzed for CO content on a Ecolyzer 2000 (National Draeger, Pittsburgh, PA). At the beginning and end of each monitoring period when breath samples were collected, venous blood samples were also drawn, and COHb levels were spectrophotometrically measured using an IL282 CO-Oximeter

(Instrumentation Laboratories, Lexington, MA) which was regularly calibrated against a gas chromatograph. The CO-Oximeter COHb levels were regressed on the breath CO concentrations to develop a blood COHb-to-breath CO relationship. A regression equation based on the combined data of all subjects was used to estimate COHb levels (Lambert, Colome, Wojciechowski; 1988).

A first-order, linear pharmacokinetic model developed by Ott and Mage (1978) was used to estimate minute-by-minute carboxyhemoglobin levels from the CO exposure profile of each subject (Chapter 5). This model assumed a baseline level of 0.5 percent COHb due to endogeneous CO production, and a half-life in the body of 2.49 hours. The rate of uptake and elimination was assumed to be constant, regardless of physical activity level and ventilation rates. Marcus (1980) demonstrated that when inhaled CO concentrations are less than 100 ppm and ventilation rates are low to moderate, the linear model of Ott and Mage produces estimates of COHb that are in good agreement with those estimated by the more complex model developed by Coburn, Forster, and Kane (1965). Moderate exposure conditions and physical activity levels prevailed during the monitoring of our heart patients (see Chapters 3 and 4). The estimates of COHb levels derived from the Ott and Mage model were used in the statistical analysis of cardiac response.

Breath estimates of COHb were compared to estimates of COHb derived from the pharmacokinetic model at the time each breath sample was collected. Model estimates were, on average, 0.3 COHb units lower than those calculated by the breath method (see Chapter 5). This difference is within the range of accuracy of the breath method (Lambert, Colome and Wojciechowski 1988) and is supportive of the reliability of the minute-by-minute COHb estimates derived from the CO exposure profiles.

Activity Diary: During personal exposure monitoring, subjects recorded time, location, activity, perceived symptoms, medication use, and psychological tension in an activity diary. Formatted pages (Figure 3-1) were used in the activity diary to standardize the written record maintained by the subjects. Activities were coded according to a standard system used in time-activity research (Robinson 1988). For each entry, the subject rated his psychological tension on a 1 to 7 scale, where 1 represented "very tense" and 7 represented "very relaxed".

The descriptions of activities recorded in the diaries were used to assign levels of metabolic activity according to the measurements of Passmore and Durnin (1955), who defined oxygen consumption in multiples of the resting metabolic rate (1 MET = 3.5 ml $O_2 \cdot min^{-1} \cdot kg^{-1}$). For example, sleeping was assigned 0.7 METs; quiet activities were assigned 1.5 METs; most household activities and chores were assigned 2.5 METs; and outdoor work, gardening and walking for exercise were assigned 4.0 METs.

Analysis of ECG Data: The ambulatory ECG tapes were played back on a Marquette Series 8000 Holter Analysis System (Marquette Electronics Inc., Milwaukee, WI). The reviewing technician was blinded for the CO exposure profile. Prior to

beginning the analysis, calibration pulses on the tape were used to standardize ECG waveform amplitude and recording speed. The ECG recordings were reviewed in two stages. In the first stage, the tape was printed to full disclosure hardcopy and the entire ECG monitoring record was printed out in compressed form. This record was used to identify periods of artifact and to provide counts of arrhythmia rates.

The ST-segment was analyzed in the second stage. As the tape was scanned, the analyzer digitized the entire 24-hour ECG record into random access memory and assigned the QRS complexes into morphology classes. The operator confirmed the classifications and made reassignments to other morphology classes or excluded artifact. The QRS morphology classes were then tabulated. Next, the ST-segment analysis was performed on leads CM_5 and CM_3. The ST-segment analysis program (Marquette Electronics ST-Segment Analysis Software, Level 5.5, Release 12/31/87) excluded supraventricular and ventricular ectopy from the automated analysis, considering only QRS complexes of normal morphology. ST-segment depression was defined as 1 mm or more of horizontal or downsloping depression persisting 0.08 sec after the J-point. The isoelectric point (zero reference level) was set in the middle of the PR-segment. ST-segment depression had to be sustained for at least 1 minute to be counted as an episode, and episodes were considered distinct if the ST-segment returned to baseline (< 1 mm depression) for 1 minute or longer. ST-segment level and slope was reported to a trend chart and individual episodes (i.e., time, duration, maximum depression, and heart rate at onset of episode and during peak depression) were tabulated. Hardcopy ECG strips were produced to document changes in the ST-segment, types and rates of arrhythmia, periods of high heart rate or physical exertion, episodes of angina, and baseline tracings typical of cardiac activity for that time of day.

Statistical Methodology: Some of the statistical methodology used in the analysis of the time series data is distinct from that used in other types of health effects research funded by the California Air Resources Board. Therefore, general descriptions of the logistic regression and stratified analysis methods utilized in the longitudinal analysis of the incidence data are included in this section.

