Research Contract Final Report to State

of California Air Resources Board

Title of Contract: Effects of Air Pollution on Airway Function

Contract No: A9-115-30

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Abstract

In a series of studies, we have shown that adult subjects with mild asthma develop greater bronchoconstriction on inhaling sulfur dioxide than nonasthmatic subjects. When exposed to sulfur dioxide at rest, the asthmatic subjects developed significant bronchoconstriction -- sometimes associated with wheezing and shortness of breath -- on inhaling 1 and 3 ppm of sulfur dioxide in air, whereas nonasthmatic subjects developed bronchospasm only on inhaling 5 ppm. In additional studies, we have shown that the increase in the rate and depth of breathing required for exercise potentiates the response of asthmatic subjects to sulfur dioxide: when exposed to sulfur dioxide for 10 min while performing light to moderate exercise, our subjects developed bronchospasm on inhaling 0.50 and 0.25 ppm. Additional studies showed that the nose offers partial protection against the effects of sulfur dioxide on the airways. When our subjects performed light exercise while breathing sulfur dioxide through a facemask (permitting breathing through the nose and mouth), the bronchoconstriction caused by sulfur dioxide was less than that obtained when our subjects inhaled sulfur dioxide through a mouthpiece. At higher levels of exercise, the protection afforded by oronasal breathing decreased, probably because of the greater proportion of air bypassing the nose as ventilation increased. Taken as a group, our studies show that people with asthma constitute a subgroup of the population who develop bronchoconstriction -- often with symptoms of wheezing and shortness of breath -- on brief exposure to levels of sulfur dioxide sometimes found in urban air.

We have also found that the responsiveness of asthmatic subjects to sulfur dioxide can be diminished both by treatment with disodium cromoglycate -- a drug commonly used in patients with asthma -- and by repeated exposures to sulfur dioxide at 30-min intervals. This tolerance to sulfur dioxide disappears within 24 h.

In studies of experimental animals, we have shown that inhalation of sulfur dioxide causes rapid shallow breathing and coughing and that these changes in the pattern of breathing occur even if bronchoconstriction is blocked by pretreatment with an antiasthmatic medications. Similar ventilatory responses were elicited by delivery of much smaller doses to the upper airways than to the lower airways. This suggests that the effects of sulfur dioxide inhaled through the mouth are likely to be reflex in nature and due to stimulation of nerve endings in the upper airway, possibly in the larynx.

This work was submitted in fulfillment of contract number A9-115-30 under the sponsorship of the California Air Resources Board.

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List of Studies Described in Report, identified by title on contract applications and by title of resulting publications:

1. Threshold concentration of sulfur dioxide causing a change in airway caliber in people with asthma. Published as abstract "Exercise increases sulfur dioxide-induced bronchoconstriction in subjects with asthma" Physiologist 178:3, 1980; and as article "Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects" Am. Rev. Respir. Dis. 123:486-491, 1981.

2. Studies on the route of exposure in the bronchomotor response to sulfur dioxide in asthmatic subjects. Published as article "Effect of the oronasal breathing route on sulfur dioxide-induced bronchoconstriction in exercising asthmatic subjects" Am. Rev. Respir. Dis 125:627-631, 1982.

3. Effect of progressive increase in exercise load on the bronchomotor response to a constant low concentration of sulfur dioxide. Published as abstract "Effect of exercise level and route of inhalation on the bronchomotor response to 0.5 ppm sulfur dioxide in asthmatic subjects" Am. Rev. Respir. Dis. 125:151, 1982. Article "Effect of exercise rate and route of inhalation on sulfur dioxide-induced bronchoconstriction in asthmatic subjects" has been submitted to Am. Rev. Respir. Dis.

4. Effect of repeated exposure to sulfur dioxide on bronchomotor responsiveness to sulfur dioxide, to histamine, and to other agents. "Tolerance to sulfur dioxide-induced bronchoconstriction in subjects with asthma" Environmental Research, in press.

5. Effect of disodium cromoglycate on bronchomotor responsiveness to sulfur dioxide. Published as abstract "Inhibition of sulfur dioxide-induced bronchoconstriction by disodium cromoglycate." Clin. Res. 29:70A, 1981 and as article "Inhibition of sulfur dioxide-induced bronchoconstriction by disodium cromoglycate in asthmatic subjects." Am. Rev. Respir. Dis. 124:257-259, 1981.

6. Studies of the effect of exposure to ozone on the response to ventilation in conscious dogs. Published as abstract "Effects of sulfur dioxide on ventilation in conscious dogs." Am. Rev. Respir. Dis. 125:220, 1982.

List of Figures

No figures are included in the body of this report but are presented in the published articles supported by this contract (see References).

List of Tables

No tables are included in the body of this report but are presented in the published articles supported by this contract (see References).

Acknowledgments

The investigators wish to acknowledge helpful discussions with Dr. Robert Frank of the University of Washington and with Mr. Dane Westerdahl of the California Air Resources Board.

Executive Summary and Conclusions

This report describes a series of investigations on the respiratory responsiveness of people with mild asthma to concentrations of sulfur dioxide that are often measured in urban air. The conclusions permitted by the individual studies, listed below, show that people with asthma constitute a subgroup in whom transient exposure to levels of sulfur dioxide permitted under current national ambient air quality standards while performing mild or moderate activity causes significant bronchoconstriction, often associated with wheezing, chest tightness, and shortness of breath. This abnormal responsiveness to sulfur dioxide is consistent with the known increase in sensitivity of the tracheobronchial tree that characterizes asthma. In an individual with asthma, the magnitude of the response to sulfur dioxide appears to be a function of the inherent responsiveness of the tracheobronchial tree (which is correlated with the overall clinical severity of the disease), of the level of exercise during the exposure, and of the proportion of ventilation passing through the mouth (bypassing the protective functions of the nose). The results of studies of animals suggest that sulfur dioxide probably causes its effects by a reflex mechanism, triggered by stimulation of sensory receptors in the upper airway, possibly in the larynx.

The conclusions of the individual projects completed in the contract are as follows:

1. People with mild asthma develop bronchoconstriction on inhaling concentrations of sulfur dioxide lower than those that affect airway caliber in healthy people without asthma.
2. Exercise potentiates bronchomotor responsiveness to sulfur dioxide in subjects with asthma so that bronchoconstriction results from brief exposure to levels below those currently permitted by National Ambient Air Quality Standards.
3. Unencumbered breathing through the nose and mouth reduces the bronchomotor response to inhalation of sulfur dioxide during light exercise, probably because of the effectiveness of the nose in removing sulfur dioxide from inspired air. This protection diminishes at higher levels of exercise, where a greater proportion of ventilation bypasses the nose.
4. Repeated exposures to sulfur dioxide at 30-min intervals in asthmatic subjects results in a progressive reduction in bronchomotor responsiveness. This apparent tolerance persists for less than 24 h.
5. The bronchomotor response to inhalation of sulfur dioxide in asthmatic

subjects can be inhibited by pretreatment with inhaled disodium cromoglycate.

6. In experimental animals the delivery of sulfur dioxide to the lungs causes coughing and rapid, shallow breathing through vagal afferent pathways. This reaction is independent of bronchoconstriction. Delivery of sulfur dioxide to the upper airways produces similar effects at much lower concentrations, suggesting that reflex effects of sulfur dioxide inhaled through the mouth are more likely to be mediated through receptors in the upper than the lower airways.

