EFFECTS OF OZONE INHALATION DURING EXERCISE ON SELECTED HEART DISEASE PATIENTS

H. Robert Superko, M.D.
William C. Adams, Ph.D.
Patricia A. Webb, B.A.

Human Performance Laboratory
Physical Education Department
University of California
Davis, CA 95616

Abstract

Heart and lung patients are considered at greater risk during episodes of significant oxidant pollution and, although there are no quantitative laboratory data available, are advised to curtail physical activity. In the present investigation, six male volunteers, ages 46-64 years, with clinically documented coronary artery disease and a well defined symptomatic angina pectoris threshold on physical exertion, served as subjects. Each patient was exposed on three occasions for 40 minutes to either filtered air or to ozone at concentrations of 0.20 or 0.30 parts per million, while walking on a treadmill at workloads simulating their regularly prescribed symptom limited exercise training regimen. Standard pulmonary function tests and periodic observations of exercise ventilation, respiratory metabolism, electrocardiographic changes, hemodynamic response, and clinical signs and symptoms were noted. Analysis of variance revealed that none of the patients' physiologic responses to ozone exposure were statistically significant. Furthermore, neither onset of angina pain or ischemic changes were related to ozone exposure in a dose dependent fashion. Hence, the patients not only failed to exhibit any unexpected cardiovascular strain while exposed to ozone, but also evidenced no significant pulmonary function impairment or exercise ventilatory pattern alteration as has been observed in clinically normal subjects exercising at similar ozone concentration levels. This apparent incongruity may be due to the fact that ozone toxicity is more closely related to the total amount of ozone inhaled (that is, as a function of pulmonary ventilation volume and exposure time, as well as ozone concentration). Hence, the angina patients' symptom limited exercise tolerance resulted in a lower total amount of ozone inhaled (termed effective dose) than that observed to effect ozone toxicity in clinically normal subjects, who exercised at greater intensities and for longer durations. It was concluded that the angina patients appear to be no more susceptible to ozone toxicity effects than are clinically normal subjects at the effective doses imposed. However, had the patients exercised longer, they might well have evidenced pulmonary function impairment and/or cardiovascular strain, as would other heart disease patients with greater work capacity while exercising at their higher exercise training intensities for periods approximately one hour. Hence, caution is advised in generalizing our observations to other patient groups and conditions.

Acknowledgements. The expert technical assistance of Mr. Richard Fadling, Electronics Technician, is gratefully acknowledged. We are also appreciative of the able laboratory assistance afforded by Mr. Mike Catlin, Ms. Debbie Chippendale, Messrs. Dave Condon and Mark Freitas, Ms. Susan Lauritzen, and Messrs. Pierre Rouzier, Ed Schelegle, Perry Seltz, and Jim Shaffrath. Sincere appreciation is extended to the subjects for their willing contribution of time and effort.

This report was submitted in fulfillment of ARB Contract A8-120-31, "Ozone Effects on Heart and Lung Patients," by the Regents of the University of California, Davis, under the partial sponsorship of the California Air Resources Board. Work was accomplished as of 8 December 1980.

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.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

SUMMARY AND CONCLUSIONS

The enhanced ozone toxicity effected by exercising at ozone concentrations in the range of oxidant smog alert levels has been documented utilizing clinically normal young adult males. Individuals with heart disease are thought to be more susceptible to ozone during physical exertion on the basis of reduced functional reserve or on possible potentiation of disease symptoms, although no quantitative data is currently available. Hence, the present study was designed to determine the difference in ozone toxicity, if any, in a group of angina patients undergoing prescribed exercise training, compared to that of clinically normal subjects. The patients' response during 40 minute exposures to filtered air or to ozone at concentrations of 0.20 and 0.30 parts per million, while engaged in their normal exercise training regimen, was ascertained and compared to that of two clinically normal groups. Standard pulmonary function tests and periodic observations of exercise ventilation, respiratory metabolism, electrocardiographic changes, hemodynamic response, and clinical signs and symptoms were noted. None of the patients' physiologic responses to ozone exposure were statistically significant. Furthermore, neither onset of angina pain or ischemic changes were related to ozone exposure in a dose dependent fashion. Hence, the patients not only failed to exhibit any unexpected cardiovascular strain while exposed to ozone, but also evidenced no physiologic impairment previously observed in clinically normal subjects exercising at similar ozone concentration levels. This apparent incongruity may be due to the fact that ozone toxicity is more closely related to the total amount of ozone inhaled (that is, as a function of pulmonary ventilation volume and exposure time, as well as ozone concentration). Hence, the angina patients' symptom limited exercise tolerance resulted in a lower total amount of ozone inhaled (termed effective dose) than that observed to effect ozone toxicity in our clinically normal subjects when they exercised at greater intensities and for longer durations. It was concluded that: (1) Angina patients are apparently no more susceptible to ozone toxicity effects than are clinically normal subjects at effective doses found to be below threshold in the latter group; (2) If the angina patients' exercise intensity had been reduced slightly and their exposure increased substantially, the effective dose would be increased above the normals' threshold level; (3) Heart disease patients with high functional capacity can reach above threshold effective doses in less than one hour when exercising at their prescribed training intensity; (4) Thus, caution is advised in generalizing our observations to other patient groups and conditions.

RECOMMENDATIONS

1. Further investigations of subjects exercising continuously at intensities characteristic of increasingly popular aerobic training programs should be conducted at ozone concentrations characteristic of first and second stage smog alert levels.
2. The ozone effective dose, rather than ozone concentration alone, should be utilized to identify toxicity threshold and to quantify the degree of impairment at higher levels.
3. Heart and lung disease is too broad a classification to advise patients properly relative to appropriate physical exertion levels during significant air pollution episodes. Hence, the heart and lung patient classifications with the greatest number should be subjected to laboratory controlled ozone exposures at a range of ozone effective doses approximating the toxicity threshold level observed in previously examined clinically normal subjects to determine if they evidence accentuated pulmonary function and/or disease specific symptomatic responses.
4. Coronary artery disease patients with high functional capacity are frequently advised to maintain a vigorous lifestyle and thus, are an attractive sub-population to subject to ambient smog alert levels that will effect ozone effective doses similar to those shown to be above threshold in clinically normal subjects.
5. Patients with well defined chronic lung disease, some of whom are advised to undertake systematic exercise training programs to improve their submaximal exercise response, may be particularly compromised in significant oxidant air pollution and thus, are highly meritous of study.
6. Physical exertion symptom limited angina patients who cannot sustain high intensity exercise, should be exposed to more prolonged, milder exercise to determine if they evidence ozone toxicity effects at lower effective doses than do clinically normal subjects.
7. Smokers in any sub-population studied should be isolated from non-smokers, since the effect on sensitivity to ozone exposure is, at present, still equivocal.

BODY OF REPORT

Introduction

Ozone (O_3), an ubiquitous constituent of the upper atmosphere and toxic contaminant predominant in the photochemical smog of numerous urban areas, is among the most potent oxidizing agents in the atmosphere (Jaffe, 1968; Stokinger & Coffin, 1968). O_3 has potent zootoxic properties, reacting readily with various cellular constituents, i.e., coenzymes, amino acids, lipids, and SH ligands, and can potentially disrupt biochemical and physiological function at tissue sites where the greatest amount of O_3 absorption occurs in ambient or experimental exposures (Menzel, 1970; Stokinger & Coffin, 1968).

As with other pollutants, experimental exposures of animals to levels of O_3 above those maximally seen in ambient air have provided considerable qualitative information concerning the pathophysiological changes accompanying acute and chronic inhalation of the gas (Committee on Medical Biological Effects of Environmental Pollutants, 1977; DeLucia et al, 1975; Fairchild, 1963). Ordinarily, however, especially where oxidant concentrations near ambient alert levels have been administered, the effects of O_3 intoxication have been attributed to direct oxidative lesions localized in the respiratory tract and blood (Jaffe, 1968; Stokinger & Coffin, 1968).

O_3 was originally of interest to human physiologists because of its actions as a radiomimetic gas and presence in the improperly filtered cabins of high flying aircraft (Bennett, 1962; Clamann & Bancroft, 1959). Subsequently, and in part because humans are subject to occasional acute peak levels due to the cyclic nature of O_3's genesis, laboratory studies have focused on short-term effects in O_3 exposures. As noted in Table 1, interest first centered on toxic reactions of humans at rest while exposed to O_3 levels rarely, if ever, encountered in the ambient environments (Goldsmith & Nadel, 1969; Young et al, 1964). The potentiating effects of exercise on O_3 toxicity, originally noted with rats by Stokinger et al (1956) was first observed in humans at 0.75 ppm by Bates et al (1972). Subsequently, others (Folinsbee et al, 1975; Hazucha et al, 1973; Silverman et al, 1976) have observed greater O_3 toxicity effects consequent to 2-h exposures at 0.75 ppm with alternate periods of 15 min light exercise ($\dot{V}_E$ increased 2½ times rest) and rest, i.e., with intermittent exercise (IE). In similar 2-h IE exposures, pulmonary function (PF) decrements were also observed at 0.37 ppm, a level that caused no effect in resting expo-

Table 1. Summary of Major Findings of Acute O_3 Toxicity Studies

AUTHORS	EXPOSURE DURATION	CONCENTRATION (ppm)	REST OR* EXERCISE	MAJOR FINDINGS
Young et al (1967)	2 hrs	0.6-0.8	R	Decreased VC, $FEV_{0.75}$, and DL_{co}
Goldsmith (1969)	1 hr	0.1,0.4,0.6,1.0	R	Increased airway resistance with 1.0 ppm
Bates et al (1972)	2 hrs	0.75	R and E	Exercise potentiated O_3 effect in producing PF changes and subjective symptoms
Hazucha et al (1973)	2 hrs	0.37,0.75	IE	RV increased, indicating early small airway effect
Buckley et al (1975)	2.75 hrs	0.5	IE	Blood biochemical changes with exposure and mild exercise
Folinsbee et al (1975)	2 hrs	0.37,0.50,0.75	IE	Increased f_R during exercise after O_3 exposure, with dose response
Hackney et al (1975)	2-4 hrs	0.25,0.37,0.50	IE	Certain individuals may be O_3 "reactors," i.e., more sensitive than others
Silverman et al (1976)	2 hrs	0.37,0.5, 0.75	R and IE	PF impairment more closely related to O_3 effective dose (product of O_3 concentration, $\dot{V}_E$, and exposure time) than O_3 concentration, alone
DeLucia & Adams (1977)	1 hr	0.15,0.30	CE	Demonstrated a dose response to both the level of O_3 and the level of exercise in PF and exercise ventilatory pattern. No blood biochemical changes
Folinsbee et al (1978)	2 hrs	0.1,0.3,0.5	R and IE	Using heavy workloads, confirmed observations of Silverman et al re O_3 effective dose
Savin & Adams (1979)	31 min	0.15,0.3	CE	Observed no PF impairment or reduced performance in brief maximum graded exercise test
Adams et al (1981)	30-80 min	0.2,0.3,0.4	CE	Using CE, mouthpiece exposures, observed similar PF impairment as a function of O_3 effective dose as Folinsbee et al (1978)

*R indicates rest; IE indicates intermittent exercise; CE indicates continuous exercise. See Appendix for identification of other abbreviations.

sures (Hackney et al, 1975; Hazucha et al, 1973; Silverman et al, 1976). More recently, DeLucia and Adams (1977) observed PF decrements and exercise ventilatory pattern alterations during continuous, heavy exercise ($\dot{V}_E$ increased 6 times rest) for 1 h while exposed to 0.30 ppm O_3, and at 0.15 ppm in two particularly sensitive subjects. The latter observations are of practical significance, in that many occupational or recreational pursuits entail sustained periods of moderate to heavy metabolic demand, thus increasing $\dot{V}_E$ and the total amount of O_3 inhaled in a given time at a particular ambient concentration. They are also of significance with respect to the existence of toxicity effects consequent to rather brief exposure at O_3 levels more routinely observed. For example, while peak 1 h concentrations exceeding 0.50 ppm have been recorded at certain locations in the Los Angeles Basin (Hackney et al, 1975; Mosher et al, 1970), the average daily maximum 1 h concentration during September ranges from 0.26 ppm in inland areas to less than 0.10 ppm at monitoring stations adjacent to the Pacific Ocean (Air Quality and Meteorology, 1979).

Hackney et al (1975) were apparently the first to advance a dose-response relationship with respect to an enhanced PF decrement as a function of O_3 concentration. However, Silverman et al (1976) emphasized that PF impairment was more closely related (as a second order polynomial function) to the effective dose of O_3, as calculated from the product of concentration, exposure time and $\dot{V}_E$. Recently, Folinsbee et al (1978) extended the effective dose concept in evaluating both rest and IE protocols of 2 h duration in filtered air (FA) and at three levels of O_3 concentration (0.10, 0.30, and 0.50 ppm). Further, their exercise workloads varied in intensity, entailing approximately 3, 5 and 7 times resting $\dot{V}_E$. Again, PF declined as a second order polynomial function of the effective dose of O_3. Further, we (Adams et al, 1981) have recently observed similar PF impairment as a function of O_3 effective dose in young adult male subjects exercising continuously for 30-80 min in FA and at 0.2, 0.3 and 0.4 ppm O_3.