Description of the Data Set: The data set consists of several time series of covariates, integrated over consecutive 15-minute intervals: CO, estimated COHb, metabolic activity and psychological tension. The outcome variable, the occurrence of an episode of ST-segment depression within the 15-minute interval, is binary. The covariates, which are continuous variables, were converted into a series of categories, divided at biologically meaningful cutpoints (Table 3.16). The classification allowed the development of contingency tables and provided the repeated observations within levels of independent variables necessary for logistic regression.

Each monitoring day was divided into sequential 15-minute intervals and the values of the independent variables were averaged within each interval. Night-time hours, from 10 pm to 6 am, were excluded in order to restrict the analysis to periods of the day when

subjects were usually awake and active, and therefore most prone to ischemia caused by exertion. Mean COHb levels for an interval were categorized as less than 1, 1 to 2, and 2 percent or greater. Mean CO exposures within the interval were categorized as less than 9, 9 to 35, and greater than 35 ppm. Mean metabolic activity levels were categorized as less than 1, 1 to 2.5, and greater than 2.5 METs. Mean levels of psychological tension were categorized as less than 3, 3 to 5, and greater than 5 tension scale units.

Stratified Analyses: Multiway contingency tables were constructed for the analysis of the association between incidence of ST-segment depression and levels of exposure to the independent variables. Based on dichotomized exposure categories, each level of exposure to an independent variable could be considered separately and stratum specific estimates and tests could be obtained. This approach provided some evaluation of the potential for confounding and interaction. The occurrence of ST-segment depression in 15-minute follow-up intervals was stratified by levels of CO exposure, COHb, metabolic activity and psychological tension.

Prior to modeling the data with logistic regression, the relation of ST-segment depression to each of the independent variables was evaluated. Each level of each independent variable was considered separately in comparison with a reference category to obtain separate estimates of effect. Point estimates of the Pearson chi-square statistic (Bishop, Feinberg, and Holland 1975; Feinberg 1980), unadjusted for the potential effects of the other independent variables, were obtained. The referent levels for metabolic activity and COHb were the "low" classes, and the mid or "neutral" class was used for psychological tension.

Another measure of association, the "odds ratio", was calculated from the contingency tables. The odds ratio approximates how much more likely (or unlikely) it is for the outcome condition to be present when the independent variables are present. It was calculated as the ratio of the exposure odds among the 15-minute intervals with an incident event of ST-segment depression to exposure odds among the intervals without ST-segment depression:

$$\text{Odds Ratio} = \frac{\text{Probability of exposure in intervals with ST-segment depression}}{\text{Probability of exposure in intervals without ST-segment depression}}$$

Odds ratios were calculated by stratum of metabolic activity and COHb level to complement the inference testing by logistic regression (see below). Stratum-specific estimates of the odds ratios were computed using the Mantel-Haenzel estimator of a uniform odds ratio (Mantel 1963).

Logistic Regression: The overall goal of the analyses was to estimate the effects of personal CO exposures and COHb levels on the incidence rates of myocardial ischemia while controlling for other factors, including metabolic activity and psychological tension. The simple stratified analyses described above are limited to examining only stratum-specific and summary estimates. Modeling summarizes patterns in the data in a more efficient manner. Linear regression methods (i.e., ordinary least squares regression) are a familiar type of modeling approach. However, in our data set, the dependent variable is binary and the error variance is not constant but varies in a systematic manner related to the value of the independent variables or the predicted value of the outcome variable (Figure 3-12). In this situation, the use of simple linear regression will yield estimates with larger variances than could be obtained with other procedures such as logistic regression. A logistic response function is curvilinear with asymptotes at O and 1 (Figure 3-13). Thus, as applied to our data set, the response function represents probabilities of the incidence (or new episodes) of ST-segment depression within a 15-minute follow-up interval at different levels of the independent variables, CO exposure, COHb, metabolic activity, and psychological tension.

The logistic function is expressed by:

$$E(Y) = \frac{e^{(\beta_o + \beta_1 x)}}{1 + e^{(\beta_o + \beta_1 x)}}$$

where E(Y) is the expected value of the dependent variable Y, and X is the value of the independent variable. The logistic function has several useful features. First, it can be linearized by the "logit" transformation where p is probability of response:

$$p' = \ln\left(\frac{p}{1 - p}\right)$$

Substituting into equation 1, we obtain:

$$p' = \beta_o + \beta_1 x$$

Thus, the fitted logistic function, is simply the estimated mean probability that Yi = 1 when the level of the independent variable is Xi:

$$p_i = b_o + b_1 x_i$$

The interpretation of the mean response estimate is the same whether the response function is a simple two variable case as here, or a more complex multiple regression case.

While the fitted logistic function may be used in manner similar to that of ordinary least squares regression, the interpretation of the slopes is more complex because the response per unit change of an independent variable varies by the location of the starting point on the scale of that independent variable. In our models, for example, larger increases in the probability of the occurrence of an ischemic event are associated with changes from moderate to high levels of metabolic activity relative to changes from low to moderate levels.

