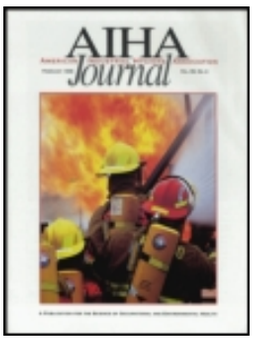

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The Effects of Sulfur Dioxide on Pulmonary Function in Healthy Nonsmoking Male Subjects Aged 55 Years and Older

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To determine whether normal nonsmoking individuals aged 55 years or greater have heightened bronchial reactivity to inhaled SO_2, ten male subjects, 55 to 73 years of age, were exposed for 20 min at rest and 10 min during moderate exercise on a treadmill to the following: 1) NaCl droplet aerosol, or 2) 1.0 ppm of SO_2 and NaCl droplet aerosol. Seven of the subjects also were exposed to 0.5 ppm SO_2 and NaCl droplet aerosol. Significant decreases in forced expiratory volume in one sec (FEV_1) were seen 2-3 min post-exercise following all three test modes. The reduction in FEV_1 seen after NaCl aerosol + 1.0 ppm SO_2 was significantly greater than that seen after NaCl aerosol alone. The results show that men aged 55 years or older are somewhat more sensitive to NaCl aerosol + 1.0 ppm SO_2 than similarly exposed normal adolescents, but not nearly as sensitive as asthmatic subjects. This study also demonstrates that investigations of air pollutants and exercise can be undertaken in subjects of this age.

Introduction

Epidemiologic studies have reported an association between high ambient levels of sulfur dioxide (SO_2) and increased respiratory morbidity and mortality. Two earlier studies indicated that those most adversely affected were the elderly.[1,2] Controlled SO_2 exposure studies with human subjects generally have centered on normal and asthmatic young adults and were supplemented by work with normal and atopic adolescents.[3-7] To the knowledge of the authors, no similar studies have been reported with subjects over 55 years of age.

In the present study a group of normal males, aged 55 years and older, were recruited and exposed to three test atmospheres: sodium chloride (NaCl) droplet aerosol, NaCl droplet aerosol + 0.5 ppm SO_2 and NaCl droplet aerosol + 1.0 ppm SO_2. This protocol allowed direct comparison of the response of this group to that of adolescent normal, atopic and asthmatic individuals studied in a similar manner.[3-5] The purpose of this study was to determine whether this age group was intrinsically more sensitive to SO_2 or whether the increase in adverse health effects observed in the epidemiologic studies was, more probably, due to underlying disease. An additional purpose was to evaluate the response to SO_2 in a group of adult male subjects who are representative of the oldest segment of the working population. Of the male workers in the United States, 14.5%, a total of over 9 million men, are over the age of 55 years.[8] In 1973, 20% of the SO_2 emissions in this country came from industrial processes such as the primary metal industry, petroleum industry, chemical manufacturing, paper and pulp mills, *etc.*[9] NIOSH records show that an estimated 51 398 workers had exposure to SO_2 during the 1972-1974 time period; during 1981 through 1983 the preliminary estimate of exposed workers was 38 528. Thus, many workers have potential for exposure to SO_2 through their jobs.[10] SO_2 gas is highly reactive and in the workplace will combine with any hygroscopic aerosols present, forming, for instance, sodium sulfate or ammonium sulfate. Thus, the SO_2 plus a NaCl aerosol exposure in this study is directly applicable to the form of SO_2 exposure likely to be found in the workplace.

Methods

The subjects were ten normal, currently nonsmoking male volunteers 55 to 73 years of age, who were informed of the risks of the experimental protocol and who signed consent forms approved by the Human Subjects Committee of the University of Washington. A health questionnaire and physician interview determined that the ten subjects did not have histories compatible with asthma or atopy. A medication and food survey identified no drugs or foods known to alter bronchial reactivity. Screening pulmonary function tests (FEV_1, FVC and $FEF_{25-75\%}$) were in the normal range for each subject's age and height.[11] A complete physical examination and an electrocardiogram were performed to exclude identifiable, asymptomatic cardiopulmonary pathology that might have interfered with experimental findings or endangered the subject.

