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Pulmonary Response to Ozone Exposures in Healthy Individuals Aged 55 Years or Greater

Christopher S. Reisenauer, Jane Q. Koenig, Michael S. McManus, Michael S. Smith, Greg Kusic and William E. Pierson
School of Public Health and Community Medicine
University of Washington
Seattle, Washington

Since minimal data are available regarding the pulmonary effects of ozone (O_3) in healthy individuals over the age of 55, this research was designed to determine if this group was at risk for pulmonary function changes when exposed to O_3 at ambient concentrations for one hour during intermittent exercise. Ten female and nine male subjects were exposed for 60 minutes in random order to one of the following O_3 concentrations: 0.0, 0.2, or 0.3 ppm. All exposures were administered through a rubber mouthpiece while the subject was either at rest or moderately exercising on a treadmill. The following pulmonary function tests (PFT) were recorded before exposure, and at periods immediately following and 20 minutes post-exposure: total respiratory resistance (R_T), thoracic gas volume at functional residual capacity (FRC), and forced expiratory volume in one second (FEV_1). Baseline PFT mean values and air exposure PFT mean values were compared through the use of repeated measure two-way analysis of variance to detect any significant effect of exposure on these parameters. Following 60 minutes of exposure at light intermittent exercise, there were no statistically significant pulmonary functional changes observed in male subjects. However, in female subjects, a statistically significant increase in R_T was observed.

Ozone (O_3) is a secondary photochemical pollutant produced by the chemical reaction of ultraviolet light with precursors such as nitrogen oxides and hydrocarbons which are both primary pollutants emitted through combustion processes. Elevated levels of O_3 are found in urban areas where automobile emissions, industrial pollutants and sunlight can interact. Ozone has been shown to cause biochemical and morphological alterations in the lungs of experimental animals at near ambient concentrations.[1]

There is consensus that asthmatic subjects, both adolescents and adults, are extremely sensitive to the inhaled effects of low concentrations of sulfur dioxide (SO_2).[2–5] However, at this time, subjects with asthma[6–8] have been shown to be no more sensitive than healthy subjects in short-term experimental exposures to other common air pollutants, specifically ozone (O_3). Patients with chronic obstructive pulmonary disease (COPD) also do not demonstrate increased sensitivity to inhaled O_3.[9,10] These results are puzzling since O_3 is known to have toxic effects on the respiratory system as stated above.[1] To date, the majority of data on the respiratory effects of ozone from controlled human studies have been derived from subjects under the age of thirty. Studies have shown that young healthy subjects exercising vigorously show significant pulmonary function changes at 0.18 ppm,[11] 0.14 ppm[12] and 0.12 ppm O_3.[13] To our knowledge, there are no published reports of the pulmonary effects of O_3 exposure in older subjects. Rationale for the hypothesis that an older study group may be at high risk for pulmonary function changes with low level O_3 exposure is derived from supportive data from animal studies. For example, animal toxicity data recording biochemical pulmonary response parameters indicative of lung injury as the result of controlled ozone exposures, reveal a significant increase in sensitivity in the lungs of older rats as compared to their younger counterparts.[14]

The Clean Air Act authorizes the Environmental Protection Agency to regulate ambient air quality standards to protect the most sensitive members of the population. Therefore, it seems important to expose a well characterized group of healthy subjects over the age of 55 to realistic concentrations of O_3 in a controlled laboratory setting to determine the pulmonary function response of this potentially susceptible population to a prevalent ambient pollutant.

Methods

Nineteen healthy volunteers, 55 to 74 years of age, served as subjects for this study. Primary anthropometric data and baseline FEV_1 values are summarized in Table I. FEV_1 values were within the range of predicted normal limits for all subjects. All potential subjects underwent extensive screening procedures, including completion of a detailed medical history questionnaire, thorough physical examination, and a methácholine challenge test to detect nonspecific bronchial hypersensitivity.

The methacholine challenge test (MCCT) consisted of each subject breathing, at tidal volume with nose clips in place, varying concentrations of methacholine (MC) aerosol (normal saline alone, 0.025, 0.25, 2.5, 5.0, 10.0, and 25.0 mg/mL) for 90 seconds. FEV_1 was measured 90 and 180 seconds after inhalation of MC. A positive response to the MCCT was defined as a 20 percent or greater reduction in FEV_1 which was sustained for 180 seconds following the test inhalation.