Another measure of association, the "odds ratio", is available from logistic regression. As described above, the odds ratio approximates how much more likely (or unlikely) it is for the outcome condition to be present when the independent variables are present. In our study, this is the ratio of the probabilities of experiencing an episode of ST-segment depression in a 15-minute follow-up interval when the levels of the independent variables are elevated relative to their referent levels. Thus, the odds ratio (OR) is defined as the ratio of the odds for Xi = 1 to the odds for Xi = 0:

$$OR = \frac{e^{\beta_o + \beta_1}}{e^{\beta_o}} = e^{\beta}$$

The log of the odds ratio is equal to the estimated slope bi. In addition to the point estimate of the odds ratio, the statistical software used in these analyses, EGRET (Statistical and Epidemiology Research Corporation, Seattle, WA), computed confidence interval estimates. Thus, if there is no association between the incidence of ST-segment depression and the independent variables, the odds ratio would be 1. Further, the inclusion of the number 1 in 95% confidence intervals is equivalent to accepting the null hypothesis, Ho, of no association at the 5% level of significance.

At the level of the individual subject, logistic models could only be fit to the data of subjects who displayed at least one episode of ST-segment depression (n = 8). In order to characterize the response function across the entire sample, a logistic function was fit for the data of all subjects combined (n = 20). Thus, the response functions derived for individual subjects who experienced some ST-segment depression during monitoring characterize the heterogeneity in response among individuals. The twelve subjects who did not experience ST-segment depression represent the "no response" or other end of the disease spectrum. By pooling the data of all subjects, we account for the potentially higher threshold of response to the independent variables among some heart patients in deriving a logistic model describing the risk of episodes of ST-segment depression.

The log-likelihood ratio and the coefficient for each variable was examined as it entered into the multivariate model. The likelihood ratio test is analogous to examination of the residual sum of squares in linear regression; the change in the log-likelihood with and without the independent variable in the model is evaluated. The level of significance for entry into the logistic model was 0.10. In addition to statistical significance, the coefficients were evaluated by the conventional criteria of plausible sign and magnitude (Greenland 1989).

Several multivariate models containing different combinations of independent variables were constructed. In order to avoid overspecification in these multivariate models, the CO variable was dropped in favor of COHb as the exposure (and dose) metric. COHb was judged to be the more appropriate measure of exposure because it was a cumulative variable, and therefore better represented the prior exposure history of the subject than current or lagged CO levels. Additionally, in our experimental design, COHb was estimated from the CO exposure time series and a high degree of collinearity existed between the two variables CO and COHb, making it necessary to eliminate one or the other.

3.5.3 Results

Perceived Symptoms: During the total 58 person-days of monitoring, 13 of the thirty subjects reported angina (Table 3-17); 45 separate episodes were recorded in the subject diaries. Six episodes of chest discomfort, distinct from typical angina, were reported by 4 subjects. Dyspnea was reported by 2 subjects on 1 occasion each. Two episodes of syncope were reported, one each by two subjects.

ST-Segment Depression: At the time that the ECG monitoring was performed, we discovered that several subjects did not meet our medical criteria for inclusion in the analysis. Left bundle branch was present on the resting 12-lead ECG of three subjects, one had left ventricular hypertrophy, one had resting ST-segment elevation, and four were taking digitalis (Figure 3-11, Table 3-15). This information had not been discovered on the medical records used for subject selection or the subjects' medical therapy had changed in the interim. These conditions precluded analysis of the ST-segment endpoint in these subjects. ST-segment analysis was performed on the 40 person-days of monitoring from 20 subjects.

Eight of the 20 subjects (40 percent) experienced one or more episodes of ECG ST-segment depression, defined as depression of 1 mm or more and lasting for at least 1 minute, during their two 24-hour periods of monitoring (Table 3.18). Among these 8 subjects, a total of 340 episodes were observed. The number of episodes per subject per 48 hours of monitoring ranged from 2 to 87, and the mean number of episodes per subject was 21 per day. The duration of episodes averaged 5.7 minutes in length, and ranged from 1.5 to 66.2 minutes. The ST-segment depression ranged from 1.0 to 4.5 mm, and averaged 1.4

mm. The integral of ST-segment depression per episode ranged from 1.4 to 115.5 mm-min, and averaged 6.5 mm-min. The majority of episodes of ST-segment depression were asymptomatic. In only three instances did diary reports of typical angina pain coincide with episodes of ST-segment depression.

The circadian distribution of ST-depression episodes is presented in Figure 3-14. In the eight subjects with ST-segment depression, four experienced some nocturnal ischemia, defined as episodes occurring between 10 pm and 6 am. Ninety-nine episodes of the total 340 episodes (29 percent) occurred during this night-time period. As mentioned in the Methods section, the night-time hours were excluded from the longitudinal analysis of the occurrence of ST-segment depression and CO exposure.