One recurring question of significance is the validity of comparison of O_3 toxicity consequent to chamber exposures at rest or with light IE to the CE mode with obligatory oral inhalation employed in our laboratory. Recently we (Adams et al, 1981) observed that the percent $FEV_{1.0}$ decrement as a function of O_3 effective dose, at least within the range of 0 to 1,200 ppm·ℓ, identifies the degree of O_3 toxicity as approximately equal for CE and IE exposures. It

also suggests that the obligatory shift from nasal breathing at rest, in light IE and recovery, to primarily oral breathing at heavier workloads noted by Folinsbee et al (1978), does not substantially affect O_3 toxicity in humans within $\dot{V}_E$ ranging from 10 to 70 $\ell \cdot min^{-1}$. Previous work with anaesthesized dogs (Yokoyama & Frank, 1972) indicates that O_3 uptake is higher when administered orally than nasally, especially at flow rates typical of resting $\dot{V}_E$ (i.e., the nasal passages are less effective O_3 "scrubbers" at higher flow rates typical of exercise). Thus, it appears that the mouthpiece obligatory oral inhalation method used in combination with the CE mode can be used interchangeably with the IE chamber method in the study of O_3 toxicity, although definitive comparison using the same subjects exposed in the same laboratory remains to be done.

Although the O_3 effective dose predicts more accurately the degree of PF impairment than does O_3 concentration alone, the latter has consistently been shown by multiple regression analysis to be the most influential of the three effective dose components (Adams et al, 1981; Folinsbee et al, 1978; Silverman et al, 1976). That is, as first noted by Silverman et al (1976), for any given effective dose, exposure to a high concentration for a short period has more effect than a longer exposure at a lower concentration. This would imply that there is not only a threshold effective dose (as denoted by the consistently observed second order relationship to PF impairment), but also a threshold effective concentration. The latter is of significance since photochemical air pollution occurs widely and because O_3 concentration has been correlated with hospital admissions for respiratory disease (Paproski & Walker, 1974). Governmental agencies have attempted to set appropriate standards of air quality, but unfortunately, there are only limited data relating a given O_3 concentration for short-term exposures to PF decrement during exercise when the total amount of O_3 inhaled in a given time is dependent both on the ambient concentration and the increased ventilatory demand characteristic of enhanced metabolic demand. Recently, however, significant advances have been made, in that Folinsbee et al (1978) observed that the O_3 concentration at which no PF impairment occurred, varied according to the level of activity. That is, in 2-h exposures, when subjects remained at rest, a PF impairment effect occurred only at 0.50 ppm. At the highest IE workload, no PF effect was observed at 0.10 ppm, while at 0.30 ppm, a moderate IE workload elicited an effect. Working independently on a similar attempt to identify a threshold O_3

concentration using a continuous exercise mode (Adams et al, 1981) we observed that for eight trained adult males, ages 21-45, there was no significant PF decrement consequent to 75 min exposure at 0.20 ppm O_3 when exercise $\dot{V}_E$ was maintained at 63 liters per min. On the other hand, after 60 min exercise at the same workload while exposed to 0.30 ppm, there was significant impairment in several PF parameters. Furthermore, even greater toxic effects were noted after only 30 min exposure to 0.40. Hence, it would appear that the threshold O_3 concentration for subjects exercising at moderate intensity during short-term exposures (< 2-h), lies between 0.20 and 0.30 ppm, although DeLucia & Adams (1977) observed PF impairment in two particularly sensitive subjects exposed to 0.15 ppm while exercising continuously for 1-h at a mean $\dot{V}_E$ of 65 ℓ/min.

Folinsbee et al (1978) have astutely noted that present data identifying the degree of PF impairment with O_3 exposure have been largely limited to young adult male, non-smokers. Thus, there would appear to be a clear need for examining the O_3 toxicity effect amongst other, presumably more sensitive sub-populations, e.g., females, children, elderly subjects, and patients with cardiopulmonary dysfunction. The current CARB advisory chart for O_3 stipulates that at concentrations between 0.10 and 0.20 ppm, "persons with existing heart or respiratory ailments should reduce physical exertion and outdoor activity." Further, at ambient O_3 concentrations between 0.20 and 0.35 ppm, it is advised that the "elderly and persons with existing heart or lung disease should stay indoors and reduce physical activity," although these "cautionary statements" are not based on any known objective data. Since an estimated 29 million Americans have cardiovascular diseases (Marx & Kolata, 1978), elucidating the degree and type of impairment caused during physical activity in photochemical smog is of vital concern to the public and the medical community. This has especial significance, in that therapeutic physical activity programs are commonly prescribed for cardiovascular patients (Haskell, 1979). Further, one of us (Superko) has frequent experience with patients inquiring whether they should modify their physical activity on days of moderate or severe air pollution, and if so, how much. Hence, it seems essential to develop data that will permit CARB and physicians to advise heart disease patients accurately about activity levels during days of significant O_3 pollution levels.

At present, clinical investigations of patients subjected to O_3 exposures

have involved rather nonspecific pulmonary disease groups. Hackney et al (1977) studied six subjects with "respiratory hyperactivity" who lived in the Los Angeles area, but no PF test patient definition was given. Hackney et al (1975) studied a group of patients with a history of hyperactive airways, but again, no documentation and definition of pulmonary dysfunction was given. Linn et al (1978) studied physician diagnosed asthmatics and did not find significant changes in PF after exposure at rest to 0.2 ppm O_3 for 2 hours. All of these investigations employed loosely defined patient groups and none involved subjects with coronary artery disease (CAD), or with well defined chronic obstructive lung disease (COLD). Reid et al (1964) estimated that between 8-17% of the American population suffer from COLD at some time. It seems reasonable to assume that heart and lung patients may have a threshold O_3 toxicity effect that is lower than that for young, clinically normal adult males. However, the degree of difference may be related to the particular disease process, as the principal area of short-term acute O_3 exposure impact is centered in the lungs and respiratory tract.

Cardiovascular impairment has not been demonstrated, although Buckley et al (1975) have reported evidence of O_3's penetrating the alveolar membrane and interacting with blood components, increasing both red blood cell fragility and specific enzyme activities. Further, symptom limited CAD patients have well defined symptom thresholds, as indicated by the triple, or more practically, the double product of heart rate (HR) and systolic blood pressure (SBP) (Robinson, 1967). This symptom threshold may be altered by O_3 effect on HR (Folinsbee et al, 1975), SBP, pulmonary edema, increased respiratory rate (F_R) and bronchoconstriction, which would increase the work of breathing and possibly lower the symptom threshold (Golden et al, 1978; Holtzman et al, 1979). The mechanism is important to elucidate, as it may be affected by cardiogenic medicines (Watanabe et al, 1973). Further, alteration in any of the above parameters in CAD patients has the potential for increasing cardiovascular stress and would be sufficient cause to alter the presumed therapeutic exercise prescription on days of significant oxidant pollution.

In a similar manner, exercise limitations can be seen in patients with COLD based on their $\dot{V}_E$ and predicted MVV (Robertson et al, 1979). Reflex bronchoconstriction (Folinsbee et al, 1975), decreased inspiratory capacity (Folinsbee et al, 1978), increased F_R (DeLucia & Adams, 1977) and decreased

diffusion capacity (Young et al, 1964) could potentially alter these patients' O_3 threshold effect during physical activity. Further, especially where activity is concerned, most of these patients will have a diminished functional reserve capacity due to aging, per se (Åstrand & Rodahl, 1977; Raven, 1979), as well as that effected by the disease itself.

Thus, although there is good reason to suspect that certain patients with heart and lung disease (especially those who are middle-age and older) will have a lower threshold for an O_3 toxicity effect, the paucity of quantitative data supporting the current CARB cautionary statements can either place undue hardship on some heart and lung disease patients by unnecessarily restricting their activity, or alternatively, may underestimate the health hazards imposed. One important patient group to study is that afflicted with angina pectoris, many of whom are advised to undertake exercise training for improvement of their physical activity tolerance and functional reserve capacity (Haskell, 1979). While there is clear evidence that there is a substantial decrease in time to onset of pain during treadmill exercise and the level of expired carbon monoxide (CO) in the lungs of angina patients exposed to freeway air, as well as laboratory induced increased COHb levels (Goldsmith & Aronow, 1975), no such direct implications for O_3 effect on angina patients has been reported.

The present study was designed to obtain quantitative data relative to the difference in O_3 toxicity, if any, in a group of angina patients undergoing prescribed exercise training, compared to young adults and middle-age clinically normal subjects, also regularly engaged in aerobic training. More specifically, the patients' response during O_3 exposures while engaged in their normal exercise training regimen was ascertained and compared to that of two clinically normal groups exercising at similar $\dot{V}_E$ and O_3 concentrations.

Methodology

Subject description and baseline measurements. The patient group consisted of six male volunteers with documented coronary artery disease (CAD). Their basic anthropometry, functional aerobic capacity, and pulmonary function data are given in Table 2. Although several had previously smoked cigarettes, none had smoked for within two years prior to the study. The diagnosis of CAD was made by a clinical history of angina pectoris associated with either a previous confirmed myocardial infarction, an ischemic graded exercise test, or coronary angiography. Each patient had a well defined symptomatic angina pectoris

TABLE 2. Anthropometry, Functional Aerobic Capacity, and Pulmonary Function of the Angina Patients.

Subj	Age, yr	Ht. cm	Wt, kg	Fat, % BW	$\dot{V}_{O_2}$ max, $\ell \cdot min^{-1}$	RV, ℓ	FVC, ℓ	TLC, ℓ	$FEV_{1.0}$, $\ell \cdot sec^{-1}$	MMFR, $\ell \cdot sec^{-1}$	$FEV_{1.0}$/FVC, %
1	46	183	81	18.2	2.69	1.85	5.13	6.98	3.95	3.75	77.0
2	62	175	106	33.4	1.89	2.62	2.84	5.46	1.89	1.44	66.5
3	61	173	88	30.6	1.70	2.62	3.81	6.43	2.10	1.00	55.1
4	64	178	78	31.0	1.51	1.72	4.15	5.87	3.40	3.75	81.9
5	59	173	66	24.7	2.23	1.60	4.16	5.76	3.20	2.99	76.9
6	64	177	83	23.5	1.90	1.94	4.27	6.21	2.95	1.79	69.1
$\bar{x}$	59.3	176.5	83.7	26.9	2.04	2.06	4.06	6.12	2.92	2.44	71.1
SD	6.8	3.8	13.2	5.7	0.60	0.45	0.74	0.60	0.79	1.19	9.7

threshold as defined by the double product of HR and SBP (Clausen & Trap-Jensen, 1970) that was determined by previous graded exercise tests. Pulmonary function tests indicated that there was no significant restrictive or obstructive lung disease that would limit exercise training.

Prior to entrance into the study, the patient's informed consent and his private physician's consent were obtained. A complete medical history and physical exam with resting 12-lead electrocardiogram (ECG), PF tests, and a symptom limited maximum treadmill graded exercise test, were performed on each subject before acceptance into the study. Prior to each experimental protocol run, recent clinical history and a 12-lead ECG were reviewed. Contraindications that disallowed participation in the study are listed in Appendix A.

Each of the six patients studied were regular participants in the UC Davis Cardiopulmonary Rehabilitation Clinic. This physician supervised program entailed an individually prescribed, educationally oriented training session three days per week. Each session included a 10-min warm-up, 40-min of endurance activity at the individual training HR, and a 10-min cool-down period. Following each session was a 20-min lecture. All subjects had participated on a regular basis for at least three months and had achieved a training plateau. Training intensities were not modified significantly during the course of the experiment.

To attentuate habituation effects, all patients completed two orientation sessions in which PF was measured, followed by a 10-min warm-up walk, a 40-min training walk, and a 5-min cool-down walk, while breathing FA through a mouthpiece. Each of these sessions was concluded with a repeat of the PF tests.

Thirteen healthy males, ages 22-54, whose basic anthropometry, $\dot{V}_{O_2}$ max, and PF data are given in Tables 3 and 4, also served as subjects. Their PF was within clinically normal limits (Anderson et al, 1968; Petty, 1975), and none smoked except subject 5, age 51 years. Each was routinely engaged in an aerobic training program which was not modified significantly in intensity during the course of the experiment. Prior to O_3 exposures, these subjects first completed an orientation testing session, in which PF and basic anthropometry, including body composition via hydrostatic weighing, were measured. $\dot{V}_{O_2}$ max was determined via a graded bicycle ergometer test to voluntary exhaustion (Adams et al, 1981). To attenuate habituation effects, all subjects completed a total of 120 min bicycle ergometer riding at submaximal workloads, including

TABLE 3. Anthropometry, $\dot{V}_{O_2}$ max, and Pulmonary Function of the Middle-Age, Clinically Normal Subjects.