Potential subjects were excluded from participation if they were found to have a positive response to the methacholine challenge test, had smoked within the past three years, or had a history of asthma, allergic rhinitis, cardiac disease, chronic respiratory illness, or any condition requiring the use of medications such as beta blockers or cholinergic agents. Accepted subjects were informed of the purposes and procedures of the experiments, as well as potential risk from participation, and each signed an informed consent. The study was approved by the University of Washington Human Subjects Committee.

Three test atmospheres were studied: (1) filtered air (2) 0.2 ppm O_3, and (3) 0.3 ppm O_3. All exposures were conducted at 75 percent or greater relative humidity and ~22°C. Subjects were studied at the same hour of the day on each visit to avoid changes in lung function due to diurnal variation. Exposures were determined at random and the subjects were not informed of the exposure atmospheric content.

The pollutant generating system has been described in detail earlier.[15] Briefly, an air supply of approximately 10 L/s was provided by compressed air. It was initially scrubbed by a series of absolute and chemical filters, humidified, and then passed through a second absolute filter. The main air flow was then turbulently mixed with the appropriate quantity of O_3 and subsequently routed through Teflon tubing to a rubber mouthpiece.

Ozone was produced by ultraviolet irradiation of clean air (OREC Model 03V1-0, Ozone Research and Equipment Co., Phoenix, AZ) and monitored at the subject's mouthpiece with an ultraviolet photometric analyzer (Model CSI 3100, Columbia Scientific Industries, Austin, TX). Zero and span calibration of the monitoring instruments were performed each week to assure accuracy.

Baseline physiologic measurements were made prior to breathing the test atmosphere exposures. The following pulmonary function tests (PFT) were recorded on a thermal recorder or *X-Y* plotter while the subject was seated in a volume-displacement body plethysmograph. First, total respiratory resistance (R_T) was obtained using the forced pressure oscillatory technique at 3 Hz.[16] R_T values were based on an average of ten breaths with pressure and flow signals being integrated through the use of a microcomputer. Second, thoracic gas volume at functional residual capacity (FRC) was measured using the gas compression techique.[17] Third, forced expiratory volume in one second (FEV_1) was calculated from a maximal forced vital capacity maneuver (FVC). Graphic displays of the FVC maneuver were evaluated and those interrupted by cough or variable effort were discarded. Finally, total lung capacity (TLC) was expressed as the sum of FRC and the inspiratory capacity (IC) as measured on the thermal recorder just prior to the FRC determination.

After the baseline measurements, the subjects were exposed to one of the three test atmospheres for one hour. Noseclips were worn throughout exposure to assure oral breathing and to reduce olfactory detection of the pollutant. Exposure periods consisted of two 20-minute rest periods alternated with two 10-minute intervals of light exercise on a treadmill except for the first seven male subjects who were exposed for 50 minutes at rest followed by 10 minutes during moderate exercise. Treadmill speed and elevation settings were adjusted to levels sufficient to increase resting minute ventilation by a factor of 3.0. Minute ventilation and respiratory frequency were measured using a respiratory integrator (Hewlett-Packard). The effective dose of 0.3 ppm (concentration × time × $\dot{V}_E$) was 222 ppm L for the first seven male subjects, 282 ppm L for the last two male subjects and 221 ppm L for the ten female subjects. End tidal CO_2 tension using a medical gas analyzer (Beckman) and electrocardiogram (Hewlett-Packard) also were monitored throughout the exposures. Finally, two additional sets of PFT measurements were recorded, one immediately following exposure and the other 20 minutes after exposure.

All physiologic measurements, except R_T, were conducted in triplicate with the mean values used to assess functional changes, although in some instances, less than three satisfactory measurements were obtained. Means of the measurements from all satisfactory maneuvers were used for parameter estimates.

Following the experiment, subjects were requested to report the development of any symptoms for the remainder of the exposure day and the following day. Each subject scored a symptom rating questionnaire containing nine questions regarding cough, substernal pain, sore throat, wheezing, dyspnea, fatigue, headache, nasal discharge, and unusual taste or smell. The subjects were asked to qualify their symptoms as none, none–mild, mild–moderate, moderate–severe, or severe, on a scale from 0 to 4.

The data were analyzed in a blind fashion; that is, the person who calculated the values for the functional parameters did not know the mode of exposure on any given experimental day. A repeated measure two-way analysis of variance was used to assess exposure effect for each pulmonary function parameter.

Table I. Anthropometric data and baseline FEV_1 values of 19 healthy subjects ≥ 55 years of age.