Eight subjects demonstrated at least one episode of ST-segment depression. For these subjects, the results of the Pearson chi-square analysis testing the association of ST-segment depression within a 15-minute follow-up interval and the independent variables of CO, COHb, metabolic activity level, and psychological tension are presented in Table 3-19. In this univariate analysis, CO level was significant in 3 of 8 subjects, COHb level in 4 subjects, metabolic level in 5 subjects, and psychological tension in 3 subjects. Level of metabolic activity and COHb showed the strongest and most consistent associations with ST-segment depression and were considered as potentially important candidate variables for inclusion in the multivariate logistic regression model. Contrary to expectations, increasing psychological tension was associated with decreasing occurrence of ST-segment depression in the data of 3 subjects and for all data combined. Because of uncertainties in the possible meaning of a negative effect of psychological tension on ST-segment depression, this variable was not used as an independent variable in the construction of multivariate logistic models. The reasons for this decision and the ambiguities surrounding the psychological tension measure are described in the Discussion (Section 3.5.4).

Using the categorical classifications for CO, COHb, metabolism, and psychological tension, univariate logistic regression models were fit to the combined monitoring data of all subjects and the odds ratios for each independent variable were calculated (Table 3.20). The odds ratios show that relative to the referant level, the probability of incidence of ST-segment depression within a 15-minute follow-up interval increases with metabolic activity and COHb level, and decreases with psychological tension.

Univariate and multivariate logistic regression models were constructed for the monitoring data of individual subjects, and to the monitoring data of all subjects combined (Table 3.21). A priori, a p-value of 0.10 was used as the level of statistical significance in these analyses; however, most variables were significant at the traditional level of 0.05.

In the multivariate logistic models for all subject data combined, the signs of the coefficients for COHb and metabolism agreed with theoretical expectations. As COHb and metabolic level increased, the probability of the onset of an episode of ST-segment depression within any 15-minute interval increased. The coefficient for the metabolic activity and COHb product term was not significant (METxCOHb coefficient = -0.240, p-

value = .353). The estimated coefficients and odds ratios are presented in Table 3.22. Adjusting, statistically, for the influence of the metabolic activity, the uniform odds ratio for COHb level was 1.34.

The fit of the final model was assessed by examining the residuals over the 15-minute follow-up periods. A residual was defined as the difference between the observed and estimated number of follow-up intervals with incidence ST-segment depression by metabolic activity level and COHb level (Table 3.23). The magnitude of the residuals was evaluated by dividing the residual by the number of follow-up intervals in that class of metabolic activity and COHb level. In general, the residuals per follow-up interval were small. Some overestimation occurs at the low metabolic activity level and some underestimation occurs at the medium metabolic activity level. No systematic deviations could be discerned by COHb level.

Using the final multivariate logistic model for all subjects, the estimated ST-segment response was plotted in Figure 3-15 as a function of metabolic activity level and COHb. At low levels of COHb, 1 percent or less, and resting metabolic levels (MET $\leq$ 1), the estimated probability of an episode of ST-segment depression within a 15-minute follow-up interval is 1.5 percent. At these low COHb levels, the probability of ST-segment depression increases to 4.5 and 13.3 percent as metabolic activity increases to moderate (1 < MET $\leq$ 2.5) and high levels (MET > 2.5), respectively. The overall effect of increases in COHb level was approximately 40 percent of that estimated for metabolic activity. At moderate metabolic levels, the estimated probability of occurrence of ST-segment depression in any 15-minute follow-up interval increases from 4.5 at low COHb levels, to 6.0 and 7.8 percent, at moderate (1.0% < COHb $\leq$ 2.0%) and high (COHb > 2.0%) COHb levels, respectively. At high metabolic levels (MET >2.5) and high COHb levels (COHb > 2.0%), the estimated probability of ST-segment depression is 21.5 percent.

Additionally, the excess numbers of follow-up periods with ST-segment depression attributable to COHb levels above 1 percent were calculated (Table 3.24). Relative to the low COHb level (COHb $\leq$ 1%), which represents nominal COHb levels caused by endogenous CO production and very low exposure to ambient CO, 26 of the 168 intervals with ST-segment depression are attributed to elevations in COHb. Thus, approximately 15 percent of the observed incidence of ST-segment depression is attributed to ambient CO exposure. Should COHb levels be reduced to the levels of the "low" COHb class, the logistic model predicts that these "excess" episodes of ST-segment depression would be eliminated.

As an alternative test of trend for COHb response, the incidence data was stratified by level of metabolic activity and the Mantel-Haenszel test statistic (Mantel 1963) was calculated (Table 3.25). The calculated odds ratio is a test of the null hypothesis of no monotone relation between COHb levels and the incidence of ST-segment depression. The Mantel-Haenszel odds ratio was 1.97 and compares favorably with the 1.34 uniform estimate calculated in the multiple logistic regression (Table 3.22).