Recommendations

The findings that some people with mild asthma develop bronchoconstriction on inhaling low concentrations of sulfur dioxide as they perform light exercise and that the nose offers partial protection against this effect of sulfur dioxide warrant further investigation. Future studies should include the following:

1. A study designed to determine whether people of different ages, with different degrees of severity of asthma or with other forms of obstructive lung disease are also sensitive to sulfur dioxide's bronchomotor effects when they are exposed under conditions closely simulating those of ordinary life.
2. Studies of the possible protective role of the nose in diminishing the pulmonary response to inhaled irritants. The influence of increases in nasal resistance and in pulmonary resistance on the distribution of flow through the nose and mouth (and, therefore, on the concentration of irritant gas delivered to the tracheobronchial tree) should be investigated. Further, studies should be conducted to investigate the possibility that some air pollutants, such as ozone, might alter nasal resistance and thereby increase the pulmonary effects of a soluble pollutant gas, such as sulfur dioxide, inhaled by freely breathing asthmatic subjects.
3. Studies should be conducted to define the mechanism by which sulfur dioxide provokes bronchoconstriction. The possibility that this highly soluble gas initiates bronchoconstriction by stimulating afferent receptors in the upper airways and/or larynx should be investigated by analyzing the effects of topical anesthesia of the pharyngeal and laryngeal mucosa on the response to inhalation of sulfur dioxide.
4. Studies of the interaction of ozone and sulfur dioxide on ventilation should be undertaken in experimental animals. Because the regulation of breathing appears to be similar in dogs and humans, any interaction found in dogs is likely also to occur in humans. If an interaction is found, further exploration should then be undertaken in human subjects with lung disease as well as in healthy volunteers.

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.

Body of Report

Human Studies of Sulfur Dioxide

RELEVANT BACKGROUND INFORMATION

People with asthma and some people with allergic rhinitis have long been known to respond to inhalation of irritating materials with intense, symptomatic bronchospasm (reviewed in [1]). The mechanism of this abnormal responsiveness -- sometimes described as "bronchial hyperreactivity" -- is unknown, but it appears to involve an exaggeration of activity at some site in the parasympathetic neural pathways that regulate airway smooth muscle tone [2]. Whatever its mechanism, bronchial hyperreactivity appears to be fundamental to the pathogenesis of asthma, for it is ubiquitous in patients with asthma, and the degree of responsiveness correlates with the overall clinical severity of the disease [3].

For the past several years, work in our laboratory has focused on the mechanisms and significance of bronchial hyperreactivity. Thus, there was good reason to suspect that patients with asthma might have exaggerated bronchomotor responsiveness to inhalation of sulfur dioxide. Work on this problem has been supported by our contract with the California Air Resources Board.

First, we studied the effect of sulfur dioxide on airway resistance in subjects with mild asthma. To determine whether subjects with mild asthma or seasonal rhinitis have greater bronchomotor responses to sulfur dioxide than normal subjects, we undertook a study in 7 asthmatic, 7 atopic, and 7 normal subjects, 23 to 37 years of age [4]. We measured the change in specific airways resistance (SRaw) provoked by 10 min of breathing 1, 3, and 5 ppm of sulfur dioxide delivered by mouthpiece on separate days at least 48 h apart. To assess the significance of parasympathetic pathways in the bronchomotor responses to sulfur dioxide, we also measured the change in SRaw provoked by 5 ppm of sulfur dioxide in 17 of the subjects after they inhaled atropine sulfate aerosol (0.1 mg/kg). We found that in the asthmatic subjects, SRaw increased significantly at all concentrations of sulfur dioxide, whereas in the normal and atopic subjects, SRaw increased only at 5 ppm. In the asthmatic group, SRaw increased more than in either of the other groups at 5 ppm ($p < 0.005$), and was sometimes associated with marked dyspnea requiring bronchodilator therapy. The increases in SRaw produced by inhalation of sulfur dioxide were prevented by treatment with atropine in asthmatic and nonasthmatic subjects, which suggested the involvement of parasympathetic pathways. These results indicated that subjects with mild asthma develop bronchoconstriction after exposure to concentrations of sulfur dioxide well below currently accepted standards for occupational exposure, and that sulfur dioxide-induced bronchoconstriction is mediated by parasympathetic pathways.

REPORTS ON INDIVIDUAL PROJECTS

In work supported by subsequent contracts with the California Air Resources Board (the subject of this report), we have explored the implications of these findings for people with asthma exposed to levels of sulfur dioxide that may be found in ambient air. This work has involved analyzing the effects of exercise and of voluntary eucapnic hyperventilation on bronchomotor responsiveness to levels of sulfur dioxide 0.5 ppm and below, the importance of the defensive function of the nose, the development of tolerance with repeated exposures, and the influence of pretreatment with disodium cromoglycate, a medication commonly used to prevent attacks of asthma. Additional background information on these various areas are presented in their individual discussions.

Other work funded in the contract period covered by this report focused on the effects of inhalation of sulfur dioxide in experimental animals. These studies are important in laying the groundwork for future studies in the interaction of ozone and sulfur dioxide.

We first reasoned that exercise, by increasing the total amount of sulfur dioxide inhaled, might potentiate the response. Therefore, we undertook a study to determine whether moderate exercise modifies the bronchoconstriction produced by sulfur dioxide in subjects with mild asthma [5]. In 7 subjects, we compared the changes in SRaw produced by 10 min of exercise alone (400 kpm/min on a cycle ergometer), inhalation of sulfur dioxide alone, and the combination of exercise and sulfur dioxide. During all studies, the subject breathed sulfur dioxide and/or air from a mouthpiece. In 6 additional subjects, we compared the increase in SRaw produced by inhalation of sulfur dioxide during exercise to that produced by eucapnic hyperventilation with sulfur dioxide. Neither inhalation of 0.50 ppm of sulfur dioxide at rest nor exercise or hyperventilation alone had any effect on SRaw. Inhalation of sulfur dioxide during exercise, however, significantly increased SRaw {from 8.46 ± 3.58 L x cm H_2O/L/s (mean ± SD) to 18.16 ± 10.05 at 0.50 ppm and from 8.07 ± 2.69 to 10.48 ± 4.49 at 0.25 ppm ($p < 0.05$)}. In the 2 most responsive subjects, inhalation of 0.10 ppm of sulfur dioxide during exercise also significantly increased SRaw. SRaw increased by the same amount whether sulfur dioxide was inhaled during exercise or during eucapnic hyperventilation at the same minute ventilation, but the time course of the rise in SRaw was different. SRaw was at or near maximal values at the first measurement (30 s) after hyperventilation but not until 2-4 min after exercise. When 4 subjects took larger breaths after inhaling sulfur dioxide during eucapnic hyperventilation to more closely match the volume of the breaths taken after exercise, the time courses of sulfur dioxide-induced bronchoconstriction after hyperventilation and after exercise were nearly identical. These results suggest that exercise increases the bronchoconstriction produced by a given concentration of sulfur dioxide in subjects with asthma by increasing the minute volume of ventilation and that the delay in bronchoconstriction after exercise is due to the large tidal volumes that persist for some minutes during recovery.