Before participation in the study, a methacholine challenge test (MCCT) was performed to characterize each subject's underlying bronchial reactivity. Each subject breathed, at tidal volume with nose clips in place, varying concentrations of methacholine (MC) aerosol (normal saline alone, 0.075, 0.31, 1.25, 2.5, 5.0, 10.0 and 25.0 mg/mL) for 2 min; 5 mL of each test solution was measured into a Turret #51 nebulizer (Diverse Respiratory Air Products, San Dimas, Calif.) for each inhalation. The airflow rate was 6 L/min at 15 psi. A blow-by system captured all exhaled air, which then was vented outside the building. Weighing the nebulizer before and after a subject breathed normal saline for 2 min determined the mean nebulizer output of 0.22 ± 0.07 mL/min. The mass median diameter of each nebulizer's aerosol was determined by a Royco particle counter to be from 1.7-1.8 μm with a geometric standard deviation (σ_g) of 1.6-2.2 μm. FEV_1 was measured 30, 90 and 180 sec after

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inhalation of MC. A positive response to the MCCT was a 20% or greater reduction in FEV_1 that was sustained for 90 and 180 sec following the test inhalation. The concentration of MC that provoked a 20% reduction in FEV_1 compared to the control exposure was defined as the provocative concentration (PC_{20}).

Once subjects were accepted for participation in the study, an interval of at least one week separated all test exposures. Subjects were interviewed immediately prior to testing to determine if they had had a recent viral illness, had taken medications known to alter bronchial reactivity, or had taken caffeine containing foods or drink. One individual developed an upper respiratory infection between exposures that, by the authors' protocol, required postponement of subsequent exposures for four weeks. Each subject was studied at the same time of day for the three exposure atmospheres.

The three exposure atmospheres were as follows:

1) Filtered air to which NaCl droplet aerosol was added to reach a particle mass concentration of 1 mg/m^3, relative humidity (RH) ~75%, temperature (T) ~22° C.
2) Filtered air to which SO_2 + NaCl droplet aerosol were added to reach concentrations of 0.5 ppm and 1 mg/m^3, respectively; RH ~75%, T ~22° C.
3) Filtered air to which SO_2 + NaCl droplet aerosol were added to reach concentrations of 1.0 ppm and 1 mg/m^3, respectively; RH ~75%, T ~22° C.

As a precaution, the first exercise session on the treadmill was always during NaCl aerosol exposure alone. The second and third exposure modes (for seven subjects who inhaled 0.5 ppm SO_2 and aerosol) were randomized through the toss of a coin. The subjects were not told which mode they were inhaling, and nose clips were in place prior to the inhalation to diminish olfactory cues. When questioned, none of the subjects remarked about any unusual smell or taste. The subject coach and record analyst did not know the exposure mode.

The methods for generating and monitoring the SO_2 + NaCl mixture have been described previously.[6] The aerosol had a particle mass median diameter (MMD) of 0.9 μm and a geometric standard deviation (σ_g) of 2.0.

Physiological measurements were recorded while subjects were seated in a volume-displacement body plethysmograph. The following measurements were recorded on an X-Y plotter and 8-channel thermal strip chart recorder:

1) Total respiratory resistance (R_T), with use of the forced oscillatory pressure technique at a frequency of 3 Hz, based on an average of ten breaths.[12]
2) Thoracic gas volume at functional residual capacity (FRC), with utilization of the gas compression technique.[13]
3) Forced expiratory volume in 1.0 sec (FEV_1) calculated from a maximal flow-volume maneuver.

Two sets of measurements that required approximately 15 min were made during the baseline period. Following the baseline measurements, the subject was seated outside the plethysmograph where he breathed one of the exposure atmospheres *via* a rubber mouthpiece with noseclips in place for 20 min. During this period the average minute ventilation ($\dot{V}_E$) was measured (respiratory integrator, Hewlett-Packard) as well as the end tidal CO_2 tension (Beckman gas analyzer) to detect if the subject was hyperventilating. Heart rate and rhythm were monitored during exposures with an electrocardiogram (Hewlett-Packard). Next, during a brief

TABLE I
Clinical Characteristics of Healthy Male Subjects

Subject ID#	Age	NS/ES[A]	FEV_1 (1) (% pred)	FVC (1) (% pred)	MCCT[B]
0106	64	ES (5 pk-year)	3.7 (109%	4.5 (102%)	10 mg/mL (22% drop)
0206	73	NS	3.5 (120%)	4.1 (109%)	25 mg/mL (22% drop)
0222	62	NS	3.9 (130%)	4.4 (116%)	25 mg/mL (6% drop)
0302	69	NS	2.9 (107%)	3.4 (97%)	25 mg/mL (7% drop)
0309	60	ES (9 pk-year)	4.6 (124%)	5.2 (111%)	25 mg/mL (13% drop)
0314	68	NS	3.0 (111%)	3.3 (94%)	25 mg/mL (0% drop)
0328	67	NS	4.1 (146%)	4.8 (137%)	25 mg/mL (14% drop)
1115	55	ES (26 pk-year)	3.8 (115%)	4.5 (107%)	25 mg/mL (11% drop)
1206	63	ES (10 pk-year)	3.5 (109%)	4.7 (115%)	25 mg/mL (3% drop)
0131	59	ES (15 pk-year)	3.9 (97.5%)	5.0 (96%)	25 mg/mL (0% drop)

[A]NS/ES = never smoked/ex-smoker.
[B]Methacholine Challenge Test.