Comparison of Ambulatory Monitoring with Controlled Clinical Testing: Nine of the subjects who participated in the ambulatory monitoring also participated in a controlled clinical study conducted by Kleinman and colleagues (1989). A randomized cross-over design was used in this laboratory study. Twenty-four men with reproducible exertional angina were exposed to 100 ppm CO or filtered room air for one hour. As the result of the exposure, mean COHb levels were increased from 1.5 to 3 percent. The subjects were exercised on a cycle ergometer until the onset of angina, and a mean reduction of 6 percent in time to onset of angina was observed after CO exposure relative to clean air. Among the 8 subjects who displayed ST-segment depression, a 20 percent reduction in time to onset of ST-segment depression was observed.

Of the 9 subjects who participated in both the laboratory and ambulatory studies, seven were eligible for ST-segment analysis of their ambulatory ECG recordings. Two subjects' data were excluded because of conduction defects or resting ST-segment abnormalities. Although this is a small sample, the response to CO exposure in the community was similar to that observed in the laboratory (Table 3.26). Two of 4 subjects who displayed earlier onset of angina after CO exposure in the laboratory demonstrated a statistically significant association between the incidence of ST-segment depression and COHb levels in the community setting. Three subjects who did not demonstrate a sensitivity to CO during laboratory testing, also did not experience any ST-segment depression in the field. Two subjects who displayed ventricular arrhythmias during exercise testing also displayed frequent ventricular ectopy in the field. One subject displayed frequent ventricular ectopy during field monitoring which was not apparent during laboratory testing.

3.5.4 Discussion

Our data indicate a positive association between elevations in COHb levels that are associated with exposures to CO in the urban environment and the incidence of myocardial ischemia, as represented by ST-segment depression, in men with IHD. These findings are consistent with current theories on the etiology of myocardial ischemia (Miller 1985) and the findings of clinical studies examining the effects of CO exposure on heart patients during exercise (Anderson et al. 1973; Kleinman et al. 1989; Allred et al. 1989). We observed consistent increases in the incidence of myocardial ischemia across three categories of metabolic activity and COHb (Tables 3-22 and 3-23). Adjusting, statistically, for the effect of COHb, the risks of ST-segment depression at moderate ($1 < MET \leq 2.5$) and high ($MET > 2.5$) levels of physical exertion, were 3.4 and 10.3 times higher, respectively, as compared to resting levels ($MET \leq 1$). Similarly, adjusting for the effect of metabolism, the risk of ST-segment depression was 1.5 and 2.1 times higher at COHb levels classified as moderate ($1 < COHb \leq 2\%$) and high ($COHb > 2\%$) COHb, respectively, relative to the low class ($COHb \leq 1\%$). In this sample of men with IHD, 15 percent of the incidence of ST-segment depression was attributed to elevated COHb levels. While the coefficients in this model are statistically significant, the number of observations

in the "high" categories of metabolic activity and COHb are relatively small, and therefore the odds ratios for these categories must be cautiously interpreted.

The spectrum of ST-segment depression observed in our study follows a logical biological gradient with increasing levels of metabolic activity and COHb. The multiple logistic regression analysis, which is premised on a multiplicative model (Rothman 1986), provided a good fit to the data. Increases in metabolic activity were observed to have a stronger influence on the incidence of myocardial ischemia than increases in COHb (Table 3.22; Figure 3-13). Increases in physical exertion in the absence of exposure to CO were sufficient to increase the occurrence of myocardial ischemia. While the ratio of the incidence of ST-segment depression between COHb levels was constant across the three classes of metabolic activity, the incidence rate difference between COHb levels increased with increasing metabolism. This result implies that metabolic activity modifies the effect of CO exposure and is consistent with the conceptualization of ischemia as an imbalance in oxygen supply and demand (Figure 3-10).

Further support for a causal relation between CO exposure and myocardial ischemia is derived from the temporal relation observed. In the multivariate analyses, the incidence of ST-segment depression was associated with COHb levels but not with current levels of ambient CO. Implicit in this finding is interpretation that ST-segment depression follows the accumulation of CO in the body. Our estimates of COHb were derived from the personal CO exposures of each subject and assumed a half-life of 2.49 hours. Therefore, ST-segment depression follows the cumulative exposures of the previous 2 to 4 hours.

We were not able to include psychological tension as an the independent variable in the multivariate model of ST-segment response. Previous research by Deanfield et al. (1984) and Selwyn et al. (1985) suggested that mental stress is biologically relevant and a potential confounder of the relation between COHb and myocardial ischemia. In general, psychological tension was not associated with ST-segment depression in chi-square tests or univariate logistic regressions for the data of individual subjects. In logistic regressions performed on all subject data combined, a negative association for psychological tension was observed. This result is attributed to the varying interpretation of the relaxation-tension scale by each subject. Future analyses will normalize the psychological tension data for each subject to allow the valid aggregation of data across subjects for this variable.

The nature of these time series data pose complex problems for statistical analysis. In our approach, we assumed ischemic response to be uncorrelated over time. However, it is likely that successive observations of the outcome variable, ischemia, and those of the independent variables, particularly COHb, are correlated. Logistic regression was used because of the dichotomous outcome variable, and as a linear model, the method is robust to departures from the assumption of independently distributed errors. However, while the estimates of the logistic coefficients are expected to be unbiased, the statistical significance of the coefficients is likely to be underestimated due to the presence of autocorrelation (Johnston 1986).