In these first 2 studies, inhalation of sulfur dioxide at rest and during exercise was accomplished through a mouthpiece, with the nose occluded by a clip. Because the nose serves an important defensive function and effectively removes sulfur dioxide from the air passing

through it [6], the relevance of our findings to determination of air quality standards has been challenged [7]. The logic behind this challenge is that breathing through a mouthpiece while wearing a noseclip is comparable to few naturally occurring circumstances. In most circumstances, breathing is "oronasal" in that airflow passes through both the nose and mouth. Even with mild or moderate exercise, about 50% of airflow continues through the nose in healthy young adults without nasal pathology (VMJ Niinimaa, Oral-Nasal Distribution of Respiratory Airflow, Ph.D. Thesis, Toronto, 1979). It is furthermore contended that the use of a mouthpiece increases the size of the space between the tongue and palate so that the quantity of soluble gases removed from inspired air is additionally decreased.

We have argued that while this criticism is theoretically valid, it is of very little practical importance [8]. Patients with asthma have a high incidence of allergic rhinitis and may be expected frequently to have partial or complete nasal obstruction. With the nose occluded, a greater proportion of airflow will pass through the mouth. Furthermore, the efficiency of the nose as a filter for sulfur dioxide decreases as inspiratory flow increases [9], and flow rates rise with the increase in ventilation required by exercise.

Although we believed that our logic was sound, we recognized that quantitative data concerning the role of the nose vs mouth was necessary. Therefore, we undertook a study to determine how the oronasal breathing route affects the bronchoconstrictor response to sulfur dioxide inhaled by asthmatic subjects during exercise [10]. In 6 subjects, we compared the changes in SRaw caused by breathing humidified air through a mouthpiece during 5 min of exercise on a bicycle ergometer (550 kpm/min) to the changes caused by breathing humidified air plus 0.5 ppm of sulfur dioxide (a) through a mouthpiece (oral breathing), (b) by facemask (oronasal breathing), and (c) by facemask with the mouth occluded (nasal breathing) during exercise. Breathing humidified air plus 0.5 ppm of sulfur dioxide through a mouthpiece or by facemask during exercise significantly increased SRaw in all 6 subjects, and breathing humidified air plus 0.5 ppm of sulfur dioxide by facemask with the mouth occluded significantly increased SRaw in 5 of 6 subjects. The increase in SRaw caused by breathing humidified air plus 0.5 ppm of sulfur dioxide through a mouthpiece was not significantly different from the increased caused by breathing sulfur dioxide by facemask ($p > 0.05$) but was significantly greater than the increase caused by breathing sulfur dioxide by facemask with the mouth occluded ($p < 0.05$). These results indicate that, although nasal breathing partially protected against sulfur dioxide-induced bronchoconstriction in our subjects, both oral and oronasal breathing of low concentrations of sulfur dioxide during exercise can cause significant bronchoconstriction in people with asthma.

Because realistic field conditions include exposure to ambient pollutants while performing different levels of exercise, we have also studied the effect of increasing levels of exercise on the response to inhaled sulfur dioxide. Furthermore, we wanted to compare the response obtained with mouth breathing to that obtained with oronasal breathing under these conditions. Therefore, we studied the influence of the level of exercise and of the route of inhalation (oral vs oronasal) on sulfur dioxide-induced bronchoconstriction in 9 subjects with mild asthma [11].

In the first phase of the study, we measured the rise in SRaw produced by 5 min of exercise on a cycle ergometer at low, moderate, and high work rates {250, 500, and 750 kilopond meters/min (kpm/min)} while subjects breathed through a mouthpiece (oral breathing). Subjects performed each level of exercise on 2 consecutive experimental days, once while breathing humidified, filtered air and once while breathing similarly treated air containing 0.5 ppm of sulfur dioxide. We randomized the order of exercise levels and delivered the sulfur dioxide in a double-blind manner. In the second phase of the study, subjects repeated this protocol breathing through a facemask (oronasal breathing) which separated and permitted independent measurement of oral and nasal airflow. At each level of exercise, minute ventilation was similar whether the subjects breathed by mouthpiece or by facemask. Mean minute ventilations at 250, 500, and 750 kpm/min were approximately 27, 41, and 61 L/min, respectively (see Table III in article, "Effect of exercise rate and route of inhalation on sulfur dioxide induced bronchoconstriction in asthmatics subjects" in Appendix). Exercise alone induced bronchoconstriction in only one subject. Mean increase in SRaw ± SD (L x cm H_2O/L/s), on breathing sulfur dioxide, above that due to exercise alone was:

	250 kpm		500 kpm		750 kpm	
Mouthpiece	1.3	2.2	9.8	8.8*	12.1	8.9**
Facemask	0.6	1.9	1.6	3.3	8.5	8.2*

*significant change, $p < 0.02$; **$p < 0.005$

Inhaled by mouthpiece, sulfur dioxide caused bronchoconstriction at moderate and high, but not at low, exercise levels. Inhaled oronasally, sulfur dioxide caused bronchoconstriction only at the high exercise level. These findings demonstrate that sulfur dioxide-induced bronchoconstriction is exercise dependent, and that oronasal breathing is partially, but not entirely, effective in preventing this response.

Because repeated exposures to environmental pollutants could affect the subject's response, we have begun to study possible tolerance to inhaled sulfur dioxide. Therefore, we undertook a study to determine whether the bronchoconstriction induced by low concentrations of sulfur dioxide in subjects with asthma decreases with repeated exposure [4]. We had 8 subjects with asthma perform 3 min of voluntary eucapnic hyperpnea with 0.5 ppm of sulfur dioxide in humidified filtered air 3 times at 30-min intervals and measured SRaw before and after each period of hyperpnea. Specific airway resistance increased significantly more after the first exposure to sulfur dioxide {from 7.6 ± 1.7 to 15.5 ± 2.0 L x cm H_2O/L/s (mean ± SEM)} than after the second (from 8.1 ± 1.3 to 10.8 ± 1.6) or third (from 7.6 ± 1.6 to 10.1 ± 1.9) exposures ($p < 0.025$). When we had 7 subjects repeat hyperpnea with sulfur dioxide 24 h and 7 days later, SRaw increased as much as it had after the first exposure (from 8.2 ± 2.5 to 15.5 ± 4.5 at 24 h and from 6.6 ± 1.4 to 15.4 ± 2.1 at 7 days). We found in 4 subjects that repeated exposures to sulfur dioxide caused short-term inhibition of the bronchomotor response to sulfur dioxide but did not

inhibit the bronchomotor response to histamine aerosol. We conclude that repeated exposures to a low concentration of sulfur dioxide can induce tolerance to the bronchomotor effects of sulfur dioxide in subjects with asthma and that this tolerance persists for less than 24 h. Tolerance to the bronchomotor effects of sulfur dioxide is not caused by decreased responsiveness of airway smooth muscle nor by a generalized decrease in the responsiveness of vagal reflex pathways, since the bronchomotor response to histamine is preserved.