Subj	Age, yr	Ht. cm	Wt, kg	Fat, % BW	$\dot{V}_{O_2}$ max, $\ell \cdot min^{-1}$	RV, ℓ	FVC, ℓ	TLC, ℓ	$FEV_{1.0}$, $\ell \cdot sec^{-1}$	MMFR, $\ell \cdot sec^{-1}$	$FEV_{1.0}$/FVC, %
1	47	178	75.5	19.8	4.16	1.63	4.67	6.30	3.56	3.40	76.3
2	50	173	64.9	4.7	3.21	2.28	5.21	7.49	3.70	3.95	71.2
3	45	182	68.1	17.3	3.79	2.13	5.25	7.38	4.08	4.49	77.9
4	46	178	79.4	22.7	3.35	2.08	5.00	7.08	4.19	5.63	83.8
5	51	183	72.3	12.5	2.87	2.13	4.93	7.06	3.50	2.44	71.0
6	54	163	63.5	7.4	3.06	1.53	4.49	6.02	3.52	4.12	78.4
7	48	185	85.0	13.5	4.67	1.70	5.65	7.35	4.25	4.44	75.2
$\bar{x}$	48.3	176.5	72.7	14.0	3.59	1.93	5.03	6.95	3.83	4.07	76.3
SD	3.3	8.0	8.6	6.2	0.65	0.30	0.39	0.57	0.33	0.99	4.4

TABLE 4. Anthropometry, $\dot{V}O_2$ max, and Pulmonary Function of the Young Adult, Clinically Normal Subjects.

Subj	Age, yr	Ht. cm	Wt, kg	Fat, % BW	$\dot{V}O_2$ max, $\ell \cdot min^{-1}$	RV, ℓ	FVC, ℓ	TLC, ℓ	$FEV_{1.0}$, $\ell \cdot sec^{-1}$	MMFR, $\ell \cdot sec^{-1}$	$FEV_{1.0}$/FVC, %
1	27	183	62.0	4.4	4.15	1.91	6.63	8.54	5.40	5.51	81.4
2	33	189	90.3	12.3	4.15	1.66	5.76	7.42	4.71	4.66	81.8
3	25	187	81.7	6.4	4.35	1.57	6.41	7.98	5.66	6.65	88.3
4	25	182	63.1	5.6	3.34	1.09	6.28	7.37	5.17	5.92	82.3
5	22	180	74.9	10.7	4.47	1.13	5.92	7.05	4.61	4.11	77.9
6	22	172	72.0	8.8	3.69	1.49	5.75	7.24	4.33	3.73	75.3
$\bar{x}$	25.6	182.2	74.0	8.0	4.02	1.48	6.13	7.60	4.98	5.10	81.2
SD	3.7	6.0	10.9	3.1	0.43	0.32	0.37	0.56	0.51	1.12	4.4

one 30 min session while breathing FA through the mouthpiece delivery system employed in the experimental procotols.

Experimental design. Following an initial 5 min seated at rest, each patient exercised on the treadmill on three separate occasions according to a protocol designed to elicit his usual training HR (after 15-20 min gentle warm-up walking), which was then maintained for a period of 25-30 min, i.e., total of 40 min. The range of warm-up speeds and that maintained for the final 25-30 min of exercise for each patient is given in Table 5. Ideally, the warm-up period was designed to bring the patient gradually up to his normal training workload, i.e., just below his 1+ angina, or ischemic ECG changes as defined by 1 mm of ST- depression at 80 msec past the J point.

During the three protocols, each patient breathed either FA, or O_3 at concentrations of 0.2 or 0.3 ppm, respectively, throughout. The order of exposure was randomized, with a minimum of three days intervening between treatments. Subjects, and the physician, who made the decision regarding any premature discontinuation of the test, were not informed whether O_3 was being administered. Upon completion of the exercise protocol, each patient continued walking at a reduced speed ("cool-down") for 5 min while breathing room air.

All experimental treatments were completed in a room, 3.0 m x 2.4 m x 3.7 m, in which dry bulb temperature and relative humidity were maintained within 22-25° C and 25-50%, respectively. To facilitate convective and evaporative cooling, a constant airflow of 2.5 m/sec was directed at the subject's anterior surface via an industrial grade floor fan.

The above design permitted each patient to serve as his own control in determining if the O_3 exposures elicited any significant changes in the physiological parameters monitored when compared to the FA exposure. Additionally, data from exposures of the clinically normal young adult and middle-age groups at similar $\dot{V}_E$ were available. That is, each of these subjects completed 1 h of continuous bicycle ergometer exercise at a mean $\dot{V}_E$ of approximately 35 ℓ/min while exposed to either FA, or to 0.2 ppm or 0.3 ppm O_3. Again, the order of experimental protocols was randomized for each subject, with a minimum of 3 days intervening between treatments. Subjects were not informed whether they were receiving O_3, and in order to mask olfactory detection, 0.3 ppm O_3 was generated for 1-2 min just prior to initiating each experimental protocol.

Pulmonary function measurements. A short battery of PF tests was adminis-

TABLE 5. Treadmill Speed and Grade for Patient's Exercise protocols*

	Time Period							
Subj	1-5 min	6-8 min	8-10 min	10-12 min	12-15 min	15-18 min	18-20 min	20-45 min
1	1.7-2.0	2.0-2.4	2.4-2.6	2.6-2.8	2.8-3.0	3.0-3.2	3.2	3.2
2	1.7-2.0	2.0-2.2	2.2	2.2-2.4	2.4-2.6	2.6	2.6-2.8	2.8
3	1.7-2.0	2.0-2.4	2.4-2.8	2.8-3.2	3.2-3.4	3.4-3.6	3.6	3.6
4	1.7-2.0	3.0-3.4	3.4-3.8	3.8-4.2	4.2-4.4	4.4, + 2%	4.4,+ 5%	4.4,+ 5%
5	1.7-2.0	3.0-3.4	3.4-3.6	3.6	3.6	3.6-4.0	4.0	4.0,+ 2%
6	1.7-2.0	2.4-2.8	2.8	2.8-3.2	3.2-3.4	3.4-3.6	3.6	3.6

*Treadmill speed in miles per hour; grade in percent

tered immediately prior to each experimental protocol and repeated within 10 min following exercise. Residual volume was determined utilizing a modified Collins 9-liter spirometer by the O_2 rebreathing method (Wilmore, 1969), with initial and equilibrium N_2 readings taken on an Ohio 700 digital N_2 analyzer. At least two determinations each of passive vital capacity (PVC) and forced vital capacity (FVC) were made on a Collins 10-liter Stead-Wells Spirometer assembly of the Basic Clinical Spirometer Module, No. 03000, with simultaneous measurement of flow volume loops on a Hewlett-Packard x-y recorder, No. 7045A. Forced expiratory volume at 1_s ($FEV_{1.0}$) and mid-maximum expiratory flow rate (MMFR) were calculated from the spirometric tracings. PF determinations for the clinically normal subjects were obtained pre- and postexposure as for the patients, except that PVC, FVC, $FEV_{1.0}$ and MMFR were determined from spirometric tracings on the Collins 9-liter spirometer.

O_3 administration and monitoring. A schematic diagram of the blow-by exposure system employed is depicted in Fig. 1. Air filtered through a Mine Safety Appliances C-B-R filter was drawn through a Rotron CHE-1 pump at a flow of approximately 600 ℓ/min. From the exhaust port of the Rotron pump, the air was pumped into a 0.91-m Teflon-lined aluminum tube, and underwent turbulent mixing at the tangential junction of 5.1-cm diameter aluminum tubing into the major 15.2-cm diameter aluminum tube. Such mixing was necessary to obtain O_3 dilution to the low levels used in this experiment, since concentrated O_3 created from silent arc discharge (Sander Ozonizer, type II) of compressed gaseous O_2 was introduced proximal to the turbulent mix. At the distal end of the 0.91-m tube, O_3-containing air was directed from an exhaust port to a Teflon-coated Hans Rudolph respiratory valve, via a 0.91-m length of fluoroflex Teflon tubing. Subatmospheric pressures generated during the inspiratory phase of breathing resulted in the flow of the O_3-air mixture into the respiratory valve. Positive expiratory pressures shut the fenestrations on the diaphragm on the inspiratory side of the valve, allowing flow of expired air unidirectionally into a 5 ℓ stainless steel mixing and sampling chamber to a Parkinson-Cowan (PC) gas meter, type CD-4. Expired air was thence routed into the distal portion of the mixing tube and, along with the pumped air mixture not inspired by the subject, exhausted via a 10-cm ID Flexaust CWC neoprene hose to the laboratory outside air ventilation outlet. Airflow resistance encountered in the breathing circuit, although not measured, was not significant at the flow

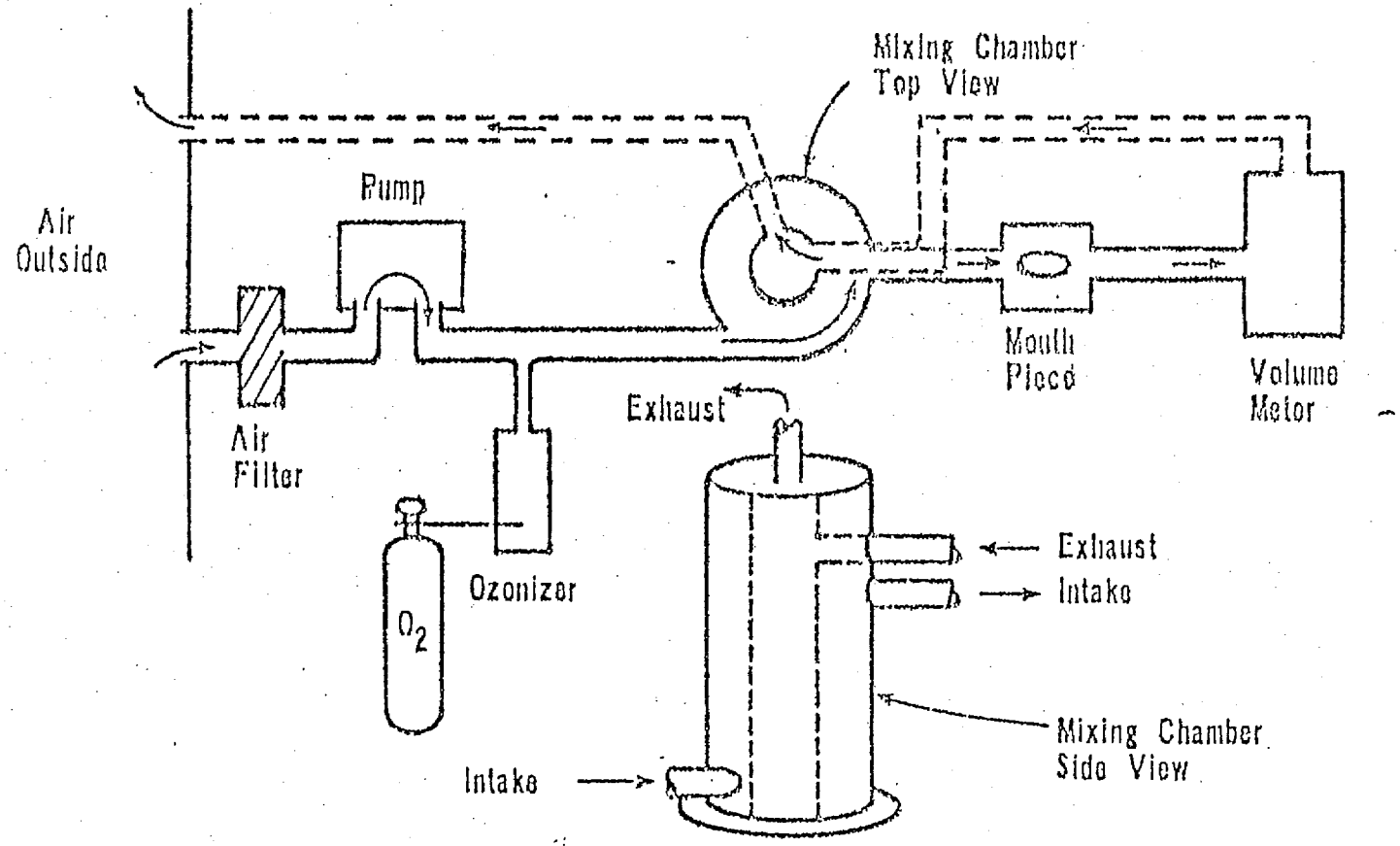

FIGURE 1 SCHEMATIC DIAGRAM OF THE O_3 EXPOSURE SYSTEM EMPLOYED.

rates incurred by the subjects.

O_3 concentration was routinely determined by sampled air from the inspiratory side of the Hans-Rudolph valve, drawn through a 0.64-cm Teflon tube connected to a Dasibi O_3 meter. The digital reading of O_3 concentration in ppm was compared on several occasions to that determined by the UV absorption photometric method (DeMore et al, 1976) at the University of California, Davis, Primate Center. The O_3 containing air from the sampling point on the inspired side of the respiratory valve to the subject was not likely reduced in concentration by passage through the respiratory valve diaphragms which, although of silicon-rubber, did not show typical deterioration indicative of reactivity with the oxidant.