Despite careful screening of coronary arteriography and exercise testing records to select subjects with advanced coronary artery disease and those who had previously demonstrated ST-segment depression during exercise testing, diverse patterns of prevalence of ST-segment depression were observed among our subjects. Of the twenty subjects eligible for ST-segment analysis, only 8 experienced ST-segment depression during their two 24-hour monitoring periods. In selecting the subjects, we relied upon treadmill tests performed under varying protocols for diagnostic purposes by the medical centers. Because many subjects began or changed their medical therapy between the time of their last exercise test and their participation in our monitoring program, it is possible that their medications may have decreased their ischemic response to exertion and CO. This hypothesis is supported by the limited data from the subjects who participated in both the ambulatory monitoring and the clinical study testing the effects of CO exposure on exercise capacity (Table 3.26). Five of the nine subjects did not show ST-segment depression during laboratory testing, and of the 4 subjects eligible for ST-segment analysis of the ambulatory ECG recordings, ST-segment depression was observed in only 1 subject. These results indicate that we cannot exclude the possibility that our sample may include some men who do not usually display ST-segment depression. If our sample is mixed, our risk estimates would be biased downwards. Future ambulatory studies of similar design might obtain greater homogeneity if standardized exercise tests to confirm the presence of an ST-segment response to exertion were performed at the time of enrollment.

We observed wide variability in the prevalence of ST-segment depression in our sample. Twelve subjects displayed no ST-segment depression during the 48 hours of ambulatory monitoring. In the 8 subjects where ST-segment depression was observed, incidence ranged from 1 to 46 episodes per day. The mean duration of individual episodes ranged from 1.5 to 66 minutes, with a mean of 5.7 minutes. Furthermore, the vast majority of ST-segment episodes were asymptomatic. The polarized pattern of prevalence in our sample differs from that observed in other ambulatory studies (Hausmann et al. 1990) and may be related to our reliance on exercise test results performed as long as 1 year prior to enrollment in the study. The wide range of episodes per subject and the mean duration of episodes are comparable to those observed by other investigators (Tzivoni et al. 1987; Coy et al. 1987; Hausmann et al. 1990).

The number of subjects participating in our ambulatory study and the clinical exposure-exercise study is too small to allow a extensive comparison of results. However, while results on 9 subjects are too limited to be supportive, neither do they appear to be contradictory. In what may be cautiously interpreted as good specificity, 3 of 4 subjects who did not display ST-segment depression during laboratory testing also did not display ST-segment depression in the field. One of 2 subjects who displayed earlier onset of angina and ST-segment depression in laboratory testing also displayed a positive association with COHb levels during ambulatory monitoring.

3.5.5 Conclusions

The findings of several clinical studies have suggested that exposure to CO may limit exercise performance and that atherosclerotic narrowing of the coronary arteries may place heart patients at high risk for myocardial ischemia and angina. The impairments in exercise performance are thought to result from decreased oxygen delivery to the heart muscle and other metabolizing tissues. CO limits oxygen transport by combining with hemoglobin to form nonfunctional carboxyhemoglobin and by limiting tissue oxygen availability by increasing hemoglobin affinity for oxygen.

Prior to our study, the acute effects of inhaled CO on heart patients was assessed by exercise tests performed in the laboratory under controlled conditions of exposure. The subjects selected for participation in these experimental exposure studies had angina and ST-segment depression on the ECG that could be induced by exercise in a reproducible manner. Subjects' performance on a cycle ergometer or treadmill was measured before and after exposure to 100 to 200 ppm CO for 1 to 2 hours. As the result of these exposures, carboxyhemoglobin levels were elevated from a baseline value of approximately 1 percent, to levels of 2 to 4 percent. During exercise testing, workloads (e.g., speed and inclination of the treadmill or pedalling resistance) were progressively increased, and the time to onset of chest pain (angina pectoris) or ST-segment depression was measured. Mean decreases in time to onset of angina or ST-segment depression were approximately 5 to 10 percent.

While these studies have established levels of adverse health effects, the conditions required to perform the experiments make it difficult to generalize the results to the community setting where many combinations of myocardial oxygen demand and supply, and CO exposure, may lead to the induction of myocardial ischemia or angina pectoris. Therefore, we conducted a monitoring study in the community to measure myocardial ischemia and exposure to CO in a group of men with IHD. In this observational design, the men were free to pursue their usual activities, and therefore, their exposures or levels of physical activity were not manipulated.