Our studies, performed under contract with the California Air Resources Board, have identified a sensitive population of individuals who respond excessively to low concentrations of inhaled sulfur dioxide. Because of the potential clinical importance of these and other chemical "irritants" on the airways of asthmatic subjects, we have initiated studies to discover novel therapeutic methods of inhibiting these asthmatic responses. Disodium cromoglycate has interesting inhibitory effects on some forms of asthmatic bronchoconstriction. Therefore, to determine whether disodium cromoglycate (cromolyn) inhibits the bronchoconstriction produced by inhalation of sulfur dioxide in people with asthma, we undertook a study of 6 asthmatic subjects [12]. Each subject inhaled 40 mg of cromolyn on one day and lactose placebo on another day 20 min before inhaling sulfur dioxide for 10 min while exercising at a moderate rate (400 kpm/min) on a bicycle ergometer. Sulfur dioxide was delivered in humidified air at ambient temperature in concentrations of 0.5 ppm (3 subjects) or 1.0 ppm (3 subjects). Cromolyn and lactose treatments were given to each subject in a randomized sequence and in a double-blind manner. On a third day, each subject exercised at the same work rate breathing humidified air without sulfur dioxide at ambient temperature. We measured SRaw in a body plethysmograph every 30 s for 10 min before and after each of the 3 periods of exercise. After treatment with lactose, sulfur dioxide inhalation significantly increased SRaw in all 6 subjects {from a baseline of 6.5 ± 0.9 to 19.0 ± 4.8 L x cm H_2O/L/s (mean ± SE) after sulfur dioxide}. After treatment with cromolyn, sulfur dioxide inhalation caused no increase in SRaw in 4 subjects and a small rise in 2 subjects. The mean increase in SRaw (from a baseline of 7.3 ± 0.9 to 10.0 ± 1.5 L x cm H_2O/L/s after sulfur dioxide) was significantly smaller than after lactose treatment ($p < 0.025$). Exercise alone had no effect on SRaw in any subject. Thus, cromolyn inhibits sulfur dioxide-induced bronchoconstriction in subjects with asthma. This finding suggests either that sulfur dioxide induces bronchoconstriction by stimulating the release of mediators from mast cells or that cromolyn inhibits bronchoconstriction by a mechanism independent of its effect on mast cells.

Studies of the Effect of Exposure to Inhaled Pollutants in Dogs.

INTRODUCTION

On August 18, 1981, we requested a reallocation of $31,780.00 from the current California Air Resources Grant from the "Personnel" and "Supplies" categories to the "Equipment" category (see letter to Dane Westerdahl dated August 18, 1981, enclosed). We felt that there was some urgency in obtaining more information concerning the effects of inhaled sulfur dioxide in asthmatic subjects. Therefore, we proposed to accelerate this work by placing equipment for monitoring purposes in the large exposure chamber. We did this within the constraints of that year's budget by: (1) deleting the salary of the personnel to perform animal studies ($26,271.00), and (2) deleting additional expenses for dogs to the extent of $5,509.00. The dog studies were proposed to continue, but at a slower rate, and this allowed us to purchase the needed equipment for the human asthma sulfur dioxide studies. This was approved and we performed the animal studies under those constraints.

PURPOSE

The overall purpose of these studies was to determine whether exposure to ozone altered ventilatory responses to inhalation of sulfur dioxide in dogs. Because published studies on ventilation in unanesthetized dogs did not exist, we first proposed to conduct a preliminary study to establish whether the response to sulfur dioxide existed for ventilation.

REPORT ON INDIVIDUAL PROJECT

Effects of sulfur dioxide on ventilation in conscious dogs

We investigated the effects of sulfur dioxide on ventilation in two dogs walking on a treadmill (1.4 mph). We applied 25-300 ppm sulfur dioxide for 4 min through a tracheostomy tube while continuously recording ventilatory variables breath by breath. Responses were dose dependent nd showed a typical time course with coughing at 0.5 min and peak effects at 2 and 5 min. With 200 ppm, there were significant decreases in time of inspiration, Ti (1.16 ± 0.07, 0.78 ± 0.09, 0.56 ± 0.06 s, control, 1st and 2nd peak, mean ± SE, n = 10), time of expiration, Te (1.61 ± 0.07, 0.95 ± 0.20, 0.48 ± 0.09), total time of breath, Tt (Ti + Te), and tidal volume, V_T (447 ± 17, 303 ± 31, 261 ± 34 ml) and significant increases in V_T/Ti (0.40 ± 0.02, 0.45 ± 0.04, 0.54 ± 0.02), Ti/Tt (0.42 ± 0.01, 0.48 ± 0.02, 0.56 ± 0.02), and ventilation (10.1 ± 0.7, 13.1 ± 1.9, 18.9 ± 2.0 L/min). The acceleration of breathing at each peak culminated in further brief coughing. Cooling both cervical vagi to +1°C prevented all of these responses which were unaffected by the inhalation of terbutaline (0.2 mg/ml, 10 min). In one experiment in each dog, we introduced a Foley catheter (with its tip cut off above the balloon) through the tracheostomy into the upper trachea. After intubation of the lower trachea, we applied sulfur dioxide alternatively to the upper and lower airways. A stream of 4 L/min sulfur dioxide (25 ppm) delivered to the upper airways produced

effects similar to 12-14 L/min sulfur dioxide (300 ppm) inhaled into the lower airways. At 2 min, Ti decreased from 1.36 ± 0.16 to 0.90 ± 0.18 s (300 ppm, 1.16 ± 0.36 to 0.70 ± 0.18), Te from 1.81 ± 0.31 to 0.70 ± 0.08 s (1.84 ± 0.66 to 0.72 ± 0.18) and V_T from 536 ± 18 to 389 ± 80 ml (453 ± 120 to 351 ± 21). Coughing was more prominent with upper than with lower airway application (41 ± 1 vs 34 ± 8 coughs/4 min), and it persisted long after the exposure. We conclude that sulfur dioxide delivered to the lungs causes coughing and rapid, shallow breathing through vagal afferent pathways, that the reaction is independent of bronchoconstriction and that sulfur dioxide applied to the upper airways produces similar responses at much lower concentrations, suggesting that reflex effects of low concentrations of sulfur dioxide inhaled through the mouth are more likely to be mediated through receptors in the upper than the lower airways.

This study demonstrated for the first time that sulfur dioxide causes changes in ventilatory pattern, we can determine whether a one- to two-hour exposure to 0.75 ppm of ozone alters the ventilatory responses to inhalation of sulfur dioxide in dogs. Because the mechanisms regulating breathing appear to be similar between dogs and humans, if an interaction between ozone and sulfur dioxide is demonstrated in dogs, it is likely also to occur in humans. Both ozone and sulfur dioxide are common atmospheric pollutants in industrialized societies. The demonstration of an alteration of responsiveness to sulfur dioxide by a prior exposure to ozone in dogs would have potentially important implications for human populations. These would require further exploration in specifically designed studies of human subjects with lung diseases as well as healthy volunteers.

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Research Contract Final Report to

State of California Air Resources Board

Title of Contract: Effects of Air Pollution on Airway Function

Contracts No: A9-115-30 (1980-81)
A0-132-32 (1981-82)

Investigators: J.A. Nadel (Principal Investigator)

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Abstract

In a series of studies, we have shown that adult subjects with mild asthma develop greater bronchoconstriction on inhaling sulfur dioxide than nonasthmatic subjects. When exposed to sulfur dioxide at rest, the asthmatic subjects developed significant bronchoconstriction -- sometimes associated with wheezing and shortness of breath -- on inhaling 1 and 3 ppm of sulfur dioxide in air, whereas nonasthmatic subjects developed bronchospasm only on inhaling 5 ppm. In additional studies, we have shown that the increase in the rate and depth of breathing required for exercise potentiates the response of asthmatic subjects to sulfur dioxide: when exposed to sulfur dioxide for 10 min while performing light to moderate exercise, our subjects developed bronchospasm on inhaling 0.50 and 0.25 ppm. Additional studies showed that the nose offers partial protection against the effects of sulfur dioxide on the airways. When our subjects performed light exercise while breathing sulfur dioxide through a facemask (permitting breathing through the nose and mouth), the bronchoconstriction caused by sulfur dioxide was less than that obtained when our subjects inhaled sulfur dioxide through a mouthpiece. At higher levels of exercise, the protection afforded by oronasal breathing decreased, probably because of the greater proportion of air bypassing the nose as ventilation increased. Taken as a group, our studies show that people with asthma constitute a subgroup of the population who develop bronchoconstriction -- often with symptoms of wheezing and shortness of breath -- on brief exposure to levels of sulfur dioxide sometimes found in urban air.