Exercise measurements. Following an initial 5 min of seated rest and another 5 min of preliminary warmup at 1.7-2.0 mph at the particular FA or O_3 exposure, the patient's physiological responses were monitored each minute. Respiratory metabolism was determined via expired air volume (PC meter) and percent O_2 and CO_2 by a semiautomated sampling method incorporating a manually rotated three-way valve sampling system (Wilmore & Costill, 1974), and utilizing Applied Electrochemistry S-3A and Beckman LB-2 gas analyzers. Expired air volumes and respiratory metabolism values were calculated according to procedures outlined by Consolazio et al (1963). Respiratory frequency (F_R) was determined via a temperature probe inserted into the respiratory valve, from which a signal was amplified in a Yellow Springs Instrument scanning telethermometer and recorded on a Hewlett-Packard 680 M stripchart recorder. Heart rate was determined from a 12-lead ECG placement which was connected to an oscilloscope and monitored continuously by the attending physician for ST-segment changes and arrythmias.

The ECG's were analyzed in a randomized manner by the physician (see Appendix B for list of factors analyzed). A full 12-lead ECG was obtained in the sitting and standing position prior to treadmill walking and at 5 min intervals throughout the run. Twelve leads were also obtained at the conclusion of the run, 1 min into recovery, and at any time angina was noted. R wave amplitude was measured in V5 as an average of 6 consecutive beats. ST depression was defined as 1 mm of depression from the baseline flat, downsloping or upsloping at 80 msec past the J point. Arrythmias were noted at time of onset and time when the frequency exceeded 6 per minute.

Systolic blood pressure was assessed via the auscultatory method by the same technician throughout, and combined with HR in the calculation of the rate pressure product (RPP), an index of myocardial O_2 consumption. Additionally, subjective symptoms were monitored via use of relative perceived exertion (Appendix C), dyspnea on exertion (Appendix D), and angina pain (Appendix E) scales.

Several criteria for cessation of the testing protocol were utilized, including the appearance of 3+ angina pain (AP), or if 2+ AP persisted for longer than 5 min. The test protocol was also broken if ischemic ECG changes occurred or arrythmias, including unifocal or multifocal premature ventricular contractions, occurred at greater than 10 per min, or if ventricular tachycardia or fibrillation occurred. Exercise induced hypotension with a systolic drop of >15 mmHg was also a reason for protocol cessation. In fact, only one testing protocol, an exposure to 0.3 ppm O_3 for patient 2, resulted in the occurrence of any of the specified criteria (in this case, 3+ AP at 14 min). All other protocols were consistently maintained for each patient.

Immediately following the postexposure PF tests, the patient completed a subjective symptoms questionnaire, indicating whether they had received O_3 and, if so, at what concentration. The patient was then cleared for release by the physician.

The clinically normal subjects completed 60 min of continuous bicycle ergometer exercise at workloads selected to elicit a steady-state $\dot{V}_E$ of approximately 35 $\ell \cdot min^{-1}$. Exercise data acquisition procedures employed with the young adult subjects incorporated an IMSAI 8080 mini-computer which was programmed to print out running one minute average values for respiratory metabolism variables every 15 sec. Instruments interfaced to the mini-computer included a Beckman LB-2 CO_2 analyzer, an Applied Electrochemistry S-3A O_2 analyzer, and the PC gas meter with linear potentiometer attachment and a thermistor located immediately adjacent to its exhaust port. Minor gas analyzer drifts, assuming linearity with time, were corrected by introducing a standard gas sample periodically. Additionally, HR was determined from the elapsed time between 5 consecutive R waves read from an ECG tracing taken every tenth minute. Respiratory frequency (F_R) was determined as described above for the patients.

Respiratory metabolism and ventilatory pattern were measured in the clini-

cally normal middle-age subjects according to methods described for the patients. Heart rate was determined as for the young adult subjects. Respiratory metabolism measurements were taken every tenth minute and ventilatory pattern measurements every fifth minute, as the previous computer data acquisition study had indicated these intervals satisfactory for detecting any significant change in response in clinically normal subjects.

Statistical procedures. Duplicate PF measurements were corrected to BTPS and averaged for pre- and postexposure. The postexposure value for each parameter was subtracted from the preexposure value to obtain differences representing the treatment effect for each protocol. Values for $\dot{V}_{O_2}$ max, $\dot{V}_E$, F_R, and HR obtained during the last minute of exercise were subtracted from those obtained in the 10th min of exercise for the clinically normal groups and from the values obtained in the 20th min of exercise (5 min after the last warmup workload increment) for the patients.

To determine if the O_3 exposures resulted in statistically significant alterations in physiological response from that for the FA control exposure, a one-way ANOVA was applied for each group. No attempt was made to compare the difference in treatment responses between groups, since the method of ergometry and exposure times differed for the patients compared to the two clinically normal groups. Statistical significance between treatment conditions within each subject group was determined from the F ratio derived by dividing treatment mean square by error mean square, with two numerator and 12 (patients), 15 (young adult normals), and 18 (middle-age normals) denominator degrees of freedom. In all analyses, the significance level was set at $p \leq .05$.

RESULTS

Individual patient and group mean PF responses, together with F ratios from one-way ANOVA for the three exposures, are given in Table 6. None of the F ratios reached significance at the .05 level of probability. The mean PF responses and F ratios for similar FA and O_3 exposures for the middle-age and young adult, clinically normal, groups are given in Table 7. Again, no significant differences in PF response were observed.

Table 8 contains individual patient and group mean exercise ventilatory pattern responses, as well as F ratios for the three exposures.* Although

---

* It should be noted that although all exercise data are reported for angina patient No. 2 for the FA and 0.2 ppm O_3 exposures, none are given for the 0.3 ppm O_3 exposure because of premature protocol cessation at 14 min due to 3+ angina pain (AP). The significance of this occurrence will be treated in the discussion.

TABLE 6. Pulmonary Function Response for the Angina Patients

Subj	RV, ℓ Pre/Post	FVC, ℓ Pre/Post	$FEV_{1.0}$, $\ell \cdot sec^{-1}$ Pre/Post	MMFR, $\ell \cdot sec^{-1}$ Pre/Post
Filtered Air, 40 min, 35.7 $\ell \cdot min^{-1}$ $\dot{V}_E$				
1	1.85/2.03	5.13/5.24	3.95/4.22	3.75/3.82
2	2.62/2.67	2.84/3.39	1.89/2.12	1.44/1.74
3	2.62/2.35	3.81/3.52	2.10/1.99	1.00/1.08
4	1.72/1.66	4.15/4.11	3.40/3.33	3.75/3.38
5	1.60/1.59	4.16/4.50	3.20/3.40	2.99/3.11
6	1.94/1.97	4.27/4.31	2.95/3.08	1.79/2.13
$\bar{x}$	2.06/2.05	4.06/4.18	2.92/3.02	2.44/2.54
SD	0.45/0.41	0.74/0.68	0.79/0.84	1.19/1.06
Δ	-0.49%	+3.0%	+3.4%	+3.9%
0.2 ppm O_3, 40 min, 34.6 $\ell \cdot min^{-1}$ $\dot{V}_E$				
1	2.07/1.85	5.36/5.33	4.17/4.27	4.00/4.04
2	2.65/2.72	3.17/2.90	2.00/1.82	1.51/1.22
3	2.39/2.64	3.73/3.65	2.06/2.11	1.05/1.00
4	1.69/1.66	4.13/4.36	3.41/3.55	3.48/3.94
5	1.57/1.59	4.24/4.40	3.00/3.37	3.18/3.37
6	2.10/2.16	4.19/4.04	3.02/2.85	2.29/2.06
$\bar{x}$	2.08/2.10	4.14/4.11	2.94/3.00	2.59/2.60
SD	0.41/0.49	0.72/0.81	0.82/0.92	1.16/1.35
Δ	+0.96%	-0.72%	+2.0%	+0.38%
0.3 ppm O_3, 40 min, 35.7 $\ell \cdot min^{-1}$ $\dot{V}_E$				
1	1.88/2.02	5.46/5.37	4.18/4.05	3.81/3.56
2	2.40/2.60	3.29/3.17	2.22/2.17	1.97/2.20
3	2.38/2.63	3.42/3.53	2.08/1.88	1.18/1.04
4	1.63/1.65	4.28/4.38	3.46/3.42	3.72/3.52
5	1.57/1.74	4.36/4.25	3.32/3.18	3.26/2.95
6	2.12/2.16	4.18/4.28	2.97/3.26	2.10/2.32
$\bar{x}$	2.00/2.13	4.17/4.16	3.04/2.99	2.67/2.59
SD	0.36/0.42	0.78/0.76	0.79/0.81	1.08/0.95
Δ	+6.5%	-0.24%	-1.64%	-3.0%
F	2.03	0.67	1.09	0.13

TABLE 7. Mean Pulmonary Function Responses for the Clinically Normal Groups

	RV, ℓ	FVC, ℓ	$FEV_{1.0}$, $\ell \cdot sec^{-1}$	MMFR, $\ell \cdot sec^{-1}$
	Pre/Post	Pre/Post	Pre/Post	Pre/Post
Middle-Age Group				
Filtered Air, 60 min, 44.8 $\ell \cdot min^{-1}$ $\dot{V}_E$				
x	1.89/1.86	5.04/5.13	3.88/3.94	4.34/4.23
SD	0.31/0.29	0.42/0.44	0.33/0.34	0.75/0.86
Δ	-1.6%	+1.8%	+1.5%	-2.5%
0.2 ppm O_3, 60 min, 34.2 $\ell \cdot min^{-1}$ $\dot{V}_E$				
x	1.83/1.84	5.06/5.05	3.92/3.95	4.36/4.34
SD	0.27/0.22	0.52/0.45	0.41/0.41	0.62/0.74
Δ	+0.5%	-0.2%	+0.8%	-0.5%
0.3 ppm O_3, 60 min, 33.1 $\ell \cdot min^{-1}$ $\dot{V}_E$				
x	1.81/1.81	5.01/5.08	3.92/3.88	4.39/4.36
SD	0.31/0.22	0.47/0.50	0.52/0.51	1.03/0.86
Δ	0%	+1.4%	-1.0%	-0.7%
F	0.08	2.24	0.30	3.85
Young Adult Group				
Filtered Air, 80 min, 37.3 $\ell \cdot min^{-1}$ $\dot{V}_E$				
x	1.56/1.60	6.06/6.20	4.97/5.06	5.26/5.24
SD	0.37/0.38	0.35/0.27	0.44/0.46	1.33/1.15
Δ	+2.6%	+2.3%	+1.8%	-0.4%
0.2 ppm O_3, 60 min, 34.7 $\ell \cdot min^{-1}$ $\dot{V}_E$				
x	1.53/1.45	6.10/6.13	5.01/5.02	5.22/5.42
SD	0.44/0.40	0.31/0.45	0.43/0.54	1.02/1.44
Δ	-5.2%	-0.5%	+0.2%	+3.8%
0.3 ppm O_3, 60 min, 35.8 $\ell \cdot min^{-1}$ $\dot{V}_E$				
x	1.38/1.44	6.24/6.15	5.01/4.92	5.24/5.06
SD	0.32/0.33	0.35/0.39	0.49/0.58	1.04/1.37
Δ	+4.3%	-1.4%	-1.8%	-3.4%
F	1.92	2.60	1.14	0.42

TABLE 8. Exercise Ventilatory Pattern Response for the Angina Patients

Exercise Ventilation ($\dot{V}_E$), $\ell \cdot min^{-1}$, BTPS

	FA		0.2 ppm		0.3 ppm	
Subj	20 min	40 min	20 min	40 min	20 min	40 min
1	57.7	56.2	54.9	50.6	51.5	53.0
2	(28.4)	(28.6)	(28.6)	(25.1)		
3	37.9	45.6	40.7	50.0	43.2	50.6
4	21.2	27.4	22.1	22.3	21.0	21.4
5	42.2	43.4	40.4	43.1	37.7	43.6
6	41.0	43.6	43.4	43.1	40.9	43.5
x	40.0	43.2	40.3	41.8	38.9	42.5
SD	13.0	10.3	11.8	11.5	11.2	12.5
Δ		+ 8.0%		+ 3.7%		+ 4.1%

F = 0.39

Respiratory frequency, (f_R), breaths·min^{-1}

	FA		0.2 ppm		0.3 ppm	
Subj	20 min	40 min	20 min	40 min	20 min	40 min
1	36	36	35	37	29	39
2	(28)	(30)	(29)	(29)		
3	28	32	27	36	29	35
4	22	30	22	22	22	23
5	27	27	25	27	26	27
6	21	24	22	24	23	24
x	26.8	29.8	26.2	29.2	25.8	29.6
SD	6.0	4.6	5.4	6.9	3.3	
Δ		+11.2%		+11.5%		+12.8%

F = 0.08

there was a tendency for increased values at the end of exercise, this was consistent in all exposures and thus, as indicated by the F ratios, no significant treatment effect was noted. The patient's HR and $\dot{V}_{O_2}$ response data and F ratios are shown in Table 9. Again, none of the F values reached statistical significance. The mean ventilatory pattern, HR and $\dot{V}_{O_2}$ responses and F ratios for the young adult and middle-age normal groups are given in Table 10. None of the F values approached statistical significance.

Table 11 shows the individual patient and group mean responses for SBP and RPP for each of the exposures. Neither of the F values were significant. Other individual patient data, including onset time for 1+ AP, $\geq$ 1 mm ST-segment depression and 1+ dyspnea on exertion (DOE), together with the calculated RPP at these occurrences are given in Table 12. Since the patients did not always evidence symptoms, there were numerous instances of missing data and thus, no statistical analyses were performed. However, careful inspection of the data revealed no systematic trends due to an O_3 treatment effect. The difference in the patients' rating of perceived exertion (RPE) at 20 min and 40 min did not demonstrate a statistically significant treatment effect (F= 1.56).