Each of the subjects was monitored for two days using electronic instrumentation to observe the occurrence of myocardial ischemia and personal exposure to CO. The subjects also maintained a written diary of their activities, locations, symptoms, medications, and psychological tension. This type of observational study design is called a "cohort" study because a group of people who share one or more characteristics in common have been assembled and they are followed to see which subjects develop disease. In our approach, subjects were monitored to see which of them developed myocardial ischemia as measured by ST-segment depression on the electrocardiogram (ECG) recording, and to see which of them were more frequently exposed to CO. Using a statistical method called logistic regression, we compared levels of CO exposure, COHb, metabolic activity, and psychological tension when episodes of ST-segment depression occurred against times when no ST-segment depression occurred.

Of the 20 men followed, twelve did not experience any ST-segment depression and eight subjects experienced at least one episode. The subject with the most frequent ST-segment depression experienced 87 episodes during his two days of monitoring. Across the sample, a total of 340 episodes of ST-segment depression were observed, with a mean duration of 5.7 minutes. When the monitoring day was divided into a series of 15-minute follow-up intervals, the probability of occurrence of ST-segment depression with an interval increased with increasing levels of metabolic activity. Generally, the risk of experiencing an episode of ST-segment depression increased 3.22 times for activities requiring moderate or high levels of exertion relative to quiet activities or resting. This finding is consistent with the evidence from clinical exercising testing that myocardial ischemia can be induced by the increased oxygen demands caused by physical activity. Psychological tension was expected to increase heart rate and oxygen demand, however, the occurrence of ST-segment depression was not associated with our measures of psychological tension.

In addition to metabolic activity, the risk of ST-segment depression increased with increasing COHb levels. The probability of experiencing an episode of ST-segment depression was 1.34 times greater when COHb levels increased above 1 percent. Relative to metabolic activity, increasing COHb levels had a smaller effect on the occurrence of ST-segment depression, and therefore, most of the observed episodes of ST-segment depression were attributed to physical activities. The proportion of episodes caused by exposure to CO was estimated to be 15 percent. Because the occurrence of angina pectoris, shortness of breath, and dizziness was rare, symptoms could not be used as endpoints in these analyses.

These findings indicate that low-level CO exposures experienced during the activities of daily life are capable of increasing the total ischemic burden of people with coronary artery disease. ST-segment depression on the electrocardiogram is an early and subclinical sign of ischemia. If the imbalance in oxygen delivery to the heart is prolonged or becomes more severe, chest pain (angina pectoris) and disturbances in the contraction of the heart muscle may occur. Extreme ischemia may lead to the death of heart muscle tissue (infarction or "heart attack"). Some studies have demonstrated that individuals who exhibit ST-segment depression on their ambulatory ECG recordings are at increased risk for myocardial infarction, and therefore, many patients with this condition are treated with drugs to reduce the occurrence of these episodes.

Over eight million people in the United States are estimated to have ischemic heart disease. For the population of California, this prevalence translates to approximately 800,000 people, many of whom live in metropolitan areas where exposure to CO is common. If the relation between CO exposure and myocardial ischemia observed in this study is causal, then CO exposures to people with IHD living in the State's urban areas is inducing a large number of ischemic episodes. Although the ischemic events are transient, an unknown number of episodes, if they continue to proceed, will develop into chest pain, and theoretically, some will develop into infarctions. Further examination of the CO exposures and cardiac response of this susceptible subgroup are clearly warranted.

4.0 SUMMARY OF RESULTS AND CONCLUSIONS WITH RECOMMENDATIONS FOR FUTURE RESEARCH

This exposure assessment provides data on the temporal and spatial distribution of CO in the community environment of persons with ischemic heart disease. Importantly, this research represents a novel extension of laboratory-based research: within the natural context of the community setting, CO exposures were quantified by location and activity, biological uptake was monitored, and the cardiac response of the heart was measured in terms of subjective anginal symptoms and electrical activity. The tiered study design produced over 250 person days of activity pattern data, over 150 person days of CO exposure data, and over 65 person days of joint CO and electrocardiographic monitoring. Before this research, the lack of exposure and activity-level data for IHD subjects impaired the evaluation of their risk from CO exposure during free-ranging activities in the community. Clinical exposure-exercise studies have been extrapolated to the population of persons with heart disease without knowledge of the group's likelihood of encountering the exposure conditions required to elevate carboxyhemoglobin levels into the range where laboratory health effects were observed. The exposure estimates derived from this community research will reduce these uncertainties, and the continuing analysis of the electrocardiographic data base will extend the utility of data produced in controlled clinical studies.