We have also found that the responsiveness of asthmatic subjects to sulfur dioxide can be diminished both by treatment with disodium cromoglycate -- a drug commonly used in patients with asthma -- and by repeated exposures to sulfur dioxide at 30-min intervals. This tolerance to sulfur dioxide disappears within 24 h.

In studies of experimental animals, we have shown that inhalation of sulfur dioxide causes rapid shallow breathing and coughing and that these changes in the pattern of breathing occur even if bronchoconstriction is blocked by pretreatment with an antiasthmatic medications. Similar ventilatory responses were elicited by delivery of much smaller doses to the upper airways than to the lower airways. This suggests that the effects of sulfur dioxide inhaled through the mouth in animals are likely to be reflex in nature and due to stimulation of nerve endings in the upper airway, possibly in the larynx. Our study of the effects of inreasing doses of an antimuscarinic agent (ipratropium bromide) on bronchomotor responsiveness to sulfur dioxide, however, suggets that mechanisms other than, or in addition to, parasympathetic reflexes must be involved in people with asthma, for we were unable to completely inhibit the rise in SRaw provokd by isocapnic hyperventilation with large doses of ipratropium bromide, even when it was given in combination with intravenous atropine sulfate, and greater inhibition was not produced by increasing the dose of the antimuscarinic agents.

This work was submitted in fulfillment of contracts number A9-115-30 and AO-132-32 under the sponsorship of the California Air Resources Board.

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Physiologist 178:3, 1980.

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ABSTRACT TITLE: EXERCISE INCREASES SULFUR DIOXIDE-INDUCED BRONCHOCONSTRICTION IN SUBJECTS WITH ASTHMA

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EXERCISE INCREASES SULFUR DIOXIDE-INDUCED BRONCHOCONSTRICTION IN SUBJECTS WITH ASTHMA. D. Sheppard,* J.A. Nadel, and H.A. Boushey* (SPON: M.B. McIlroy). Cardiovascular Research Institute, University of California, San Francisco, CA 94143

We undertook a study to determine whether moderate exercise modifies the rise in specific airway resistance (SRaw) produced by sulfur dioxide (SO_2) in subjects with mild asthma. In seven subjects, we compared the bronchomotor effects of exercise alone (400 Kpm/min on a cycle ergometer), inhalation of SO_2 alone, and the combination of exercise and SO_2. The inspired gas were the same for each experiment. Neither inhalation of 0.50 ppm of SO_2 at rest nor exercise alone had any effect on SRaw ($p > 0.5$). Inhalation of SO_2 during exercise, however, produced a significant increase in SRaw [from 8.46 ± 1.35 L x cm H_2O/L/s (mean ± SE) to 18.16 ± 3.80 with 0.50 ppm and from 8.07 ± 1.02 to 10.48 ± 1.70 with 0.25 ppm ($p < 0.05$)]. In the two most responsive subjects, inhalation of 0.10 ppm of SO_2 also caused a significant increase in SRaw ($p < 0.05$). We conclude that moderate exercise increases the bronchoconstriction produced by a given concentration of SO_2 in subjects with asthma and that concentrations as low as 0.10 ppm can cause bronchoconstriction in these subjects. (Supported in part by USPHS Program Project Grant HL-24136)

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Exercise Increases Sulfur Dioxide-induced Bronchoconstriction in Asthmatic Subjects[1-3]

DEAN SHEPPARD,[4] ALBERT SAISHO, JAY A. NADEL, and HOMER A. BOUSHEY[5]

SUMMARY We undertook a study to determine whether moderate exercise modifies the bronchoconstriction produced by sulfur dioxide (SO_2) in subjects with mild asthma. In 7 subjects, we compared the changes in specific airway resistance (SRaw) produced by 10 min of exercise alone (400 kpm/min on a cycle ergometer), inhalation of SO_2 alone, and the combination of exercise and SO_2. During all studies, a subject breathed SO_2 and/or air from a mouthpiece. In 6 additional subjects, we compared the increase in SRaw produced by inhalation of SO_2 during exercise with that produced by eucapnic hyperventilation with SO_2. Neither inhalation of 0.50 ppm of SO_2 at rest nor exercise or hyperventilation alone had any effect on SRaw. Inhalation of SO_2 during exercise, however, significantly increased SRaw (from 8.46 ± 3.58 L × cm H_2O/L/s (mean ± SD) to 18.16 ± 10.05 at 0.50 ppm and from 8.07 ± 2.69 to 10.48 ± 4.49 at 0.25 ppm ($p < 0.05$)). In the 2 most responsive subjects, inhalation of 0.10 ppm of SO_2 during exercise also significantly increased SRaw. The SRaw increased by the same amount whether SO_2 was inhaled during exercise or during eucapnic hyperventilation at the same minute ventilation, but the time course of the increase in SRaw was different. The SRaw was at or near maximal values at the first measurement (30 s) after hyperventilation but not until 2 to 4 min after exercise. When 4 subjects took larger breaths after inhaling SO_2 during eucapnic hyperventilation to more closely match the volume of the breaths taken after exercise, the time courses of SO_2-induced bronchoconstriction after hyperventilation and after exercise were nearly identical. These results suggested that exercise increases the bronchoconstriction produced by a given concentration of SO_2 in subjects with asthma by increasing the minute volume of ventilation and that the delay in bronchoconstriction after exercise is due to the large tidal volumes that persist for some minutes during recovery.

AM REV RESPIR DIS 1981; 123:486-491

Introduction

Several epidemiologic studies have demonstrated an association between increased concentrations of sulfur dioxide (SO_2) in polluted urban air and increased morbidity in people with asthma (1-3). Because urban air always includes many other pollutants, however, these studies do not conclusively implicate SO_2 as the agent responsible for this increased morbidity. In a previous study, we showed that the bronchomotor responses of persons with asthma are greater to inhaled SO_2 than are those of normal persons (4), but the concentrations we studied (1 to 5 ppm) were higher than those generally encountered in polluted air. This earlier study was performed in resting subjects, whereas persons exposed to SO_2 in cities or industrial workplaces are usually active. In resting subjects, probably less than 5% of inspired SO_2 reaches the lower airways (5) because of the efficiency with which it is removed from inspired air by the mucous membranes of the upper airways. As inspiratory airflow increases, however, this efficiency decreases (5), so a larger percentage of inspired SO_2 probably reaches the lower airways of the same subjects when they exercise. We undertook this study to assess whether moderate exercise increases SO_2-induced bronchoconstriction in subjects with mild asthma and, if so, whether these subjects develop bronchoconstriction when they breathe concentrations of SO_2 encountered in polluted urban air. To determine whether the effects of exercise on SO_2-induced bronchoconstriction are entirely a function of the increased minute ventilation associated with exercise, we also compared the bronchoconstriction caused by breathing SO_2 during exercise with that caused by performing eucapnic hyperventilation with SO_2 at a similar minute ventilation.