The mean $FEV_{1.0}$ response, calculated as a 2d order polynomial function of O_3 effective dose (the product of concentration, $\dot{V}_E$, and exposure time) for young adult males exercising continuously at both a moderate and heavy workload, while exposed to O_3 concentrations of 0.2, 0.3, and 0.4 ppm for 30-80 min (Adams et al, 1981), is depicted as a solid line in Fig. 2. The patients' mean values for each protocol are shown as open circles, while those for the clinically normal middle-age males are represented by darkened circles. It is apparent that neither group exhibited a consistent difference from the young adult's regression line.

DISCUSSION

Ozone, a principal constituent of photochemical smog, has been implicated as the primary agent effecting increased hospital admissions amongst those afflicted with respiratory disease (Paproski & Walker, 1974), as well as reduced athletic performance (Wayne et al, 1967). In acute laboratory chamber exposures ($\leq$2 h), numerous investigators have demonstrated that light exercise, usually performed for 15 min, with 15 min rest, intermittently (IE), intensifies PF impairment at a particular O_3 concentration, even as low as 0.37 ppm (Bates et al, 1972; Folinsbee et al, 1975; Hackney et al, 1975;

TABLE 9. Heart Rate and Oxygen Uptake Response for Angina Patients

Heart Rate (HR), beats·min^{-1}

	FA		0.2 ppm		0.3 ppm	
Subj	20 min	40 min	20 min	40 min	20 min	40 min
1	122	132	129	130	128	129
2	(90)	(92)	(85)	(83)		
3	84	90	80	94	87	98
4	69	73	69	69	69	71
5	102	102	96	98	96	99
6	82	86	76	83	82	87
x	91.8	96.6	90.0	94.8	92.4	96.8
SD	20.6	22.3	23.9	22.7	22.2	21.2
Δ		5.2%		+5.3%		+4.8%

F = 0.01

Oxygen Uptake ($\dot{V}_{O_2}$), ℓ·min^{-1}

	FA		0.2 ppm		0.3 ppm	
Subj	20 min	40 min	20 min	40 min	20 min	40 min
1	1.71	1.70	1.71	1.59	1.75	1.64
2	(0.99)	(0.98)	(0.88)	(0.78)		
3	1.10	1.18	1.09	1.20	1.10	1.20
4	0.72	0.74	0.71	0.71	0.59	0.64
5	1.30	1.31	1.30	1.37	1.28	1.31
6	1.21	1.27	1.21	1.20	1.19	1.26
x	1.21	1.24	1.20	1.21	1.18	1.21
SD	0.36	0.34	0.36	0.32	0.41	0.36
Δ		+2.5%		+0.8%		+2.5%

F= 0.13

TABLE 10. Ventilatory Pattern, Heart Rate and Oxygen Uptake Responses for the Clinically Normal Groups

	$\dot{V}_E$, $\ell \cdot min^{-1}$, BTPS		F_R, breaths$\cdot min^{-1}$		HR, beats$\cdot min^{-1}$		$\dot{V}_{O_2}$, $\ell \cdot min^{-1}$	
	10 min	60 min	10 min	60 min	10 min	60 min	10 min	60 min
Middle-Age Group								
FA, 60 min, 44.8 $\ell \cdot min^{-1}$ $\dot{V}_E$								
$\bar{x}$	44.9	44.6	19.2	23.6	111.3	116.5	1.74	1.75
SD	2.2	4.1	3.9	3.4	13.1	13.8	0.16	0.09
Δ		-0.7%		+22.9%		+4.7%		+0.6%
0.2 ppm O_3, 60 min 34.2 $\ell \cdot min^{-1}$ $\dot{V}_E$								
$\bar{x}$	35.7	32.6	19.5	18.7	96.3	99.0	1.35	1.33
SD	2.3	1.8	3.6	3.9	14.5	12.7	0.18	0.17
Δ		-8.7%		-4.1%		+2.8%		-1.5%
0.3 ppm O_3, 60 min, 33.1 $\ell \cdot min^{-1}$ $\dot{V}_E$								
$\bar{x}$	33.6	32.7	18.3	20.3	96.8	96.0	1.31	1.33
SD	1.1	3.3	4.8	3.9	10.8	10.5	0.17	0.18
Δ		-2.7%		+10.9%		-0.8%		+1.5%
F		0.80		0.46		1.23		0.06
Young Adult Group								
FA, 80 min, 37.3 $\ell \cdot min^{-1}$ $\dot{V}_E$								
$\bar{x}$	36.8	37.8	24.8	25.9	105.2	111.5	1.40	1.45
SD	2.2	2.9	2.8	3.7	8.8	12.6	0.19	0.24
Δ		+2.7%		+4.4%		+6.0%		+3.6%
0.2 ppm O_3, 60 min, 34.7 $\ell \cdot min^{-1}$ $\dot{V}_E$								
$\bar{x}$	33.7	35.7	22.1	22.1	102.8	101.7	1.31	1.38
SD	3.3	2.2	3.3	2.9	11.6	13.2	0.19	0.19
Δ		+5.9%		0%		-1.1%		+5.3%
0.3 ppm O_3, 60 min, 35.8 $\ell \cdot min^{-1}$ $\dot{V}_E$								
$\bar{x}$	34.9	36.8	24.5	26.2	101.0	100.3	1.29	1.37
SD	3.6	2.7	5.5	5.7	10.7	13.9	0.24	0.17
Δ		+5.4%		+6.9%		-0.7%		+6.2%
F		3.09		0.45		2.06		0.26

TABLE 11. Systolic Blood Pressure and Rate Pressure Product.

Systolic Blood Pressure (SBP), mmHg

	FA		0.2 ppm		0.3 ppm	
Subj	20 min	40 min	20 min	40 min	20 min	40 min
1	162	156	156	156	168	154
2	(152)	(166)	(164)	(168)		
3	134	148	142	144	170	176
4	164	166	158	154	164	162
5	108	114	110	116	112	114
6	106	112	90	104	112	120
$\bar{x}$	134.8	139.2	131.2	134.8	145.2	145.2
SD	28.0	24.8	30.0	23.5	30.4	27.0
Δ		+3.3%		+2.7%		0%

F = 0.47

Rate-Pressure Product, (HR x SBP) = (RPP)

	FA		0.2 ppm		0.3 ppm	
Subj	20 min	40 min	20 min	40 min	20 min	40 min
1	19,764	20,592	20,124	20,280	21,504	19,866
2	(13,680)	(15,272)	(13,940)	(13,944)		
3	11,256	13,320	11,360	13,536	14,790	17,244
4	11,316	12,118	10,902	10,626	11,316	11,502
5	11,016	11,628	10,560	11,368	10,752	11,286
6	8,683	9,632	6,840	8,632	9,184	10,440
$\bar{x}$	12,407	13,458	11,957	12,888	13,509	14,068
SD	4,256	4,204	4,907	4,489	4,916	4,219
Δ		+8.5%		+7.8%		+4.1%

F = 0.27

TABLE 12. Time of Onset of Symptoms for the Angina Patients*

1+ Angina pain lasting ≥ 2 min

	FA		0.2 ppm		0.3 ppm	
Subj	Onset Time	RPP	Onset Time	RPP	Onset Time	RPP
1	25	20,898	(No chest pain)		18	20,252
2	15	13,870	13	13,393	3	12,600
3	23	11,592	20	11,360	16	13,944
4	18	11,664	27	11,218	(No chest pain)	
5	7	9,078	7	8,352	7	7,990
6	7	7,200	8	6,750	11	8,470

1 mm ST depression

	FA		0.2 ppm		0.3 ppm	
Subj	Onset Time	RPP	Onset Time	RPP	Onset Time	RPP
1	18	18,960	34	21,222	18	20,252
2	16	13,248	14	13,393	1	12,136
3	(No ST depression)		30	12,780	14	13,440
4			(No ST depression)		19	11,016
5	(No ST depression)		(No ST depression)		(No ST depression)	
6	17	8,216	20	6,840	18	9,348

+1 dyspnea on exertion lasting ≥ 2 min

	FA		0.2 ppm		0.3 ppm	
Subj	Onset Time	RPP	Onset Time	RPP	Onset Time	RPP
1	(Not evidenced)		(Not evidenced)		21	20,916
2	(Not evidenced)		(Not evidenced)		(Not evidenced)	
3	23	11,592	14	10,902	16	13,944
4	38	12,240	(Not evidenced)		(Not evidenced)	
5	(Not evidenced)		(Not evidenced)		(Not evidenced)	
6	7	7,200	8	5,984	11	8,470

*Onset time expressed as minutes into exercise prescription workload.

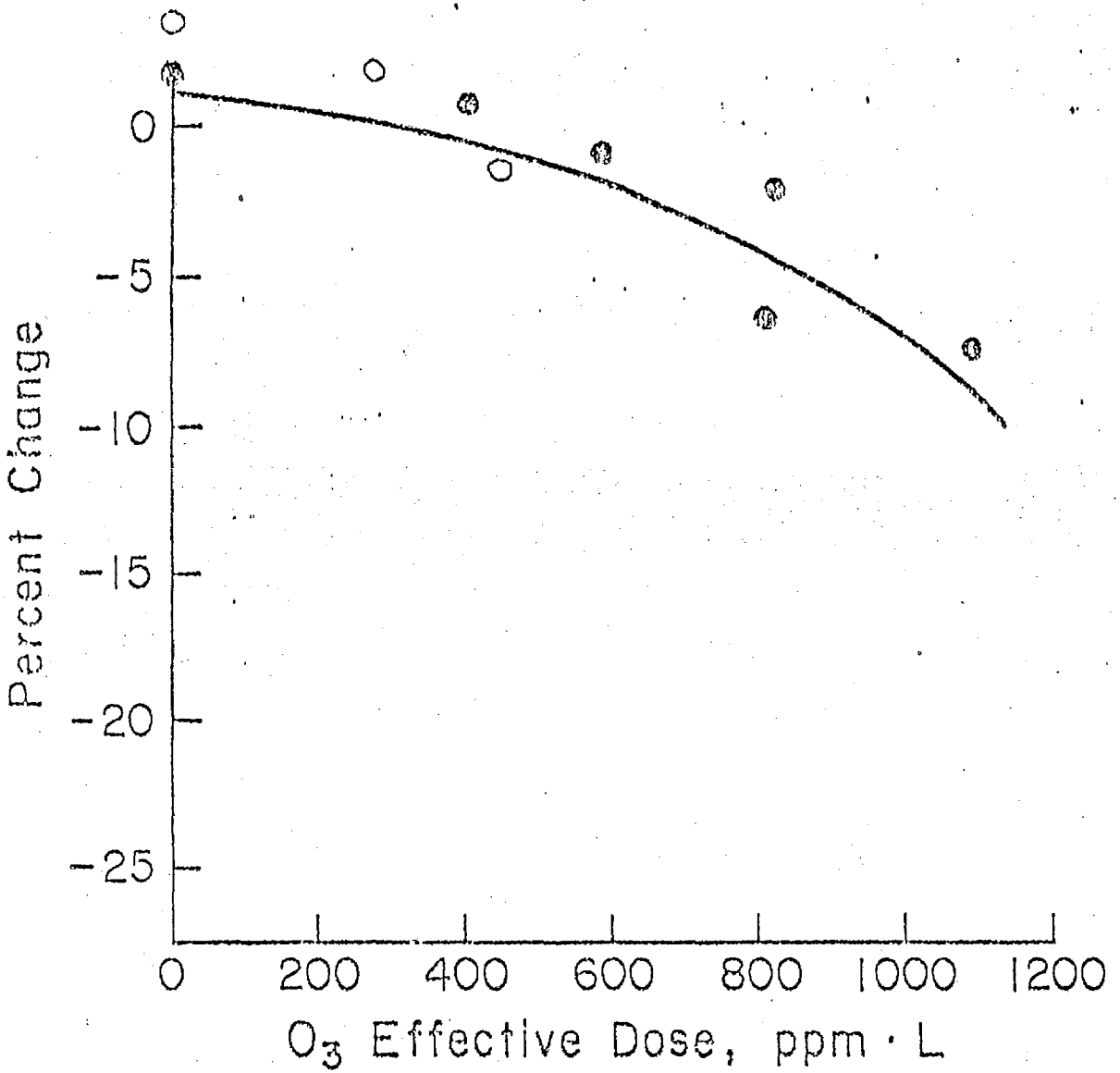

FIGURE 2 COMPARISON OF PERCENT CHANGE IN $FEV_{1.0}$ AS A FUNCTION OF O_3 EFFECTIVE DOSE FOR THE PATIENTS (OPEN CIRCLES), MIDDLE-AGE NORMALS (DARKENED CIRCLES), AND YOUNG ADULT MALES (REGRESSION LINE).

Hazucha et al, 1973), a level that did not elicit an effect at rest (Hackney et al, 1975; Hazucha et al, 1973; Silverman et al, 1976). Recently, Folinsbee et al (1978) and Adams et al (1981) have shown that for apparently healthy young adults exercising at moderately heavy intensities during short-term exposures ($\leq$2 h), the threshold O_3 concentration for inducing a toxic effect lies between 0.20 and 0.30 ppm.