TABLE II
FEV_1 Values Before, During and After Exposure in Ten Healthy Male Subjects Over 55 Years of Age

Subject ID#	Test Atmosphere	Baseline	Post-Rest Exposure	Post-Exercise Exposure
0106	NaCl	4.2	4.0	3.9
	NaCl + 1 ppm SO_2	4.1	3.6	3.9
	NaCl + 0.5 ppm SO_2[A]	4.1	4.2	3.4
0206	NaCl	3.5	3.2	3.4
	NaCl + 1 ppm SO_2	3.8	3.5	3.4
	NaCl + 0.5 ppm SO_2	3.4	3.3	3.2
0222	NaCl	4.0	3.8	3.7
	NaCl + 1 ppm SO_2	3.8	3.8	3.5
	NaCl + 0.5 ppm SO_2	3.8	3.7	3.7
0302	NaCl	4.6	4.4	4.4
	NaCl + 1 ppm SO_2	4.8	4.7	4.4
	NaCl + 0.5 ppm SO_2	4.6	4.6	4.5
0309	NaCl	2.7	2.8	2.4
	NaCl + 1 ppm SO_2	2.8	2.7	2.2
	NaCl + 0.5 ppm SO_2	2.9	2.6	2.4
0314	NaCl	3.5	3.5	3.4
	NaCl + 1 ppm SO_2	3.5	3.5	3.4
	NaCl + 0.5 ppm SO_2	3.3	3.2	3.3
0328	NaCl	3.8	4.0	3.6
	NaCl + 1 ppm SO_2	4.1	4.1	3.8
	NaCl + 0.5 ppm SO_2	4.0	3.9	3.8
1115	NaCl	3.7	3.6	3.6
	NaCl + 1 ppm SO_2	3.6	3.5	3.4
1206	NaCl	3.8	3.8	3.8
	NaCl + 1 ppm SO_2	3.9	3.8	3.8
0131	NaCl	4.2	3.9	3.9
	NaCl + I ppm SO_2	4.1	3.8	3.8
Mean ± s.d. NaCl		3.8 ± 0.5	3.7 ± 0.4	3.6 ± 0.5
Mean ± s.d. NaCl ± 1 ppm So_2		3.8 ± 0.5	3.7 ± 0.5	3.6 ± 0.6[B]
Mean ± s.d. NaCl ± .5 ppm SO_2		3.7 ± 0.6	3.6 ± 0.7	3.5 ± 0.6

[A] N = 7
[B] $p < 0.025$ when compared with NaCl exposure.

interruption in exposure (5-7 min), the subject returned to the plethysmograph for one set of functional measurements. The subject then walked on a treadmill while inhaling the test atmosphere by mouthpiece. Since each individual had a different exercise tolerance, the degree of exercise was dictated by the work necessary to increase the resting minute ventilatory volume three to four times. After 10 min of exercise, the subject again entered the plethysmograph for functional measurements over the ensuing 15-18 min.

After each session the subject was given a symptom rating form to record any subjective reactions (including unusual taste or smell) immediately post-exposure, during the remainder of the test day and on the following day.

The records were analyzed in a single blind fashion; *i.e.*, the individual who did the record analysis and calculations did not know what test atmosphere was given for a particular record. Each subject's mean baseline values for FEV_1, R_T, and FRC were compared with the same mean measurements recorded post-rest and post-exercise.

All baseline values were compared with post-exposure values for each functional parameter by use of a paired *t*-statistic. The change in function following exposure to NaCl was compared to the change following SO_2 and NaCl exposure, also with the use of a paired t-test. The symptom rating responses were compared with use of a Wilcoxon sign rank test.