Methods

The subjects were 13 nonsmoking volunteers, 10 men and 3 women 20 to 30 years of age, who were informed of the risks of the experimental protocol and who signed consent forms approved by the Committee on Human Experimentation of the University of California. All 13 subjects had a history of recurrent episodes of wheezing, chest tightness, and reversible airway obstruction previously documented by a physician. Screening tests of pulmonary function (spirometry, single-breath carbon monoxide diffusing capacity, single-breath oxygen test of gas distribution, and maximal expiratory flow-volume curve) were normal in 9 subjects. Two subjects had mild airway obstruction at the time of testing, indicated by a ratio of $FEV_1/FVC\%$, of 69 and 70%, and 4 subjects had slight maldistribution of inspired gas on the single-breath oxygen test. No subject required chronic bronchodilator therapy, and none had taken any medication within 48 h of any experiment.

We conducted 2 separate sets of studies on 2 separate groups of subjects. In the first set of studies, we assessed the effect of exercise on SO_2-induced bronchoconstriction in 7 subjects (6 men and 1 woman). In the second set of studies, we compared the bronchoconstriction produced by breathing SO_2 during exercise with that produced by eucapnic hyperventilation with SO_2 in 6 subjects (4 men and 2 women).

We conducted the first set of studies in 4 stages. We designed the first 2 stages to de-

(Received in original form July 29, 1980 and in revised form December 4, 1980)

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[2] Supported in part by Program Project Grant No. HL-24136 from the U.S. Public Health Service and by Contract No. A9-115-30 from the California Air Resources Board.

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termine whether exercise alters SO_2-induced bronchoconstriction. In the first stage, each subject breathed 0.50 ppm of SO_2 or filtered, humidified air while performing moderate exercise (400 kpm/min) on a cycle ergometer. Air and SO_2 were delivered on separate days in a randomly assigned order in single-blind fashion. In the second stage, each subject breathed 0.50 ppm of SO_2 again but, instead of exercising, merely sat resting on the cycle ergometer. We designed the third and fourth stages to determine whether inhalation of SO_2 in concentrations lower than 0.50 ppm causes bronchoconstriction in any asthmatic subjects. In the third stage, each subject repeated the protocol for the first stage, except that the concentration of SO_2 was 0.25 ppm. In the fourth stage, the 2 subjects who developed the greatest bronchoconstriction during the first and third stages repeated the protocol again, breathing 0.10 ppm of SO_2.

At the beginning of each experiment, the subject sat in a constant-volume body plethysmograph (6), and we measured airway resistance (Raw) and thoracic gas volume (Vtg) every 30 s for 10 min to obtain baseline values. The subject then exercised for 10 min on a calibrated cycle ergometer (Elemr-Schonander, Stockholm, Sweden) at a work rate of 400 kpm/min (or, in the second stage, sat resting) while breathing filtered, humidified air with or without added SO_2. During this period, we continuously measured the subject's exhaled tidal volume, minute ventilation, and respiratory rate, and averaged the values of each variable during the last 2 min of each exposure. The subject then returned to the body plethysmograph, and we again measured Raw and Vtg every 30 s for 10 min. When the values of Raw and Vtg measured at 10 min were higher than the baseline values, we continued to measure Raw and Vtg every 5 min until they returned to baseline. We multiplied Raw by Vtg to obtain specific airway resistance (SRaw).

The second set of studies consisted of 4 experiments conducted on separate days in random order. On the first day, the subject exercised on a cycle ergometer at 350 kpm/min for 5 min while breathing 1 ppm of SO_2 from a mouthpiece. We chose 350 kpm/min because preliminary studies showed that these subjects breathed approximately 30 L/min when they exercised at this work rate. We chose 1.00 ppm of SO_2 to insure significant bronchoconstriction in every subject. We limited the duration of exercise to 5 min because it was difficult for subjects to mimic the increased ventilation that occurred during exercise by voluntary hyperventilation any longer than that. We measured the subject's Raw and Vtg in the plethysmograph every 30 s for 5 min before and immediately after the subject breathed SO_2. On another day, we repeated the same protocol again with 1 ppm of SO_2, but the subject was instructed to hyperventilate, breathing 20 times/min with a tidal volume of 1,500 ml. We chose this pattern of hyperventilation to approximate the pattern of breathing of our subjects determined in preliminary studies during exercise at 350 kpm/min. The subject controlled her/his respiration rate by following a metronome and controlled her/his tidal volume by watching a signal proportional to volume displayed on a screen mounted above the mouthpiece. We kept the end tidal carbon dioxide concentration in the expired gas constant by adding a metered flow of 100% carbon dioxide to the inspired gas mixture. As a control, on the other 2 days, we repeated the above protocols for exercise and hyperventilation, but the subject breathed filtered, humidified air without SO_2. As in the first set of studies, these studies were conducted in a single-blind manner.

Because deep breathing may modify bronchoconstriction (7) and because hyperpnea occurs after exercise, we assessed the effect of increased tidal volumes on our measurements of SRaw after SO_2-induced bronchoconstriction in 1 subject. We had the subject perform voluntary eucapnic hyperventilation while she inhaled SO_2, and then we measured SRaw every 30 s while the subject took occasional large breaths at various tidal volumes. Four of the subjects then inhaled SO_2 on 2 additional days while they exercised on the first day and performed eucapnic hyperventilation on the second. After the subject exercised, we continuously monitored tidal volume by electrically integrating the flow signal from the pneumotachygraph in the phethysmograph, and we noted the largest tidal volume the subject achieved during the 30-s interval preceding each measurement of SRaw. After the subject hyperventilated while breathing SO_2, we tried to mimic the pattern of breathing after exercise by instructing the subject to precede each measurement of SRaw with a breath equal in volume to the largest breath that subject took during the corresponding time interval after exercise. The subject controlled her/his inspired volume by watching a calibrated line, proportional to inspired volume, which we displayed on a screen mounted in the plethysmograph.

During each exposure, the subject breathed from a mouthpiece. To achieve the desired concentration of SO_2, we mixed a known flow from a calibrated tank of SO_2 (500 ppm) with air delivered from a compressed air source to a 3-L glass mixing chamber. Before entering the mixing chamber, the air was filtered through a HEPA filter and two vapor filters (Mine Safety Appliances No. 8185), then humidified by a bubble humidifier, and, finally, filtered again through a second HEPA filter (Mine Safety Appliances No. CU-86444) to remove any water particles added during humidification. For the second set of studies (comparing exercise with eucapnic hyperventilation), the subject breathed from a one-way valve. After leaving the mixing chamber, the air/SO_2 mixture entered a meteorologic balloon to provide a ready supply of conditioned gas. Although some SO_2 was adsorbed to the surface of the balloon, we were able to adjust the flow of SO_2 to the mixing chamber to deliver the desired SO_2 concentration. For these studies, we measured the concentration of carbon dioxide in the expired gas from a port in the expiratory tubing just distal to the subject's mouthpiece with a carbon dioxide analyzer (Beckman No. LB-1).

To document that temperature and relative humidity of the inspired air were relatively constant, we measured temperature and dew point continuously with a digital humidity analyzer equipped with a mirrored dew point hygrometer and a platinum temperature probe (Model No. 911; E.G. and G., Waltham, MA), and calculated relative humidity from standard tables. We measured SO_2 concentrations continuously from a needle just proximal to the subject's mouthpiece with a pulsed fluorescent SO_2 analyzer (Model No. 43; Thermo-Electron Corp. Bohemia, N.Y.).