Subject No.	Age (yrs)	Height (cm)	Weight (kg)	Baseline FEV_1
Males				
11	58	190	89	3.90
12	64	170	77	3.90
13	70	171	80	3.00
14	74	170	75	3.00
15	68	170	79	3.70
17	55	173	70	3.65
18	63	175	74	3.70
19	56	184	80	4.85
20	55	182	73	5.20
Mean	62.6	176.1	77.4	3.85
SD	±7.04	±7.41	±5.50	±0.73
Females				
25	56	128	62	2.85
28	64	177	93	2.85
31	68	158	77	2.60
34	61	173	84	3.15
35	72	161	78	2.10
36	71	164	82	2.95
39	74	169	72	2.15
41	70	161	68	2.00
47	68	163	67	2.70
49	62	166	84	2.55
Mean	66.6	162.0	76.7	2.59
SD	±5.68	±13.29	±9.49	±0.39

Results

The means and standard deviations for the pulmonary function values are summarized in Table II. Mean ozone concentrations for the two non-control test atmospheres were 0.201 ± 0.00 ppm and 0.299 ± 0.00 ppm as measured by photometric analysis.

Average minute ventilation values ($\dot{V}_E$) in the males at rest (9.0 ± 1.35, 9.1 ± 0.82, 9.0 ± 0.98) served as control values for determining proper treadmill settings to achieve the desired experimental average $\dot{V}_E$ while exercising (28.7 ± 5.15, 27.7 ± 3.45, 29.0 ± 5.44) during exposure to air, 0.2 ppm O_3, or 0.3 ppm O_3 respectively. No significant changes in the pulmonary function parameters following exposure to either air, 0.2 or 0.3 ppm O_3 were observed in male subjects.

Average resting $\dot{V}_E$ values for female subjects totaled 7.9 ± 2.18, 8.3 ± 1.70, and 7.2 ± 1.23 while exercise $\dot{V}_E$ measured 22.9 ± 4.74, 24.9 ± 5.5, and 22.9 ± 3.56 following exposure to air, 0.2 or 0.3

Table II. Pulmonary function measurements in healthy subjects aged 55 years or greater before and after exposure: 0.2 and 0.3 ppm O_3 (means ± standard deviations).

Functional measurement	Exposure atmosphere	Baseline	1–2 min post exposure	3–4 min post exposure	20–22 min post exposure
Males ($N = 9$)					
R_T	Air	2.55 ± 0.83		2.53 ± 0.85	2.68 ± 1.01
cm H_2O/L/sec	0.2 ppm O_3	2.68 ± 1.00		2.46 ± 1.00	2.64 ± 1.01
	0.3 ppm O_3	2.69 ± 0.87		2.48 ± 1.01	2.76 ± 1.14
FRC	Air	3.51 ± 0.58		3.47 ± 0.47	3.41 ± 0.45
L	0.2 ppm O_3	3.76 ± 0.83		4.07 ± 1.06	4.18 ± 1.29
	0.3 ppm O_3	3.72 ± 0.87		3.72 ± 0.92	4.12 ± 1.09
TLC	Air	7.02 ± 0.89		7.31 ± 1.28	7.03 ± 0.93
L	0.2 ppm O_3	6.95 ± 1.46		7.30 ± 1.52	7.94 ± 1.77
	0.3 ppm O_3	6.59 ± 1.27		6.90 ± 1.21	7.63 ± 1.61
FEV_1	Air	3.80 ± 0.66	3.97 ± 0.75	4.00 ± 0.80	3.77 ± 1.13
L	0.2 ppm O_3	3.85 ± 0.68	4.02 ± 0.67	4.05 ± 0.74	4.00 ± 0.67
	0.3 ppm O_3	3.76 ± 0.71	3.86 ± 0.76	3.91 ± 0.74	3.90 ± 0.76
Females ($N = 10$)					
R_T	Air	3.49 ± 1.12		3.56 ± 1.15	3.44 ± 1.21
cm H_2O/L/sec	0.2 ppm O_3	3.43 ± 1.24		3.51 ± 1.11	3.63 ± 1.12
	0.3 ppm O_3	3.40 ± 1.04		3.82 ± 1.09[a]	3.82 ± 1.19[b]
FRC	Air	3.32 ± 0.63		3.23 ± 0.71	3.39 ± 0.76
L	0.2 ppm O_3	3.11 ± 0.45		3.17 ± 0.56	3.05 ± 0.45
	0.3 ppm O_3	3.05 ± 0.41		3.04 ± 0.47	3.10 ± 0.51
TLC	Air	5.93 ± 0.78		6.05 ± 0.83	6.08 ± 0.93
L	0.2 ppm O_3	5.84 ± 0.66		5.83 ± 0.77	5.74 ± 0.62
	0.3 ppm O_3	5.73 ± 0.42		5.73 ± 0.50	5.82 ± 0.59
FEV_1	Air	2.63 ± 0.41	2.58 ± 0.37	2.55 ± 0.36	2.56 ± 0.43
L	0.2 ppm O_3	2.56 ± 0.34	2.51 ± 0.31	2.55 ± 0.32	2.51 ± 0.34
	0.3 ppm O_3	2.60 ± 0.38	2.57 ± 0.38	2.58 ± 0.38	2.54 ± 0.40

