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Asthma and Respiratory Irritants (Ozone)

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Asthmatics appear to be more susceptible to the effects of air pollutants than nonasthmatics. The present studies were undertaken to examine the effects of exposing asthmatics to ozone concentrations that occur in the environment. Seventeen well-documented male and female asthmatics have been exposed for 2 hr in an environmental chamber to 0.25 ppm of ozone on one occasion (ozone) and to air on another occasion (air). Effects were assessed by measurements of pulmonary function obtained prior to (0 hr), every half-hour during and at the end of all exposures (2 hr). Paired *t*-test analysis of lung volumes, forced expiratory volume in 1 sec ($FEV_{1.0}$), and maximum expiratory flow rates at 50% of vital capacity ($\dot{V}_{50\%VC}$) showed no significant changes ($p > 0.05$) when the following comparisons were made: 0 hr air vs 0 hr *ozone, 0 hr air vs. 2 hr air, 0 hr ozone vs. 2 hr ozone, 2 hr air vs. 2 hr ozone. There was variability in* severity of asthma and pulmonary function status; most subjects were taking some form of medication at the time of study. Some asthmatics showed no change or improvement with both air and ozone and others developed greater reductions in pulmonary function with ozone than with air. Approximately one-third of the asthmatics demonstrated greater changes in $\dot{V}_{50\%VC}$ with exposure to 0.25 ppm of ozone relative to air exposure. These studies indicate that acute exposures to ozone at realistic concentrations in the environment can produce adverse responses in some asthmatics.

Introduction

Air pollution has been associated with an increased incidence of asthma (*1–9*) and other respiratory diseases (*10–16*). Ozone, the major portion of oxidant in photochemical smog, can produce symptoms and physiologic changes in the lung when inhaled at concentrations occurring in the environment. Ozone-induced symptomatology includes cough, substernal soreness, pharyngitis, and some wheeze and dyspnea, indicating irritation of the respiratory tract (*17, 24*). Changes in measures of lung function (*17–27*) include increases in pulmonary and airway resistance, residual volume and "closing volume"; reductions in vital capacity, forced expiratory volume in 1 sec ($FEV_{1.0}$), maximum expiratory flow rates, maximum static elastic recoil pressure of the lung, diffusing capacity and fractional uptake of the lung for carbon monoxide. Ozone exposure may stimulate irritant receptors and increase resistance in large and small airways of the lung (*17, 18, 21*). There is evidence to suggest that 2 hr exposure to 0.1 ppm of ozone significantly decreases arterial partial pressure of oxygen and increases airway resistance in healthy male volunteers (*28*).

Studies in Los Angeles have shown an increased incidence of asthmatic attacks (*5*) on days when oxidant levels exceeded 0.25 ppm. Asthma is characterized by irritable airways leading one to expect that asthmatics may be abnormally sensitive to an irritant like ozone and therefore demonstrate a lower threshold or more severe responses to ozone than nonasthmatics. The present study was designed to examine the response of well documented asthmatics, under good control for their disease, to 0.25 ppm of ozone.

Methods

Subjects

The subjects were 17 nonsmoking asthmatics (5 men, 12 women) selected from The Gage Research Institute Asthma Clinic patient population. These patients were comprehensively documented with respect to history, physical examination, biochemistry, serology, radiology, sputum analysis, urinalysis, allergy skin tests, pulmonary function status, and therapy, according to a uniform documentation protocol. The subjects were under good control for their asthma at the time of study and were not withdrawn from their routine medication regimens. They gave fully informed consent. All the subjects had diagnosed asthma apparently

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unassociated with other cardiac or pulmonary disease. The asthma diagnosis was based on a history consistent with intermittent diffuse airways obstruction, pulmonary function tests showing reversible airways obstruction as demonstrated by an increase of 15% or more above the baseline value of at least one test of airway obstruction following four puffs of the bronchodilator salbutamol.

Exposure Technique

The exposure chamber and methods of generating and monitoring ozone have been described previously (*23*), except that ozone concentrations were measured by the chemiluminescence technique using the Bendix Ozone Analyzer. Each subject was exposed at least twice, once to filtered air for 2 hr (air) and once to 0.25 ppm of ozone for 2 hr (ozone). During both exposure periods, the subjects were seated quietly at rest.

Pulmonary Function Measurements

Lung volumes (functional residual capacity, FRC; vital capacity, VC; residual volume, RV; total lung capacity, TLC), maximum expiratory flow-volume (MEFV) curves, minute ventilation, tidal volume and respiratory frequency were obtained prior to the beginning of each exposure. Subsequently, MEFV curves and ventilations were repeated at 30-min intervals (0.5 hr, 1 hr, 1.5 hr, and 2 hr), and at the end of the 2-hr exposure lung volumes were repeated as well.