To check for conversion of SO_2 to sulfate in our system, we collected samples of particles on Teflon filters from approximately 6.0 m^3 of humidified air mixed with 1.00 ppm of SO_2. The samples were analyzed for sulfate by the Air Industrial Hygiene Laboratory micromethod (8), and no sulfate was detected, so there was less than 0.008% conversion of SO_2 to sulfate.

To obtain a record of respiratory rate and minute ventilation during exercise, we measured airflow with a pneumotachygraph (Fleisch No. 3 Lausanne, Switzerland) and a differential pressure transducer (Model No. DP-45; Validyne Co., Northridge, CA), electrically subtracting the baseline flow. We then amplified and electrically integrated the flow signal to obtain a volume signal, which we recorded on a rapid writing device (Model No. DR-12; Electronics for Medicine, Pleasantville, NY).

We statistically analyzed each subject's change in SRaw during each experiment by comparing the 4 highest consecutive baseline values of SRaw with the 4 highest consecutive postexposure values using the unpaired *t* test. To determine the effect of exercise on the response to inhalation of 0.50 ppm of SO_2, we compared the change in SRaw (ΔSRaw) produced by inhalation of 0.50 ppm of SO_2 during exercise with ΔSRaw produced by inhalation of 0.50 ppm of SO_2 at rest and with ΔSRaw produced by exercise itself using an analysis of variance and then the Neuman-Keuls multiple range test (9). To analyze the group's response to 0.25 ppm of SO_2, we used the paired *t* test to compare ΔSRaw produced by inhalation

of 0.25 ppm of SO_2 while exercising with ΔSRaw produced by exercise alone.

To determine the significance of the change in SRaw during each study, we compared the baseline values of each variable with the poststudy values using the paired *t* test.

Results

In 7 subjects with mild asthma, inhalation of 0.50 and 0.25 ppm of SO_2 during the performance of moderate exercise significantly increased SRaw, whereas neither inhalation of 0.50 ppm of SO_2 at rest nor inhalation of humidified, filtered air during exercise had any effect on SRaw (figure 1). Inhalation of 0.50 ppm during exercise significantly increased SRaw in all 7 subjects ($p < 0.05$), and 3 developed wheezing and shortness of breath. During the corresponding period of exercise alone and during inhalation of 0.50 ppm at rest, SRaw did not increase in any subject. After inhalation of 0.50 ppm of SO_2 during exercise, ΔSRaw was significantly greater than after exercise alone or inhalation of 0.50 ppm of SO_2 at rest ($p < 0.05$). Inhalation of 0.25 ppm during exercise significantly increased SRaw in 3 of the 7 subjects, and the increase in SRaw for the group was significant ($p < 0.05$) (figure 1). No subject developed wheezing or shortness of breath. During the corresponding period of exercise alone, SRaw did not increase in any subject. In the 2 most responsive subjects, inhalation of 0.10 ppm of SO_2 as well as 0.25 and 0.50 ppm significantly increased SRaw, and there appeared to be a dose-response relationship (figure 2).

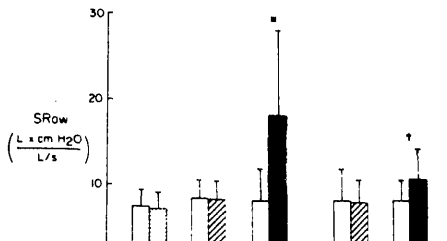

Fig. 1. Specific airway resistance (SRaw) before (□) and after inhalation of SO_2 during exercise (■), exercise alone (▨), and inhalation of SO_2 at rest (□) in 7 subjects with asthma. Data are mean ± SD. (* ΔSRaw after exercise with SO_2 significantly different from ΔSRaw after exercise alone and ΔSRaw after SO_2 at rest, $p < 0.05$. † ΔSRaw after exercise with SO_2 significantly different from ΔSRaw after exercise alone, $p < 0.05$. [1] Control for inhalation of 0.50 ppm of SO_2. [2] Control for inhalation of 0.25 ppm of SO_2.)

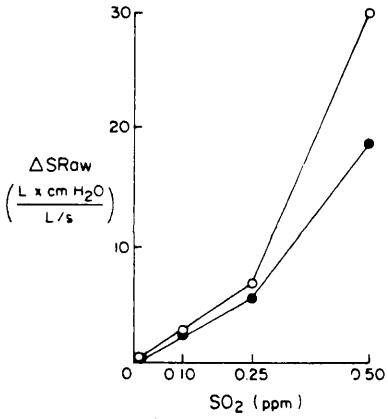

Fig. 2. Dose-response to SO_2 inhaled during exercise in 2 subjects (● and ○). The ΔSRaw is the difference between baseline specific airway resistance and specific airway resistance after inhalation of SO_2.

In the second set of studies, in all 6 subjects, inhalation of 1 ppm of SO_2 dramatically increased SRaw, both when it was delivered during exercise and during eucapnic hyperventilation. In every case, the increase in SRaw was accompanied by dyspnea and audible wheezing. The magnitude of the increase in SRaw was the same when the subjects inhaled SO_2 while they exercised or while they performed eucapnic hyperventilation at the same minute ventilation (figure 3).

The bronchoconstriction produced by inhalation of 0.50 ppm of SO_2 during exercise was gradual in onset (figure 4). Immediately after exercise, SRaw did not differ significantly from baseline values. It then increased over the first 3.5 min, reached a plateau, and gradually returned to baseline values by 30 min after exposure. A similar time course was seen in those subjects who developed bronchoconstriction after exposure to 0.25 and 0.10 ppm of SO_2.

In contrast, the bronchoconstriction produced by inhalation of SO_2 during eucapnic hyperventilation was rapid in onset. Maximal or near maximal values were noted when the first measurement of SRaw was made, 30 s after the end of hyperventilation (figure 5). In 1 subject after bronchoconstriction was induced by voluntary hyperventilation during inhalation of SO_2, breaths of 1.2, 1.5 and 2.2 L inspired volume decreased SRaw by 3.7, 5.8, and 7.4 L × cm H_2O/L/s, respectively (figure 6). In 4 subjects, studies were also performed in which each subject's largest breath during each 30-s interval after exercise while breathing SO_2 was mimicked by

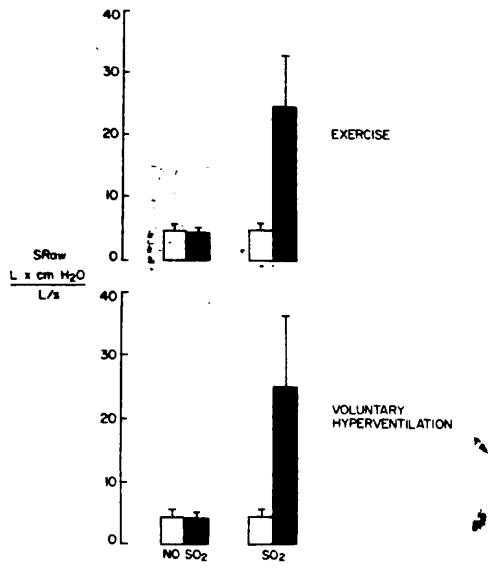

Fig. 3. Effect of exercise (*upper bars*) and voluntary eucapnic hyperventilation (*lower bars*) on the response of specific airway resistance (SRaw) to inhaled SO_2 (1.00 ppm) in 6 asthmatic subjects. (□ = control value during normal breathing at rest. ■ = value after intervention.) Neither exercise alone nor hyperventilation alone (*left columns*) had any effect on SRaw. Exercise while breathing SO_2 and voluntary hyperventilation with SO_2 (*right columns*) both increased SRaw ($p < 0.005$).

a similar respiratory maneuver during the corresponding time period after voluntary hyperventilation with SO_2. In each subject, maximal bronchoconstriction caused by inhalation of SO_2 was delayed after hyperventilation as well as exercise, and the curves plotting SRaw against time were superimposable (figure 7).