Results

Table I summarizes the important clinical characteristics of the ten subjects. The mean age was 64 years, with a range of 55-73 years. Five subjects had never smoked (NS), and five were ex-smokers (ES). Subject 0106 had a 5-pack-year history of smoking, ending in 1959; subject 0302 had a 9-pack-year history, ending in 1965; subject 1115 had a 26-pack-year history, ending in 1964; subject 1206 had a 10-pack-year history, ending in 1957; and subject 0131 had a 15-pack-year history ending in 1980. Subject 0206 had hypertension controlled with chlorthalidone and captopril; subject 0302 took trazodone, and subject 0222 frequently took aspirin for osteoarthritis.

All pulmonary function values were 94% or greater of the predicted value for age and height. During the MCCT only subjects 0106 and 0206 had a significant reduction (>20%) in FEV_1 at 10 mg/mL and 25 mg/mL MC, respectively. These two subjects were only moderately sensitive to the SO_2. Subject 0106 had a 15% and 1% decrease in FEV_1 following 0.5 and 1 ppm SO_2 respectively; subject 0206 had a 6% and 19% decrease.

Table II summarizes the FEV_1 values before, during and after exposure for each subject. When baseline FEV_1 was compared with FEV_1 following 1.0 ppm SO_2 exposure at rest, there was a significant 4% decrease ($p < 0.025$). This change was not significantly different, however, than the 2% decrease seen following NaCl dose. When baseline FEV_1 was compared with the FEV_1 at 2-3 min post-exercise exposure, there was a significant decrease for all test atmospheres: NaCl droplet aerosol (5% decrease, $p < 0.001$); NaCl aerosol + 0.5 ppm SO_2 (7% decrease, $p < 0.05$); and NaCl aerosol + 1.0 ppm SO_2 (8% decrease, $p < 0.001$). When the magnitude of the difference from baseline to the 2-3 min post-exercise exposure was compared for NaCl droplet aerosol exposure and both the SO_2 exposure atmospheres, a significant difference between the control exposure (NaCl droplet aerosol) and the NaCl aerosol + 1.0 ppm SO_2 ($p < 0.025$) was found. This difference suggests that even though there is a significant reduction in FEV_1 post NaCl aerosol alone following exercise, the 1.0 ppm SO_2 exerted an additional, significant pulmonary functional effect on the performance of FEV_1.

R_T and FRC demonstrated no significant changes from baseline measurements. There were no consistent differences in answers to the symptom rating form between the sham NaCl droplet aerosol exposure and the SO_2 + NaCl aerosol exposures.

Discussion

The mean changes in several pulmonary function parameters were compared in men aged 55 years and older after three test exposure atmospheres: NaCl droplet aerosol, NaCl drop-

let aerosol + 0.5 ppm SO_2, and NaCl droplet aerosol + 1.0 ppm SO_2. A significant reduction from baseline FEV_1 was noted for exposure to NaCl aerosol + 1 ppm SO_2 at rest and for each exposure atmosphere 2-3 min post-exercise. When the magnitude of the difference between baseline to post-exercise values was compared for NaCl aerosol and NaCl aerosol + 1.0 ppm SO_2, a significant difference ($p < 0.025$) was demonstrated. Thus, the presence of 1.0 ppm SO_2 in the aerosol produced an additional, significant decrement in FEV_1 beyond the exercise-induced bronchoconstriction following normal saline exposure. The average percentage FEV_1 reduction following increasing concentrations of SO_2 (7% following 0.5 ppm SO_2 and 8% following 1.0 ppm SO_2) demonstrates a dose response trend which further supports this contention. The response was short-lived, as was demonstrated by the fairly rapid recovery toward baseline within 5-8 min post-exercise.

It should be noted that the subjects in this study breathed the SO_2 through a mouthpiece. It has been shown in human subjects that when SO_2 is inhaled nasally, over 99% of the gas is taken up by the nose.[14] Thus, since the subjects breathed the SO_2 through a mouthpiece, an important defense mechanism was bypassed. To that extent, this exposure may represent a "worst case" situation. On the other hand, the exercise time chosen in this study is representative of light exercise such as level walking at 2 mph or light yard work that seems realistic for this age group. Also, the subject population is representative of the oldest segment of the work force involved in work at this ventilation rate.