[a] $p < 0.27$.
[b] $p < 0.035$.

ppm O_3 respectively. Female subjects showed no significant alterations in FEV_1, FRC, or TLC following air or either ozone exposure. However, a statistically significant increase was observed in R_T in female subjects following exposure to 0.3 ppm O_3. Measurements made 3–4 minutes post exposure (PE_1) revealed a 13 percent increase in total respiratory resistance compared to baseline values ($p < 0.027$) based on a one-tailed test. Measurements recorded 20–22 minutes following ozone exposure (PE_2) also revealed a 13 percent increase in R_T ($p < 0.035$). Additionally, PE_1 and PE_2 measurements of R_T following 0.2 ppm O_3 exposure revealed a 2 and 6 percent increase respectively, but these values did not represent a significant alteration from baseline. The R_T changes following air exposure were not statistically significant. A graphic account of these data is illustrated in Figure 1.

There was a gradation of complaints of lower, upper, and non-respiratory symptoms with the intensity of ozone exposure, although comparisons of mean symptom rating scores revealed no statistically significant alterations between the three experimental atmospheres as determined by the Student t test. Female subjects reported higher symptom rating scores than males, a total of 28, 34, and 60 following exposures to air, 0.2 ppm O_3, and 0.3 ppm O_3 respectively, as compared with totals of 15, 17 and 22 reported by male subjects. Six subjects, four female and two male, reported the persistence of a mild cough for several hours after termination of exposure.

Ambient air concentrations of ozone in the Seattle area during the period of exposures for this study (June through

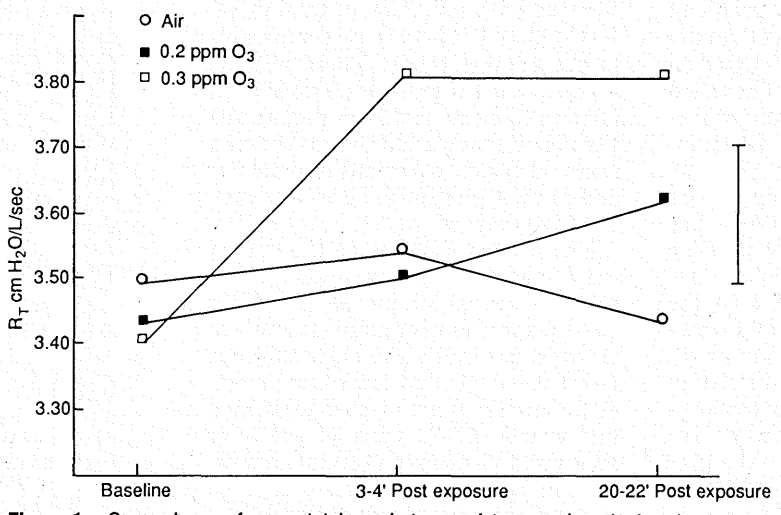

Figure 1. Comparisons of mean total respiratory resistance values in female subjects following exposure to filtered air, 0.2 ppm O_3 and 0.3 ppm O_3. Bar represents the standard error of the difference.

August 1986) were low. During this time period, the maximal hourly averages were 0.04 to 0.08 ppm O_3. Therefore, the subject population was not exposed to significant concentrations of O_3 outside of our laboratory.