Similar quantitative data is not available for presumably more sensitive populations, including patients with cardiopulmonary diseases, even though the current CARB O_3 advisory chart states that "persons with existing heart or respiratory ailments should reduce physical exertion and outdoor activity." However, since the short-term acute exposure effect in the first stage alert range (0.20-0.35 ppm) appears to be limited to the respiratory tract (Hackney and Linn, 1979), heart patients primarily limited in functional capacity by cardiovascular factors may not suffer any greater toxic effect due to PF impairment than does the clinically normal person. However, no quantitative data are available relative to ozone's possible alteration of cardiovascular response to exercise in CAD patients, as is available in the case of carbon monoxide (Goldsmith and Aronow, 1975).

In the present investigation, we studied angina patients' physiologic response to FA and two concentrations of O_3 within the first stage alert level during and after exercising at their normally prescribed exercise training load. One-way ANOVA indicated that none of the patients' PF, exercise ventilatory pattern ($\dot{V}_E$, F_R), $\dot{V}_{O_2}$, or cardiovascular responses (HR, SBP, and RPP) to O_3 exposures of 40 min were statistically significant. Furthermore, neither AP or ECG ST-segment depression, DOE, or RPE were related to O_3 exposure in a dose dependent fashion. Hence, the patients evidenced not only no cardiovascular strain with exercise equivalent to their normal training load while exposed to O_3 up to 0.30 ppm, but also no significant PF or exercise ventilatory pattern alteration as has been observed previously in clinically normal subjects exercising continuously at the same O_3 concentration (Adams et al, 1981; DeLucia & Adams, 1977).

This apparent incongruity is the essence of the improved validity of the O_3 effective dose (i.e., the product of O_3 concentration, $\dot{V}_E$ and exposure time) relative to O_3 concentration, alone (Adams et al, 1981; Folinsbee et al, 1978;

Silverman et al, 1976). That is, at a particular O_3 concentration, both exercise enhanced $\dot{V}_E$ and exposure time will result in an increased O_3 dosage. For example, Silverman et al (1976) observed no O_3 toxicity effect when subjects at rest were exposed to 0.37 ppm for 2-h, while with light IE for 2-h they did. Similarly, Folinsbee et al (1978) observed no toxic effect on exposure to 0.30 ppm for 2-h, but did in their IE exposures at moderately severe workloads. Exposure time is also of importance as demonstrated by DeLucia & Adams' (1977) observation that exercise ventilatory pattern alteration was not evidenced at the heaviest workload ($\dot{V}_E$ = 66 $\ell \cdot min^{-1}$) until after 45 min of the 1-h exposure to 0.30 ppm O_3. Even at a higher O_3 concentration, 0.38 ppm, but only for 30 min of CE on a graded increment test to voluntary exhaustion, no significant PF impairment was noted (Savin & Adams 1979).

In the present study, the O_3 effective dose for the patients was calculated as 277 ppm·ℓ for the 0.20 ppm exposure, and 428 ppm·ℓ for the 0.30 ppm exposure, while those for the clinically normal groups were 414 and 621 ppm·ℓ, respectively. In Fig. 2, the 2d order polynomial regression line of percent decrement in $FEV_{1.0}$ as a function of O_3 effective dose, was calculated from data obtained on young adult males exercising at two workloads ($\dot{V}_E$ = 35 and 63 $\ell \cdot min^{-1}$) for periods of 30 to 80 min while exposed to FA or to 0.20, 0.30, or 0.40 ppm O_3 (Adams et al, 1981). Neither the patients or the middle-age normals mean responses exhibit a consistent variance from the line. Thus, it appears that the effective dose must exceed 700 ppm·ℓ before a $FEV_{1.0}$ decrement of 3% (about 100-120 $m\ell \cdot sec^{-1}$) is to be expected. Thereafter, there is a progressively enhanced decrement as evidenced by the regression line for the young adults and the two exposures to 0.40 ppm O_3 for the middle-age group.

In addition to $FEV_{1.0}$, we have observed relatively similar impairment in other PF variables as a function of O_3 effective dose (Adams et al, 1981). They are particularly evident at O_3 concentrations $\geq$ 0.30 ppm, in combination with exercise $\dot{V}_E$ and exposure times resulting in effective doses exceeding 800 ppm·ℓ. Mechanisms for these transient changes (usually allayed within 4 h) (DeLucia & Adams, 1977) are not definitely identified. However, Folinsbee et al (1978) have suggested that reduced FVC is due to decreased maximum inspiration resulting from either a voluntary or reflex reduction of inspiratory effort, which could also account, in part, for reduced maximum expiratory flow

via a lower absolute lung volume on the flow volume curve. In our study of young adults (Adams et al, 1981), we noted a significant increase in RV following the most severe protocols, as have others (Folinsbee et al, 1978; Hazucha et al, 1973), which together with decreased maximal inspiratory position noted by other investigators (Folinsbee et al, 1977; Hackney et al, 1975; Silverman et al, 1976), contributes to a decreased FVC. Increased RV may result from gas trapping and premature airway closure due to direct effect of O_3 on small airway smooth muscle (Folinsbee et al, 1978). It seems likely that O_3 inhibits inspiration via stimulation of irritant receptors involved in a vagally mediated bronchoconstrictor reflex (Silverman et al, 1976), and may inhibit maximal expiration by the same mechanism (Cohen & Gold, 1975).

The patients' mean response for $FEV_{1.0}$ shown in Fig. 2 suggests that they incur no greater PF impairment than do clinically normal subjects, but again are not definitive in this respect because of the low O_3 effective doses imposed. A possible etiology for decreased work tolerance may be due to the increased work of breathing (McKerrow & Otis, 1956) when bronchoconstriction results from O_3 exposure (Folinsbee et al, 1978). It has been suggested that epithelial irritation in the airways due to O_3 exposure may result in bronchial hyperirritability (Golden et al, 1978) and tachypnea (Lee et al, 1979), which if extreme, could affect exercise tolerance. Further, airway permeability may be increased with "sensitized" vagal sensory nerve endings causing tachypnea (Boushey et al, 1980), and possible other vagal effects that may be of importance in the cardiac patient. This could result in a lower threshold for cardiovascular symptoms or cardiac irritability that would necessitate altering physician prescribed exercise in these individuals. In the present investigation, however, we did not observe any relation of changes in F_R, $\dot{V}_E$, or DOE with changes in RPP (proportional to myocardial oxygen consumption) or ECG abnormalities that were systematically related to O_3 exposure in a dose dependent fashion.

Medication effectiveness may be altered by O_3 exposure, in that many drugs exert their effect by manipulating the RPP (HR x SBP) response to work demands. If O_3 at above threshold effective dose is found to alter either the HR response or BP response in patients on therapeutic doses of cardiogenic medications, then modification of daily therapy may be indicated on days of high air pollution. Neurogenic B-blocking agents are widely used and known to exacer-

bate tendencies to bronchial hyperactivity (Orehek et al, 1975). This in itself may result in an increased myocardial oxygen consumption (proportional to RPP) due to increased work of breathing and adverse tolerance in CAD patients with a tendency to bronchospasm.

In one case (patient #2) the protocol at 0.30 ppm O_3 was prematurely terminated at minute 12 of the 40 min exposure due to 2 mm of downsloping ST-segments and 3 min of 2+ AP. The AP occurred at a lower RPP than in the other protocols, but reversible ischemic dysfunction, such as attributed to coronary artery spasm, may have been responsible. At the time of protocol cessation, the subject's O_3 effective dose was only 105 ppm·ℓ. Further, there was no apparent loss of pulmonary function and no unusual pulmonary symptomatology. Unfortunately, we were unable to retest this individual due to the intervention of a prolonged vacation. When he was eventually available for retesting, he had become detrained and had gained a significant amount of weight, thus invalidating comparisons with previously completed protocols.

While the angina patients exercising at their usual workload prescription suffered no PF impairment or enhancement of their cardiovascular symptom limitations in the first stage alert O_3 exposures imposed in the present study, it should be noted that this may be due to the low effective dose (< 500 ppm·ℓ). This contention is substantiated by our observation of significant PF impairment in clinically normal subjects exercising at workloads necessitating $\dot{V}_E$ of 35 $\ell \cdot min^{-1}$ when exposed to 0.30 ppm if continued for 80 min, and for only 60 min when exposed to 0.40 ppm - both protocols at an effective dose of 840 ppm·ℓ (Adams et al, 1981). This implies that in regards to O_3 air pollution only, therapeutic cardiovascular exercise prescriptions need not be altered if the effective dose is less than 500 ppm·ℓ and the O_3 concentration is $\leq$ 0.30 ppm. However, caution must be advised since individual patient's status is quite variable and individual sensitivity must be considered, as well (Hackney et al, 1975; Adams et al, 1981). Further, prolonging an exercise training session will impose O_3 effective dose levels beyond that studied in the present investigation.

Folinsbee et al (1978) emphasize that physiological responses to specific O_3 effective dose levels may be different according to smoking habits, sex and age. Previous studies examining decrement in PF relative to effective dose of O_3 have utilized young male subjects (Folinsbee et al, 1978; Silverman et al,

1976). Recently (Adams et al, 1981), we studied the O_3 toxicity response of 8 males, none of whom smoked, but who varied in age from 22 to 46 years. Comparison of the mean change in PF between the three oldest subjects (33-46) and the five youngest subjects for protocols at effective doses above threshold, depicted in Fig. 3, revealed only small, inconsistent differences. In the present study, the middle-age, clinically normal group's PF and exercise ventilatory pattern response was similar to that of the young adult group (Tables 7 and 10, and Fig. 2). That is, inspite of the expected age associated decline in FVC (which is only partially accounted for by an increased RV) and flow rates ($FEV_{1.0}$ and MMFR) - even when expressed as a percent of FVC - there was no appreciable difference in O_3 toxicity through the full range of effective doses studied (Fig. 2). Thus, it appears that the primary factors effecting lung function deterioration with age advanced by Cotes (1975), viz., (1) deterioration in the tissues of which the lung is composed, (2) reduction in the strength of the respiratory muscles, and (3) an increase in stiffness of the thoracic cage, do not materially affect the O_3 toxicity response of clinically normal individuals, at least within the effective dose range studied. That is, the effective dose threshold and progressive impairment thereafter, seem to be similar for clinically normal middle-age and young adult males, with about the same relative impairment as a function of increasing effective dose. The possibility remains, however, that older less well trained subjects might respond differently than do healthy young adult males. Further, whether the older angina patients studied in the present investigation, who demonstrated significantly lower FVC, $FEV_{1.0}$, and MMFR than the middle-age normals, might have an enhanced O_3 toxicity response relative to that of the clinically normal subjects is not definitively apparent, since the highest effective dose imposed (428 ppm·ℓ) was below threshold.

Conflicting results relative to whether smokers are more sensitive to O_3 than non smokers have been reported. Light IE exposures to 0.37 ppm (Hazucha et al, 1973) and 0.50 ppm O_3 (Kerr et al, 1975), revealed that smokers showed less $FEV_{1.0}$ decrement. On the other hand, Hackney et al (1977) and Hazucha et al (1973) have found smokers slightly more sensitive to IE exposures at 0.30 and 0.75 ppm O_3, respectively. We have not examined this question definitive-