Four hypotheses were addressed in this research:

1. IHD subjects are at risk of developing levels of carboxyhemoglobin reported in clinical studies to cause ischemia and shorten the time to onset of angina;

2. The normal activities of the IHD population at times require increased myocardial oxygen demand (thereby decreasing angina thresholds);

3. Periods of high physiologic activity at times coincide with elevated CO concentrations and resulting elevations in carboxyhemoglobin; and

4. Elevated CO is associated with ischemic episodes measureable by electrocardiographic instrumentation.

To test these hypotheses, the study design implemented a diverse set of clinical and analytical methods, and personal air pollution exposure and biomedical monitoring protocols. The high degree of research subject compliance attained demonstrates that complex monitoring procedures were successfully reduced to simple and relatively unburdensome tasks. Activity and symptoms were logged by subjects in greater detail than heretofore believed possible in exposure assessment research. Subjects were trained to be self-sufficient in breath sampling and provided high-quality samples at intervals throughout the monitoring day without supervision. Comparison of breath estimates of COHb to those directly measured in blood samples allowed more precise estimation of COHb by breath methods and identified new analytic needs. Aerometric monitoring methods were advanced by adapting instrumentation from the occupational setting to the community environment; CO measurements were recorded in one-minute averages allowing, for the first time, approximation of real-time exposure profiles within the interval of the activity and setting. The PEM instrumentation was sensitive, and by virtue of its data logging capabilities, verified exposures measured in other urban studies, and identified several high exposure situations not observed previously. The coding of activity and location in human exposure assessment studies was advanced by the development of a hypercode system which allowed hierarchical grouping of activities and locations by class, and facilitated comparison of measurements against sociological and

CO exposure literatures. Similarly, the state-of-the-art of coding time-series ECG data was advanced by refining existing medical classification systems for use in correlational analyses with environmental factors.

The major conclusions of this research include:

- Heart disease subjects spend less time in the ambient (outdoor) environment than members of the general population but the time spent in transit is similar to that of the general population. (Highest CO personal exposures are generally encountered in transit-related microenvironments.)
- Heart subjects engage in less strenuous activities but experience activity patterns similar to the non-diseased population.
- Highest CO exposures are experienced while commuting and near internal combustion engines.
- Average personal CO exposure for all time spent in automobiles was 8.6 ppm; maximum auto exposure was 239 ppm (one-minute average).
- CO exposures on freeways typically averaged 10-12 ppm.
- Elevated residential CO concentrations were observed.
- Elevated CO concentrations were observed in parking lots and parking structures. Average exposure in these microenvironments was 7.9 ppm.
- Service stations and motor vehicle repair facilities also had average exposures of 7.9 ppm CO.
- Residential CO exposures (in-house) were generally low and averaged 2.0 ppm.
- Personal ambient exposure was highly variable. Highest exposures were found in proximity to running automobiles and small gas-powered garden equipment. Transient peaks as high as 134 ppm were observed with use of a gasoline powered chain saw and 226 ppm with use of a gasoline lawn edger.
- Occupational exposures to CO are highly variable. Persons working in warehouses, assembly lines, and garages had an average CO exposure of 6.0 ppm. Proximity to internal combustion engines provides the greatest potential for elevated CO exposures.
- With the measured PEM distributions of CO, most IHD subjects (56%) are expected to have experienced COHb levels in excess of 2.5% during the 142 person days of monitoring. This level of COHb% is modeled to occur 1.8% of the monitoring time.
- One subject was modeled from CO exposure to attain 5% COHb (without cigarette exposure).
- The IL282, commonly used for COHb determinations in clinical and research applications, may be subject to interferences or reliability problems at low COHb levels.

- At low COHb levels, breath samples may be more reproducible than blood samples analyzed by the IL282. The relationship between blood and breath CO should be better characterized in order to confidently use breath CO determinations in community exposure and health studies.

The exposure assessment on IHD subjects has evoked several promising areas for further research. Topic areas that may be recommended include:

- Further characterization of CO exposures occurring during motor vehicle use. Although commuting was an infrequent activity amongst the IHD subjects studied, motor vehicle use was the single largest contribution to total exposure. In separate studies on the general population, a similar observation has been made; commuting behavior is expected to be more frequent in the general population.

- Further characterization of exposures associated with small internal combustion engines used to power yard equipment (e.g., lawn mowers, chain saws, weed-eaters). High exposures may occur due to close user proximity.

- Quantification of relative contribution of the evaluation of environmental factors (e.g., appliance type, ventilation) that lead to elevated indoor CO exposures. Relatively higher CO exposure was observed in the indoor residences of several research subjects. Given the large amount of time spent indoors at home, increased exposures occur to some persons with IHD.

- Validation studies of the standard breathhold method to estimate blood COHb should be performed for subsequent application in community health studies. Breathhold maneuver parameters should be varied, and contrasts made between non-diseased persons and those with IHD or chronic obstructive pulmonary disease. Artificial dosing of subjects could be used to extend the range of observations.

- Concurrent with breathhold method studies, analytic techniques to directly measure COHb in blood should be systematically evaluated. IL282 performance should be compared against reference method s including gas chromatography and manometric (Van Slyke) methods. Interfering constituents in blood should be examined for each respective method.

- "Silent" ischemia events have been observed in the ECG records. Silent ischemia as manifested by ST-segment changes without angina, and the occurrence of arrhythmias suggest that ischemic stress may occur which the angina subject does not perceive. Arrhythmias and electrical instability are serious cardiac events because of association with fibrillation and sudden cardiac death. Research on the health effects of CO has focused on the aggravation of angina pain and objective evidence of ischemia, and ambulatory studies in the community environment may be the most appropriate means of research on this question.

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