Discussion

The purpose of this study was to discern if older healthy individuals are more susceptible to the acute effects of inhaled ozone as a result of their increased age. Previous work in our laboratory demonstrated that healthy adolescent subjects (four males and six females, aged 12–19 years) showed a significant 15 percent increase in R_T following exercise exposure to 0.18 ppm O_3.[18] The protocol used in the adolescent study was very similar to the present study; the exposure dose differed (0.18 ppm versus 0.2 and 0.3 ppm in this study) and the time was shorter (40 minutes including 10 minutes of exercise versus 60 minutes intermittent exercise in this study). The ventilation rates during exercise also differed; mean $\dot{V}_E$ was 41.3 L/min in the adolescent study and 22.9 L/min for females and 29.0 L/min for males in the present study. We calculated the effective dose of O_3 (concentration × time × $\dot{V}_E$) to be 115 ppm L for the adolescents, 236 ppm L for male subjects over the age of 55 years and 221 ppm L for female subjects over the age of 55 years. (The male subjects were grouped together since the effective doses of 0.3 ppm O_3 were similar for the two exposure protocols.) The adolescent subjects showed a slightly greater increase in R_T than the older subjects even though their effective dose was lower. These data suggest that this group of older, healthy individuals are no more susceptible to the acute affects of O_3 than a group of healthy adolescent subjects. It should be noted that significance was based on a probability derived from a one tailed test. It was assumed that any ozone-induced change in R_T would be an increase.

Previous research revealing similar elevations in airway resistance has speculated upon a variety of possible mechanisms for this physiologic response to ozone.[5,11,19] In view of the speed of the response, a vagally mediated reflex bronchoconstriction or direct muscarinic receptor stimulation seem more probable than mucosal congestion, pulmonary edema, or increased mucus production as the proposed cause for increase in R_T. However, it is interesting that changes in FEV_1 values were not observed which would be expected with a smooth muscle reflex constriction. These results are supported by data presented by McDonnell and associates who reported a lack of consistency between resistance and flow changes following experimental ozone exposures.[11,19]

Other than the increase in R_T, there were no changes in pulmonary function parameters in this group. However, many subjects became aware that they had been exposed to a noxious gas as symptoms developed. Cough was the most common lower respiratory symptom observed during O_3 exposure and was most frequently mild and not productive. Cough appeared to be precipitated by exercise and deep inspiration, but in most cases it did not interfere with the performance of the required spirometric maneuvers.

It has been established that use of effective dose rather than simple concentration of O_3 aids in the interpretation of the O_3-induced effects. In the present study, female subjects inhaling a slightly lower effective dose than male subjects nevertheless showed a larger increase in respiratory resistance. This increase in pulmonary effects observed in the female subjects as compared to the male subjects is consistent with data reported by Lauritzen and Adams.[20] Their study examined the pulmonary effects of 0.2, 0.3, and 0.4 ppm inhaled O_3 during 1 hour continuous exercise exposures in a population of six healthy young adult females. Comparisons of female responses to those of a group of young adult males at the same total O_3 effective dose revealed significantly greater effects on respiratory frequency, FVC, and FEV_1 for the females. R_T was not calculated in their study. Additionally, these investigators reported a considerable attenuation of these gender response differences with reduction of total O_3 effective dose levels to those comparable to the present study. These authors suggest that the enhanced response of females to ozone is due in part to the significant lung size difference between sexes, although other anthropometric and physiological differences also may be of importance.

The present study is, to the best of our knowledge, the first report of results illustrating an increased risk for PFT changes at near ambient levels of O_3 exposure in healthy older subjects. Drechsler-Parks and coworkers reported pulmonary function changes in men and women 57–76 years of age after exposure to 0.45 ppm O_3.[21] It is admitted that the small increases in R_T seen in our study have marginal clinical significance, however, these data are interesting because of the relatively short exposure periods and low exercise level. This study adds important information about the responses of a potentially susceptible, ever increasing segment of our population following exposure to O_3 at realistic ambient air concentrations. With a rapidly growing elderly population in suburban areas, and recent data[22] revealing that these areas may be exposed to maximum hourly average concentrations exceeding 0.2 ppm O_3, these results may be cause for concern.

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Christopher S. Reisenauer is a medical student at the University of Washington School of Medicine. Jane Q. Koenig, Ph.D., is research associate professor, Department of Environmental Health (DEH), University of Washington. Michael S. McManus, M.D., is a resident in the Occupational Medicine Program, DEH. Michael S. Smith is a research technologist, DEH. Greg Kusic, M.D., is a former occupational medicine resident, DEH. His present address is Redding Industrial and Occupational Health Clinic, Redding, CA. William E. Pierson is clinical professor, DEH and Pediatrics. This work was conducted in the pulmonary physiology/air pollution laboratory in DEH, University of Washington, Seattle, WA 98195. This paper was submitted for peer review February 20, 1987; the revised manuscript was received November 4, 1987.