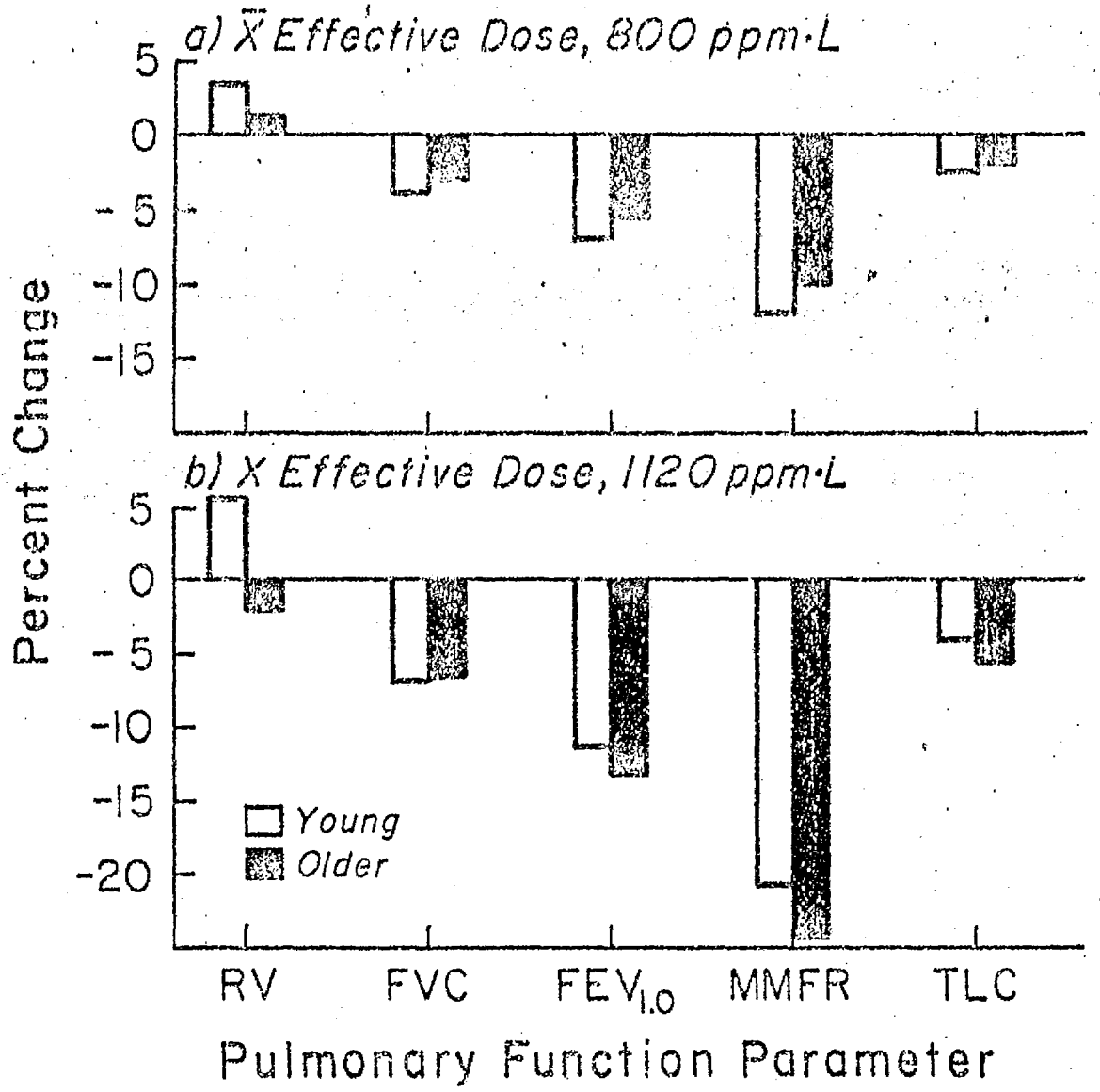

FIGURE 3 COMPARISON OF PERCENT CHANGE IN PULMONARY FUNCTION IMPAIRMENT BETWEEN YOUNG (N=5) AND OLDER (N=3) CLINICALLY NORMAL MALES (ADAMS ET AL, 1981)

ly, but did note that subject 5 in the middle-age normal group is a regular smoker (1 pack per day for 30 years). While his lung volumes were not significantly different from others in this group, his flow rates were substantially lower (Table 3). However, he was amongst the least sensitive to O_3 exposure. For example, at an effective dose of 1104 ppm·ℓ, his $FEV_{1.0}$ percent decrement was 4.0, while the group mean was 7.4. Subjects 6 and 7, however, both of whom have never smoked, evidenced $FEV_{1.0}$ decrements of 1.0 and 1.7 percent, respectively, for this protocol. Patient #3, a former smoker (4 packs per day for 40 years), but who had given up the habit 10 years before the study, had substantially lower flow rates than the other patients (Table 2). However, his PF response did not appear to differ systematically in a dose dependent fashion, although his HR, SBP, and RPP responses were all greater at 0.30 ppm than for FA, while AP, ST-segment depression and DOE all occurred earlier in the 0.30 ppm exposure. Patient #4 also had a significant smoking history (up to 2 packs per day before quitting 11 years prior to the study). However, he evidenced no PF, RPP, or clinical signs or symptoms systematically related to O_3 in a dose dependent fashion.

The wide range in sensitivity of PF response to a given O_3 concentration has been noted by numerous investigators (DeLucia & Adams, 1977; Folinsbee et al, 1977; Folinsbee et al, 1978; Hackney et al, 1975; Silverman et al, 1976). The comparison of % $FEV_{1.0}$ decrement depicted in Fig. 4 (from Adams et al, 1981) shows that even among a healthy, relatively homogenous population with respect to aerobic power (53-66 $m\ell \cdot min^{-1} \cdot kg^{-1}$), there is a disparate sensitivity of individual subjects to the O_3 effective dose. An explanation for this difference in sensitivity, which was generally consistent in all PF and exercise ventilatory pattern variables, is not readily apparent. Both subjects had similar physical characteristics, PF, and exercised at the same workload with near equivalent physiological response to FA protocols. The fact that the patients did not evidence any apparent individual differences in O_3 toxicity sensitivity as evidenced by PF response, may be due to their exposure to O_3 effective doses below threshold (i.e., <700 ppm·ℓ). This contention is further supported, in that the patients' mean exposure $\dot{V}_E$ at their individual exercise prescription workloads varied from 20 $\ell \cdot min^{-1}$ for patient 4 to 45.5 $\ell \cdot min^{-1}$ for patient 1, which at the 0.30 ppm exposure, yielded an effective dose of 240

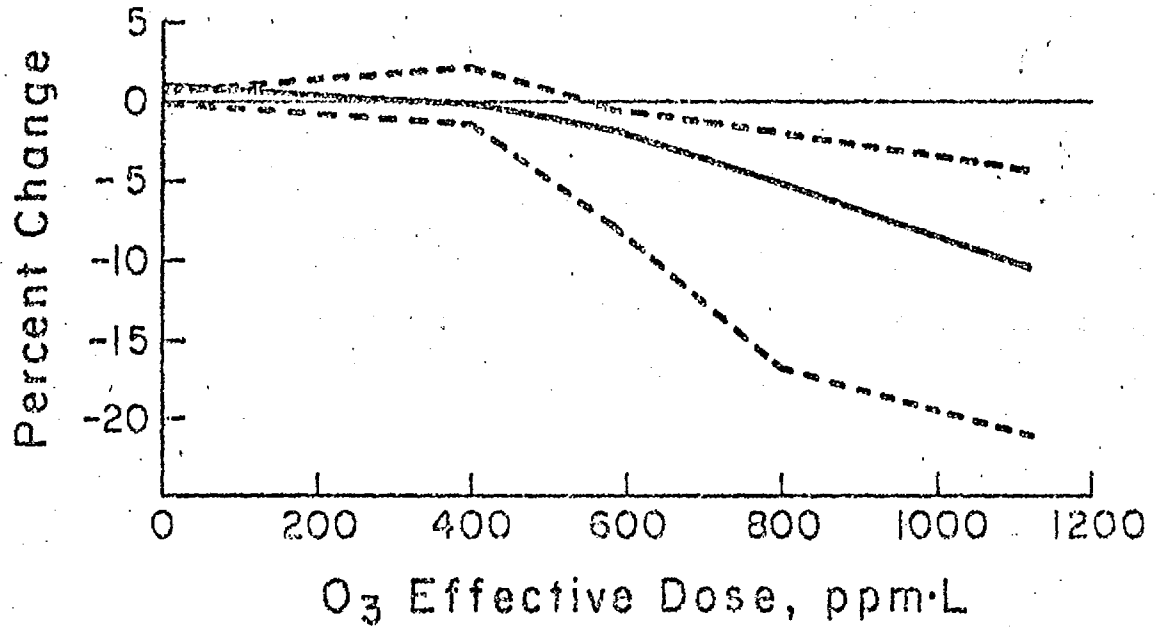

FIGURE 4 COMPARISON OF GROUP MEAN PERCENT CHANGE IN $FEV_{1.0}$ (SOLID LINE) TO THAT FOR THE LEAST SENSITIVE (UPPER DASHED LINE) AND THE MOST SENSITIVE (LOWER DASHED LINE). (ADAMS ET AL, 1981)

and 546 ppm·ℓ, respectively (both well below threshold for clinically normal subjects).

In the group of symptom limited CAD patients studied in the present investigation, there appeared to be no measurable detrimental effect of fulfilling their exercise therapy while exposed to the first stage alert levels of O_3 imposed. Although some ischemic changes and arrythmias were observed, angina pain and arrythmias, as well as RPP, RPE, DOE, and pulmonary function test response were not altered in a dose dependent fashion by exposure to O_3. However, our subjects had relatively low functional capacity and the lack of significant changes in the above parameters was very likely due to not achieving the effective dose of 700 ppm·ℓ at which PF alterations have been observed in normal subjects (Adams et al, 1981). These observations imply that in this sub-group of cardiac patients, routine exercise therapy of 40 min duration is not contraindicated at an O_3 concentration of 0.30 ppm or lower (O_3 effective dose $\leq$500 ppm·ℓ). This finding is somewhat paradoxical, in that these symptom limited patients' restricted exercise intensity tolerance partially protects them from O_3 toxicity effects. However, were these patients to undertake a golf game lasting 3 hours at the same 0.30 ppm O_3 concentration and requiring 2½ times resting $\dot{V}_E$, their O_3 effective dose would be 1350 ppm·ℓ for this IE exposure. This represents a potentially vital factor that clinicians must keep in mind when prescribing physical activity for CAD patients.

Numerous investigators have noted exaggerated symptoms, including dyspnea, wheezing, cough and chest tightness, in combination with PF impairment when subjects engage in exercise during O_3 exposure at levels above the effective dose threshold (Adams et al, 1981; Bates et al, 1972; DeLucia and Adams, 1977; Hackney et al, 1975). It is important to be able to differentiate clinically between pulmonary discomfort that might accompany O_3 exposure at above threshhold levels and that stemming from true AP. Symptomatic angina patients are commonly taught to cease physical activity when angina occurs and sublingual nitroglycerin is frequently used to both relieve the symptom and prophylactically to avoid it. In the present study, with sub-threshold O_3 exposures, no pulmonary pain that could be confused with AP was experienced. Nevertheless, caution must be advised, as angina is quite variable in nature and any undiagnosed chest discomfort should be considered ischemic in nature until proven otherwise.

Another factor of significance to physicians prescribing exercise for cardiac patients who might be exposed to significant ambient oxidant levels, is that a significant number of these patients have a relatively high functional capacity and can undertake substantial amounts of exertion. A few patients are in jogging programs and some have successfully completed 42 km marathon races. In one study, CAD patients completed a 42 km race with a mean of $\dot{V}_{O_2}$ of 29.8 $m\ell/kg \cdot min^{-1}$ (Dressendorfer et al, 1977). This is quite impressive, although others have advised against this form of unmonitored ultraendurance activity in CAD patients due to the possibility of fatal cardiovascular events (Hellerstein, 1977). This group of patients may easily achieve and surpass the O_3 effective dose threshold of 700 ppm $\cdot$ ℓ characteristic of clinically normal male subjects. For example, exercise at a workload requiring 30 $m\ell/kg \cdot min^{-1}$ $\dot{V}_{O_2}$ will necessitate a $\dot{V}_E$ of approximately 65 ℓ/min for an average size adult male. If this level of exercise is maintained for 1 hour at an O_3 concentration of 0.30 ppm O_3, an O_3 effective dose exposure of 1170 ppm$\cdot\ell$ would be achieved. This could result in pulmonary alterations that might adversely affect exercise tolerance and cardiovascular response through neurogenic and as yet other undetermined mechanisms. Of course, if the O_3 concentration was greater than 0.30 ppm, the effect at the same effective dose (i.e., 1170 ppm$\cdot\ell$) would be greater, reflecting the preeminent role of O_3 concentration in the effective dose equation (Adams et al, 1981; Folinsbee et al, 1978; Silverman et al, 1976).

It should be apparent from the results of the present study and the discussion developed above, that not all classifications of heart and lung patients are similarly affected on exposure to ambient alert levels of oxidant air pollution. Thus, it is of vital importance that precise answers be found to the clinical implications of such air pollution. Only then can clinicians and scientists give adequate advice on the possible need to modify physical activity on days of poor air quality.

References

1. Adams, W.C., W.M. Savin, and A.E. Christo. Detection of ozone toxicity during continuous exercise via the effective dose concept. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 1981 (In press).

2. Air Quality and Meteorology. 25(9):16, September, 1979, South Coast Air Quality Management District, El Monte, Calif.

3. Anderson, T., J. Brown, J. Hall, and R. J. Shephard. The limitations of linear regressions for the prediction of vital capacity and forced expiratory volume. Respirat. 25:140-158, 1968.

4. Åstrand, P.-O., and K. Rodahl. Textbook of Work Physiology. New York: McGraw-Hill, 1977 (2d edit.), pp. 385-6.

5. Bates, D.V., G.M. Bell, C.D. Burham, M. Hazucha, J. Mantha, L.D. Pengelley, and F. Silverman. Short-term effects of ozone on the lung. J. Appl. Physiol. 32:175-181, 1972.

6. Bennett, G. Ozone contamination of high altitude aircraft cabins. Aerospace Med. 33:969-973, 1962.

7. Boushey, H.A., M.J. Holtzman, J.R. Sheller, and J.A. Nadel. Bronchial hyperactivity. Am. Rev. Respir. Dis. 121:389-413, 1980.

8. Buckley, R.D., J.H. Hackney, K. Clark, and C. Posin. Ozone and human blood. Arch. Environ. Health 30:40-42, 1975.

9. Clamann, H., and R. Bancroft. Toxicity of ozone in high altitude flight. Advan. Chem. 21:352-359, 1959.

10. Clausen, J.P., and J. Trap-Jensen. Effects of training on the distribution of cardiac output in patients with coronary artery disease. Circulat. 42:611-624, 1970.