The effects of NaCl droplet aerosol and NaCl droplet aerosol + 1.0 ppm SO_2 inhaled *via* a mouthpiece in normal adolescents were compared previously.[3] The only differences in that testing protocol compared to the present study were that each test mode was breathed at rest for 30 min, rather than 20 min, and the minute ventilation achieved during exercise was five to six rather than three to four times resting minute ventilation. The subjects in this study breathed an average $\dot{V}_E$ = 9.6L for 20 min at rest and an average $\dot{V}_E$ = 31.1L for 10 min during exercise (effective dose = 502 ppm·L). The normal adolescent subjects breathed an average $\dot{V}_E$ = 7.0L for 30 min at rest and an average $\dot{V}_E$ = 40L during exercise (effective dose = 610 ppm·L). Therefore, the adolescent subjects inhaled approximately a 20% greater effective dose of SO_2. That study demonstrated a small (6%) but statistically significant reduction in average FEV_1 values following exposure to the 1 ppm SO_2-NaCl aerosol combination during exercise. The larger average decrement in FEV_1 (8%) following a smaller effective dose in this experiment suggests that elderly individuals may be slightly more sensitive to SO_2 than normal adolescents. Both adult asthmatic subjects and adolescent asthmatic subjects have been shown to be quite sensitive to 0.5 and 1.0 ppm SO_2.[5,7,15] Also, nonasthmatic atopic adolescent subjects show moderate to large changes in pulmonary function following inhalation of 1 ppm SO_2 or 1 ppm SO_2 plus NaCl droplet aerosol during moderate exercise.[4] A comparison of the average percentage changes in FEV_1 in adolescent and adult subjects is shown in Table III.

Other laboratories have studied SO_2 effects in normal young adults, but their testing methods have differed from the authors in that a NaCl aerosol was not used to carry the SO_2 and/or pulmonary functional measurements varied in type and timing. Snell and Luchsinger[16] studied nine normal subjects (aged 20 to 40 — five male, four female) during a 15 min resting exposure by mouthpiece to 0.5, 1.0 and 5.0 ppm SO_2 combined with NaCl aerosol and the same SO_2 concentrations with filtered air. Maximum expiratory flow at 50% of vital capacity (MEF_{50}) was measured 15 sec after each exposure. Significant MEF_{50} changes with 5.0 ppm plus NaCl aerosol, 1.0 ppm plus filtered air and 5.0 ppm plus filtered air were found. Sheppard and coworkers[7] studied seven nonsmoking normal subjects (23 to 27 years, five male, two female) by measuring specific airway resistance (SR_{aw}) during 10 min of resting exposure to 1.0, 3.0 and 5.0 ppm SO_2 plus filtered air. A significant group mean SR_{aw} increase was seen only with 5.0 ppm SO_2 plus filtered air.

Both of these comparison groups were composed of males and females. Certain methacholine studies suggest that females have an increased bronchial reactivity to methacholine.[17,18] Also, Horvath and coworkers[19] and Laurtizen and Adams[20] observed that young adult female subjects showed larger decrements in FEV_1 following exposure to 0.75 ppm and 0.4 ppm ozone, respectively, than did young adult male subjects. No one has published a comparison by sex of the pulmonary responses to SO_2. The authors' laboratory study of the magnitude of change in FEV_1, R_T and $\dot{V}_{max50}$ in 16 male and 9 female adolescent asthmatic subjects following exposure to 1 ppm SO_2 was re-examined. There was no

TABLE III
Average Change (%) in Pulmonary Functional Values in Four Groups of Subjects After Exposure to 1.0 ppm SO_2 Plus NaCl Droplet Aerosol During Moderate Exercise.[A]

Pulmonary Functional	Extrinsic Asthmatic Adolescents (5)	Atopic Non-asthmatic Adolescents (4)	Normal Adolescents (3)	Normal Males Greater 55 Years[B]
FEV_1	-23%	-18%	-6%	-8%

[A]Two to three min after a 30 min resting and 10 min exercising (5-6 times resting minute volume) exposure.
[B]Two to three min after a 20 min resting and 10 min exercising (3-4 times resting minute volume) exposure.

significant difference based on sex between the mean values for any of the comparisons.

This present study does not support the hypothesis that older individuals show greater bronchial reactivity to inhaled SO_2 than normal adolescents, although the former did show a slightly greater response. This effect was short-lived and small in magnitude. Clearly, these changes do not represent a life-threatening pulmonary response to SO_2. Prolonged SO_2 exposures such as might occur in the workplace may have greater effects, however, especially in individuals with pre-existing cardiopulmonary disease and/or with prolonged exertion, leading to increased morbidity and mortality. The current TLV® for SO_2 is 2 ppm. Obviously, within an 8-hr period, peaks considerably higher than the 1 ppm investigated in this study could exist for at least 10 min without violating the TLV. Thus, the effects reported here represent the lowest end of a potential workplace exposure, and larger changes in pulmonary function could be expected in many situations. Further study also should characterize the response to low levels of SO_2 in older individuals who are women, smokers or who have chronic bronchitis, emphysema or cardiovascular disease.

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