Lung volume (BTPS) was determined by a standard helium dilution technique using a Collins modular lung analyzer. MEFV curves were obtained by displaying the volume and flow signals from a wedge spirometer (Med-Science Electronics) on the X and Y axes of a Tektronix (R5103N) storage oscilloscope. An electronic timer was started automatically at the beginning of expiratory flow; this circuit interrupted the oscilloscope display briefly after an elapsed time of 1 sec. The following were derived from the MEFV curve: forced vital capacity (FVC), forced expiratory volume in 1 sec ($FEV_{1.0}$), maximum expiratory flows at 50% of vital capacity ($\dot{V}_{50\%VC}$), and 25% of vital capacity ($\dot{V}_{25\%VC}$) measured, respectively, at 50% and 25% of the vital capacity for the specific curve; maximum expiratory flow at 60% of total lung capacity was obtained as well at zero time and 2 hr. Subjects breathed through a modified Otis-McKerrow valve connected on the inspiratory side to a Parkinson-Cowan dry gas-meter equipped with a recording potentiometer, and the resulting volumes were recorded on a graphic recorder (HP 7745A).

Statistical Analysis

Data for each test obtained at 0.5, 1.0, 1.5 and 2.0 hr air exposure were compared with the 0 hr values by the Student paired t-test. The same comparison was made for the ozone exposure data. Similarly differences between air and ozone exposure data at each half-hour were assessed by the Student paired t-test. Chi-square analysis was performed on the number of decreases in $\dot{V}_{50\%VC}$ of greater than 10% with air exposure as compared with the number of decreases with ozone exposure. There were 66 test points each with air and ozone.

Results

Physical and clinical characteristics of the asthmatics are shown in Table 1. There were 5 males and 12 females. The mean age was 41 years, and the ages ranged from 20 to 71 years. The mean duration of asthma was 16 years but ranged from 1 year to 48 years prior to the subjects undertaking our study. Five subjects had cough and sputum and two reported cough only. Seven subjects were former smokers and none were current cigarette smokers. Thirteen of the 17 subjects had significant + ve skin test responses to one or more of the common inhaled allergens.

The objective was to study asthmatics irrespective of the severity of their disease under the best degree of control which could be achieved, that is, in the condition in which they live and work. They were not withdrawn from their routine medication regimens. Table 2 indicates the medications the patients were taking at the time of study. Twelve sub-

Table 1. Physical and clinical characteristics of asthmatics.[a]

Number of asthmatics	Ratio male/ female	Height, cm	Weight, kg	Age, yr	Duration of asthma, yr	Cough and sputum[b]	Number of former smokers
17	5/12	166 (153-186)	63 (53-81)	41 (20-71)	16 (1-48)	7	7

[a] Values are mean and range in parentheses.
[b] Number of asthmatics reporting cough or cough and sputum.

jects were using some form of inhaled broncholidator, nine of these and one other patient used oral broncholidators. Four were on oral steroid therapy. Five were using the inhaled steroid beclomethasone dipropionate and five were on Intal. In general these were mild asthmatics or moderately severe asthmatics whose condition was under good control.

Table 3 shows the baseline pulmonary function data obtained from these patients. Mean values expressed as percentage of predicted (*29, 30*) are within normal limits, but, the ranges shown beneath are indicative of the variability in pulmonary function status of these patients and reflect the obstructive nature of their disease as does the low mean $FEV_{1.0}/FVC$ ratio. There is variability in severity of asthma in these patients, as reflected by the functional capacity of their lungs.

Table 4 shows the results obtained from 2 hr exposure to 0.25 ppm of ozone of the subjects described above. There were no dramatic changes as a result of either air exposure or ozone exposure. No statistically significant differences were demonstrated by the following paired *t*-test comparisons of the data: 0 hr air vs. 0 hr ozone, 0 hr air vs. 2 hr air, 0 hr ozone vs. 2 hr ozone, 2 hr air vs. 2 hr ozone. Similarly there were no significant ozone induced changes at any time during exposure compared with corresponding air exposure or pre-ozone exposure data in the group as a whole.