11. Cohen, A.B., and W.M. Gold. Defense mechanisms of the lungs. Ann. Rev. Physiol. 37:325-350, 1975.

12. Committee on Medical and Biologic Effects of Environmental Pollutants: Ozone and Other Photochemical Oxidants. National Academy of Sciences, 1977, pp. 280-436.

13. Consolazio, C.F., R.E. Johnson, and L.J. Pecora. Physiological Measurements of Metabolic Functions in Man. New York: McGraw-Hill, 1963, pp. 5-9.

14. Cotes, J.E. Lung Function: Assessment and Application in Medicine. Oxford: Blackwell, 1975 (3rd edit.), pp. 369-383.

15. DeLucia, A.J., and W.C. Adams. Effects of O inhalation during exercise on pulmonary function and blood biochemistry. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 43:75-81, 1977.

16. DeLucia, A.J., M.G. Mustafa, C.E. Cross, C.G. Plopper, D.L. Dungworth, and W.S. Tyler. Biochemical and morphological alterations in the lung following O exposure. In: Air. I. Pollution Control and Clean Energy, edited by C. Rai and L.A. Spielman. A.I. Ch. E. Symp. Ser. 71:93-100, 1975.

17. DeMore, W.B., J.C. Romanovsky, M. Feldstein, W.J. Hamming, and P.K. Mueller. Interagency comparison of iodometric methods of ozone determination. In: Calibration in Air Monitoring. ASTM Technical Publication No. 598. Philadelphia: American Society for Testing and Materials, 1976, pp. 131-143.

18. Dressendorfer, R.H., J.H. Scaff, Jr., J.O. Wagner, and J.D. Gallup. Metabolic adjustments to marathon running in coronary patients. Ann. N.Y. Acad. Sci. 301:466-483, 1977.

19. Fairchild, E.J. Neurohumoral factors in injury from inhaled irritants. Arch. Environ. Health 6:79-86, 1963.

20. Folinsbee, L.J., B.L. Drinkwater, J.F. Bedi, and S.M. Horvath. The influence of exercise on the pulmonary function changes due to low concentrations of ozone. In: Environmental Stress. (L.J. Folinsbee et al, editors). New York: Academic Press, 1978, pp. 125-145.

21. Folinsbee, L.J., S.M. Horvath, P.B. Raven, J.F. Bedi, A.R. Morton, B.L. Drinkwater, N.W. Bolduan, and J.A. Gliner. Influence of exercise and heat stress on pulmonary function during ozone exposure. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 43:409-413, 1977.

22. Folinsbee, L.J., F. Silverman, and R.J. Shephard. Exercise responses following ozone exposure. J. Appl. Physiol. 38:996-1001, 1975.

23. Golden, J.A., J.A. Nadel, and H.A. Boushey. Bronchial hyperirritability in healthy subjects after exposure to ozone. Am. Rev. Respir. Dis. 118:287-294, 1978.

24. Goldsmith, J.R., and W.S. Aronow. Carbon monoxide and coronary heart disease: A review. Environ. Res. 10:236-248, 1975.

25. Goldsmith, J.R., and J.A. Nadel. Experimental exposure of human subjects to ozone. J. Air Pollut. Control Assoc. 19:329-330, 1969.

26. Hackney, J.D., and W.S. Linn. Koch's postulates updated: A potentially useful application to laboratory research and policy analysis in environmental toxicology. Am. Rev. Respir. Dis. 119:849-852, 1979.

27. Hackney, J.D., W.S. Linn, S.K. Karuza, R.D. Buckley, D.C. Law, D.V. Bates, M. Hazucha, L.D. Pengelly, and F. Silverman. Effects of ozone exposure in Canadians and Southern Californians: Evidence for adaptation? Arch. Environ. Health, 32:110-116, 1977.

28. Hackney, J.D., W.S. Linn, D.C. Law, S.K. Karuza, H. Greenberg, R.D. Buckley, and E.E. Pedersen. Experimental studies on human health effects of air pollutants. III. Two-hour exposure to ozone alone and in combination with other pollutant gases. Arch. Environ. Health 30:385-390, 1975.

29. Haskell, W.L. Mechanisms by which physical activity may enhance the clinical status of cardiac patients. In: Heart Disease and Rehabilitation. (M.L. Pollock and D.H. Schmidt, eds.). Boston: Houghton Mifflin, 1979, pp. 276-296.

30. Hazucha, M., F. Silverman, C. Parent, S. Field, and D.V. Bates. Pulmonary function in man after short-term exposure to ozone. Arch. Environ. Health 27:183-188, 1973.

31. Hellerstein, H. Limitations of marathon running in the rehabilitation of coronary patients: Anatomic and physiologic determinants. N.Y. Acad. Sci. 301:484-494, 1977.

32. Holtzman, M., et al. Effect of ozone on broncial reactivity in atopic and nonatopic subjects. Clin. Res. 27:56A, 1979.

33. Jaffe, L.S. Photochemical air pollutants and their effects on men and animals. II. Adverse effects. Arch. Environ. Health 16:241-255, 1968

34. Kerr, H.D., T.J. Kulle, M. McIlhany, and P. Swidersky. Effects of ozone on pulmonary function in normal subjects. Am. Rev. Respir. Dis. 111:763-773, 1975.

35. Lee, L.-Y., C. Dumont, T.D. Djokic, T. E. Menzel, and J.A. Nadel. Mechanism of rapid, shallow breathing after ozone exposure in conscious dogs. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 46:1108-1114, 1979.

36. Linn, W.S., et al. Health effects of ozone exposure in asthmatics. Am. Rev. Resp. Dis. 117:835-843, 1978.

37. Marx, J.L., and G. Kolata. Combating the #1 killer. Amer. Assoc. for the Advancement of Science. Publication 78-3, p. 3, 1978.

38. McKerrow, C.B., and A.B. Otis. Oxygen cost of hyperventilation. J. Appl. Physiol. 9:375-379, 1956.

39. Menzel, D.B. Toxicity of ozone, oxygen, and radiation. Ann. Rev. Pharmacol. 10:379-394, 1970.

40. Mosher, J.C., W. G. MacBeth, M.J. Leonard, T.P. Mullins, and M.F. Brunelle. The distribution of contaminants in the Los Angeles Basin resulting from atmospheric reactions and transport. J. Air Pollut. Control Assoc. 20:35-42, 1970.

41. Orehek, J, R. Gayrard, Ch. Grimaud, and J. Charpin. Effect of beta-adrenergic blockade on bronchial sensitivity to inhaled acetycholine in normal subjects. J. Allergy Clin. Immunol. 55:164-169, 1975.

42. Paproski, D.M., and J.R. Walker. Air Quality in Canadian Urban Areas. Discussion Paper 18. Ottawa: Economic Council of Canada, 1974.

43. Petty, T.L. Pulmonary Diagnostic Techniques. Philadelphia: Lea and Febiger, 1975, pp. 1-30.

44. Raven, P.B. Heat and air pollution: The cardiac patient. In: Heart Disease and Rehabilitation. (M.L. Pollock and D.H. Schmidt, eds.). Boston: Houghton Mifflin, 1979, pp. 563-586.

45. Reid, D.D., et al. An Anglo-American comparison of the prevalence of bronchitis. Br. Med. J. 2:1487-1495, 1964.

46. Robertson, H.T. Exercise testing for patients with dyspnea. In: Weekly Update: Pulmonary Medicine. M.A. Sackner, editor. Lesson 37, 1979, American Thoracic Society, pp. 2-7.

47. Robinson, B.F. Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. Circulat. 35: 1073-1083, 1967.

48. Savin, W.M., and W.C. Adams. Effect of ozone inhalation on work performance and V max. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 46:309-314, 1979.

49. Silverman, F., L.J. Folinsbee, J. Barnard, and R.J. Shephard. Pulmonary function changes in ozone-interaction of concentration and ventilation. J. Appl. Physiol. 41:859-864, 1976.

50. Stokinger, H.E., and D.L. Coffin. Biological effects of air pollutants. In: Air Pollution, edited by A.C. Stern. New York: Academic, 3rd edition, 1968, Vol. 1, p. 401-456.

48.

51. Stokinger, H.E., W. Wagner, and P. Wright. Studies of ozone toxicity. 1. Potentiating effects of exercise and tolerance development. AMA Arch. Ind. Health 14: 158-162, 1956.

52. Watanabe, S., R. Frank, and E. Yokoyama. Acute effects of ozone on lungs of cats. 1. Functional. Am. Rev. Respir. Dis. 108:1141-1151, 1973.

53. Wayne, W., P. Wehrle, and R. Carroll. Oxidant air pollution and athletic performance. J. Am. Med. Assoc. 199:901-904, 1967.

54. Wilmore, J.H. A simplified method for determination of residual lung volumes. J. Appl. Physiol. 27:96-100, 1969.

55. Wilmore, J.H., and D.L. Costill. Semiautomated systems approach to the assessment of oxygen uptake during exercise. J. Appl. Physiol. 36:618-620, 1974.

56. Yokoyama, E., and R. Frank. Respiratory uptake of ozone in dogs. Arch. Environ. Health 25:132-138, 1972.

57. Young, W.A., D.B. Shaw, and D.V. Bates. Effects of low concentrations of ozone on pulmonary function in man. J. Appl. Physiol. 19:765-768, 1964.

GLOSSARY OF TERMS, ABBREVIATIONS AND SYMBOLS

ANOVA	Analysis of Variance
AP	Angina Pain
CAD	Coronary Artery Disease
CARB	California Air Resources Board
CE	Continuous Exercise
CO	Carbon Monoxide
COHb	Carboxyhemoglobin
COLD	Chronic Obstructive Lung Disease
DL_{CO}	Lung Diffusion for Carbon Monoxide
DOE	Dyspnea on Exertion
ECG	Electrocardiogram
FA	Filtered Air
$FEV_{1.0}$	Forced Expiratory Volume at 1 sec
FR	Respiratory Frequency
FVC	Forced Vital Capacity
HR	Heart Rate
IE	Intermittent Exercise
MMFR	Mid-maximum Expiratory Flow Rate
O_3	Ozone
PC	Parkinson-Cowan
PF	Pulmonary Function
ppm	Parts per Million
ppm	Parts per Million x Liters $\dot{V}_E$
PVC	Passive Vital Capacity
R	Rest
RPE	Rated Perceived Exertion
RPP	Rate Pressure Product
RV	Residual Volume
SBP	Systolic Blood Pressure
TLC	Total Lung Capacity
VC	Vital Capacity
$\dot{V}_E$	Pulmonary Ventilation Volume
$\dot{V}_{O_2max}$	Maximal Oxygen Uptake Volume

APPENDIX

A. Contraindications to Angina Patient Participation in the Present Study

1. Changing angina pattern.
2. Inability to reliably identify angina pain.
3. Gastrointestinal or mitral stenosis distress that may imitate angina.
4. Clinical infections, viral or bacteria.
5. Uncontrolled hypertension.
6. Uncontrolled congestive heart failure.
7. Significant lung disease (PFT's < 80% of predicted normal)
8. Valvular heart disease.
9. Dangerous arrythmias.
10. Metabolic abnormalities.
11. Congenital abnormalities.

B. List of Electrocardiogram Factors Analyzed

1. ST-segment shifts - type, degree and timing.
2. R wave amplitude change.
3. Arrythmias - type, time of occurence, frequency.

C. Borg Rate Perceived Exertion (RPE) Scale

6
7 very, very, light
8
9 very light
10
11 fairly light
12
13 somewhat hard
14
15 hard
16
17 very hard
18
19 very, very, hard
20

D. Dyspnea on Exertion (DOE) Scale

0 normal, no difficulty
1+ Minimal breathing discomfort
2+ some difficulty breathing

3+ very difficult to breathe, but can continue to exercise

4+ must stop due to lack of breath

E. Angina Pain (AP) Scale

1+ Minimal pain, some degree of uncertainty regarding its presence

2+ Clear cut pain, but tolerable

3+ Pain severe enough to cease activity

4+ unacceptable pain

F. Summary of Patients Smoking History

Subj.	Smoking History
1	Never
2	Quit 2 yrs before; formerly smoked 1 pack of cigarettes per day for 30 yrs.
3	Quit 10 yrs before; formerly smoked 4 packs of cigarettes per day for 40 yrs.
4	Quit 11 yrs before; formerly smoked 1-2 packs of cigarettes per day for 30 yrs.
5	Quit 5 yrs before; formerly smoked ½-1 pack of cigarettes per day for 40 yrs.
6	Never

G. Subjective Symptom Report

Exposure date: Time:

Subject:

We would like you to assist in our evaluation of the effects of ozone inhalation on human subjects performing exercise. This you can provide by noting below: 1) Which symptoms you noticed during your exercise today. 2) Designating your own subjective feeling of the severity of these disturbances, and 3) Logging (to your recollection) an approximate time of onset. In addition, you are requested to rate the difficulty of today's testing compared to the others (if any) of this experiment which you participated in.

Symptom	No	Yes (subjective description)	Time of Onset (min into exposure)
Shortness of breath			
Cough			
Excessive sputum			
Throat tickle			
Raspy throat			
Wheezing			
Congestion			
Headache			
Nausea			
Dizziness			
Chest pain (angina)			
Other (please describe briefly)			

y's experiment involve ozone inhalation? _____

____ ppm