Examination of data on individuals suggested that some asthmatics do appear to respond to ozone exposure with a deterioration in lung function. To identify individuals who may have demonstrated a response to ozone, we used a range of ± 10% of the pre-exposure value on each exposure for $\dot{V}_{50\%\,VC}$. $\dot{V}_{50\%\,VC}$ is a measurement we have found to be sensitive and useful for detecting objective changes in lung function in previous experiments on normals with ozone exposure (*24*). Figure 1 shows individual data obtained at each half hour of air exposure and ozone exposure. The horizontal lines indicate ± 10% of the pre-exposure value. With air exposure, there were nine test points for which $\dot{V}_{50\%\,VC}$ was greater than 110% of the pre-exposure value. There were eight test points where $\dot{V}_{50\%\,VC}$ was less than 90% of the 0 hour value. During ozone exposure, there were 10 increases of greater than 10% with ozone and 25 test points where $\dot{V}_{50\%\,VC}$ was less than 90%. Using chi-square analysis, there were a statistically significantly greater number of decreases of more than 10% in $\dot{V}_{50\%\,VC}$ with ozone (n = 25) than with air (n = 8). The data suggest that there are asthmatics who respond to 0.25 ppm of ozone as compared with their responses to parallel air exposures.

Figure 2 shows mean data for $\dot{V}_{50\%\,VC}$ expressed as percent of the zero time value. There was no significant difference between air exposure and ozone ex-

Table 2. Medications.

Medication	Number of subjects[a]
Inhaled bronchodilator	12
Oral bronchodilator	10
Oral steroid	4
Inhaled steroid	5
Intal	5

[a] Number of subjects out of a total of 17 using indicated medications at the time of ozone studies.

Table 3. Routine pulmonary function measurements.[a]

	RV	RV/TLC, %	VC R	VC F	$FEV_{1.0}/FVC$, $FEV_{1.0}$	%	$\dot{V}_{50\%\,VC}$
Mean	111	33	103	102	80	64	63
Range	81–182	19–49	72–120	57–131	23–119	34–92	9–122

[a] Values % predicted except RV/TLC and $FEV_{1.0}/FVC$; n = 17.

Table 4. Results of exposures of asthmatics to ozone (0.25 ppm).[a]

Parameter	0 hr[b] Air	0 hr[b] Ozone	2 hr, % of zero time value[c] Air	2 hr, % of zero time value[c] Ozone
FVC	3.89 ± 0.25	3.75 ± 0.27	99 ± 3	99 ± 2
$FEV_{1.0}$	2.65 ± 0.25	2.60 ± 0.27	99 ± 3	95 ± 3
$\dot{V}_{50\%\,VC}$	2.0 ± 0.29	1.96 ± 0.28	102 ± 4	95 ± 5
$\dot{V}_{60\%\,TLC}$	1.65 ± 0.31	1.59 ± 0.30	96 ± 5	90 ± 8
RV	1.85 ± 0.16	1.66 ± 0.12	96 ± 4	112 ± 8

[a] Values are mean ± S.E. n = 17.
[b] Values at zero time expressed in liters for FVC, $FEV_{1.0}$, and RV and l./sec for $\dot{V}_{50\%\,VC}$ and $\dot{V}_{60\%\,TLC}$.
[c] Value after 2 hr exposure expressed as percentage of pre-exposure value.

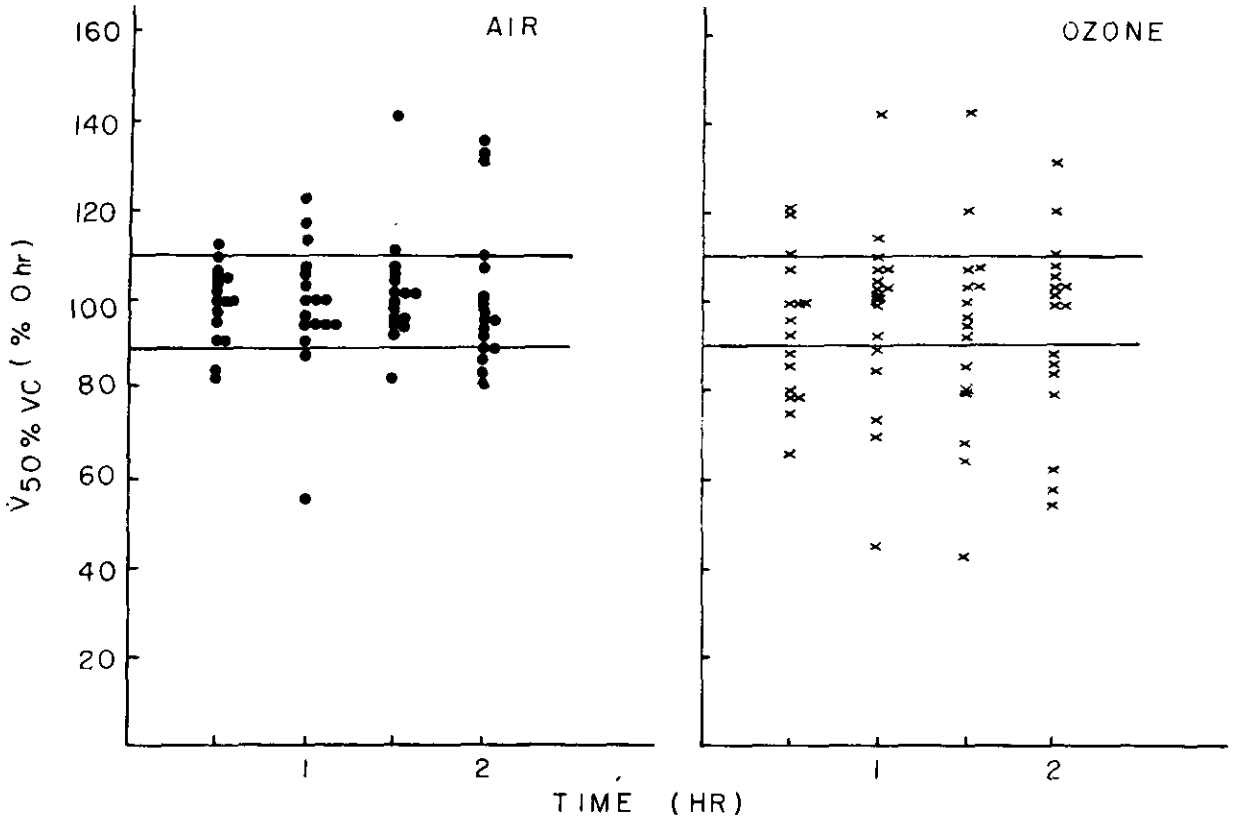

FIGURE 1. $\dot{V}_{50\%\,VC}$ as a percentage of values at zero time against time: (●) individual data obtained during air exposure on 16 subjects at 0.5 hr, 1.0 hr, 1.5 hr and 2.0 hr and for one subject at 1.0 hr and 2.0 hr; (X) corresponding data during ozone exposure. Horizontal lines represent ±10% of zero time value in each case. Significant difference ($p < 0.05$) between air exposure values of less than 90% (*8*) and ozone exposure values less than 90% (*25*) by chi-square analysis.

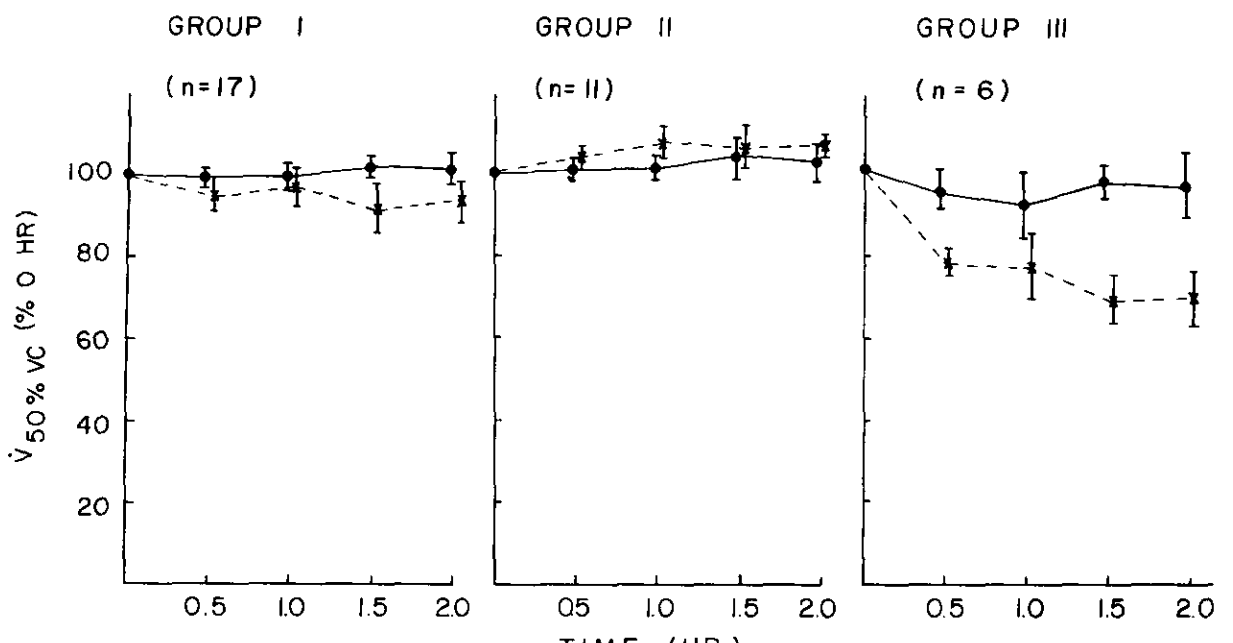

FIGURE 2. $\dot{V}_{50\%\,VC}$ expressed as percentage of values at zero time as a function of time of exposure: (●) mean ± S. E. of air values obtained at 0.5 hr, 1.0 hr, 1.5 hr, and 2.0 hr of air exposure; (X) mean ± S. E. of corresponding data for ozone exposure. Group I (n = 17 subjects); group II, 11 subjects who showed no greater decreases (>10%) on ozone than air; Group III, 6 subjects who had more decreases (>10%) on ozone than air.

posure for the group as a whole (group I) although the ozone values are consistently lower than the air values. In group II, made up of individuals who had no greater responses to ozone than air, the mean $\dot{V}_{50\%\,VC}$ did not change appreciably in ozone or air. Group III consists of individuals who appeared to have more functional change in ozone than air. There was a mean reduction of $\dot{V}_{50\%\,VC}$ of approximately 7% after 1 hr of air exposure, and by 2 hr $\dot{V}_{50\%\,VC}$ had returned to 98% of the pre-exposure value. However with 1 hr of ozone exposure there was a mean decrease in $\dot{V}_{50\%\,VC}$ of 22%, and by 2 hr it was approximately 30%. Four subjects in group III had symptoms with ozone exposure ranging from trace to moderately severe cough, shortness of breath, wheeze and chest tightness; two subjects had no symptoms. Of the subjects in group II, four had only trace or mild symptoms and seven had no symptoms. Two subjects (one in group II and one in group III) had trace to moderately severe symptoms with exposure to air.

Discussion

The present studies were carried out to examine whether acute exposure of asthmatics to a realistic environmental concentration of an irritant pollutant, ozone, can result in any detectable changes in lung function. The asthmatics had varying degrees of severity of asthma; most were taking medications for their therapy. The results indicate that although there was a trend for $\dot{V}_{50\%\,VC}$ to fall during ozone exposure, the difference from that in air was not statistically significant. However, the results of the individual subjects demonstrated a drop in $\dot{V}_{50\%\,VC}$ in six subjects on ozone compared with air while in the remaining 11 subjects it did not change appreciably.

Linn et al. (*31*) have recently reported on studies of exposure of asthmatics to 0.2 ppm of ozone with secondary stresses of heat and exercise. They found no significant changes in pulmonary function. They did observe small but significant blood biochemical changes which included: increased glucose-6-phosphate dehydrogenase and lactate dehydrogenase activities; increased red cell fragility and decreased concentration of reduced glutathione, hemoglobin concentration and acetylcholinesterase activity. Our results agree with those of Linn et al. in that no dramatic effects were demonstrated in the group of asthmatics with 2 hr exposure to ozone. Linn et al. (*31*) did not demonstrate any clear excess of effect in individuals with ozone as compared with control studies. The results of the present studies indicate that some individuals do respond to 0.25 ppm of ozone over a 2-hr exposure period.

As a result of previous studies of healthy or mildly asthmatic persons, Hackney et al. (*32, 33*) suggested that prior ambient exposures elicit an adaptive response decreasing the subjects reactivity to ozone. The asthmatics in Linn's studies (*31*) all lived in urban southern California and had been exposed to ozone on occasion. The subjects in the present study live in Toronto, Canada, where exposures to ozone are to lower concentrations and much less frequent.

In terms of relating response to ozone with historical and clinical features of asthma in these subjects, no relationship was seen between response to ozone and the following parameters: (1) pulmonary function status prior to exposure, (2) duration of asthma, (3) cough and sputum, (4) allergies. Five of six subjects who appeared to respond were taking Intal and none of the others were; five were former smokers, and only two of those who did not appear to respond to ozone were ex-smokers.

It is concluded from these studies that individual asthmatics can demonstrate deterioration in objective measures of lung function at 0.25 ppm. From the point of view of environmental health standards, it is important to note that higher concentrations of ozone do occur in and around urban environments and may have adverse effects on some people suffering from asthma. Additional studies are required to examine whether the asthmatics who appear to respond are a subgroup of a larger group thought to have increased sensitivity and to establish whether these people have any unique characteristics which increase their response to ozone.

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