The relative humidity and temperature (and therefore the water content) of inspired gas were constant during all experiments (temperature = 22.4 ± 0.8° C, relative humidity = 71.8 ± 2.1%; mean ± SD). Mean values for minute ventilation were 30.7 ± 5.3 L/min (mean ± SD) during exercise and 31.2 ± 2.0 during eucapnic hyperventilation.

Discussion

This study showed that moderate exercise increases the bronchomotor effect of SO_2 in subjects with asthma so that concentrations as low as 0.10 ppm can cause significant bronchoconstriction. That exercise at the same work rate without SO_2 did not cause bronchoconstriction in any subject suggests that our findings could not be explained merely by the known bronchoconstrictive effect of exercise itself.

Our finding that 1.00 ppm of SO_2 increased SRaw by the same amount

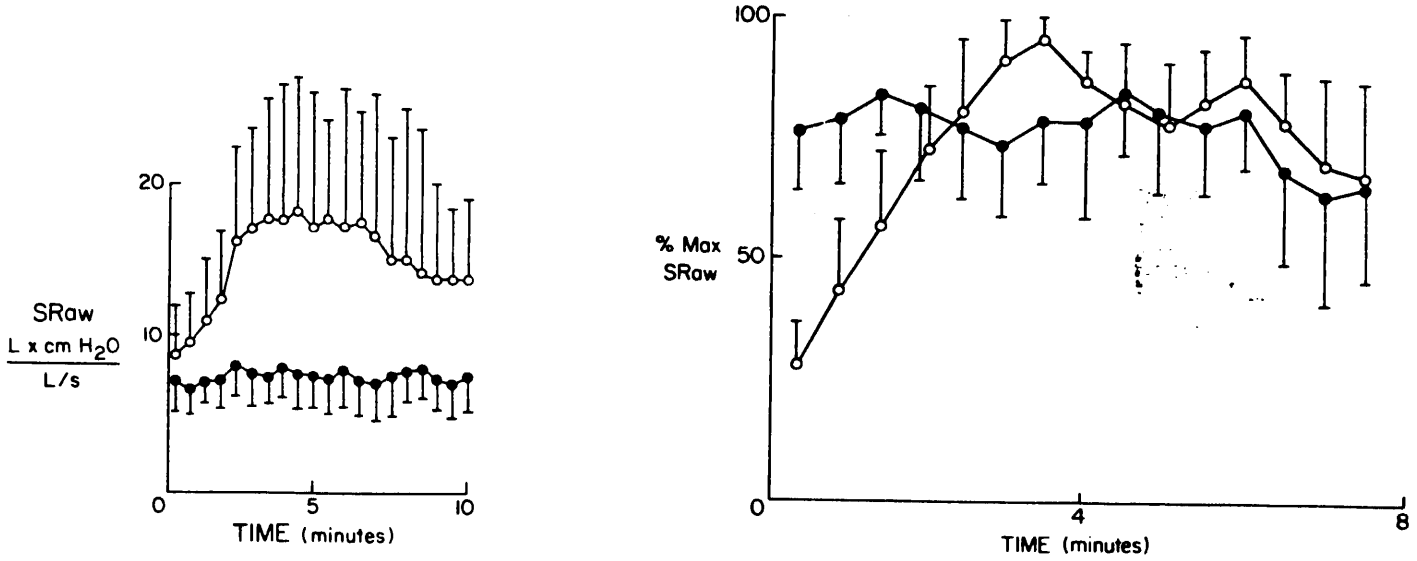

Fig. 4. (*left*) Specific airway resistance (SRaw) measured at 30-s intervals after inhalation of SO_2 (0.50 ppm) during exercise (O) and after exercise alone (●) in 7 subjects with asthma. Each data point represents the mean ± SD for all 7 subjects. Fig. 5. (*right*) Per cent of maximal specific airway resistance (% max SRaw) plotted at 30-s intervals after voluntary eucapnic hyperventilation breathing 1.00 ppm of SO_2 (●) and after exercise breathing 1.00 ppm of SO_2 (O) (n = 6). Data are mean ± SD.

whether delivered during eucapnic hyperventilation or during bicycle exercise suggested that the increase in SO_2-induced bronchoconstriction caused by exercise is entirely a function of an increase in the minute volume of ventilation.

There are several ways to explain how an increase in minute ventilation could increase SO_2-induced bronchoconstriction. Certainly, the total dose (concentration × volume) of SO_2 delivered to a subject's mouth was increased. In addition, the percentage of inspired SO_2 actually reaching the tracheobronchial tree increased with increases in inspiratory flow (5). In resting subjects, more than 95% of inspired SO_2 was probably deposited in the aqueous environment of the upper airways (5) because SO_2 is highly soluble in water. But at the higher airflows seen with increases in minute ventilation, larger concentrations of SO_2 probably reached the lower airways (5). In this study, inhalation of 0.50 ppm of SO_2 during exercise increased SRaw more than a concentration of SO_2 10 times greater (5.0 ppm) inhaled at rest in a previous study (4), whereas minute ventilation during exercise in this study was only 3 to 4 times that at rest. Thus, the dose of SO_2 inhaled in the resting study with 5.0 ppm of SO_2 was 2.5 to 3 times the dose with 0.50 ppm in the present study. This calculation supports the view that increases in both the dose of SO_2 inhaled and the percentage of inhaled SO_2 reaching the tracheobronchial tree contribute to the increase in SO_2-induced bronchoconstriction produced by exercise. Finally, exercise may itself alter the responsiveness of airways to any given dose and distribution of SO_2. Certainly, exercise can cause bronchoconstriction in persons with asthma (10–12), and although the exact mechanism of exercise-induced bronchoconstriction is unknown, the magnitude of exercise-induced bronchoconstriction correlates with the magnitude of heat loss from the airway mucosa during exercise (10). Thus, conditions that increase the magnitude of airway heat loss, including decreased temperature (11) or relative humidity (12) of inspired air and increased minute ventilation, also increase the magnitude of exercise-induced bronchoconstriction. Because, in our experiment, the temperature of the inspired gas was less than body temperature and the relative humidity was less than 100%, there was some heat loss from the respiratory mucosa. Although the heat loss was insufficient by itself to induce bronchoconstriction, it is possible that this heat loss may have increased bronchomotor responsiveness to SO_2.

The time course of the rise in SRaw produced by inhaled SO_2 in exercising subjects in this study differed from the previously reported time course of the increase produced by inhaled SO_2 in resting subjects (4, 13). In resting subjects, bronchoconstriction is greatest during inhalation of SO_2 and gradually decreases after exposure stops [4, 13], whereas in exercising subjects, bronchoconstriction gradually increases over the first few minutes after exposure. The time course of bronchoconstriction produced by SO_2 in exercising subjects is remarkably similar to the time course of the bronchoconstriction caused by exercise itself (14). The fact that after voluntary hyperventilation with SO_2, SRaw was at or near maximal values within 30 s, suggested that the delay in bronchoconstriction after SO_2 inhala-

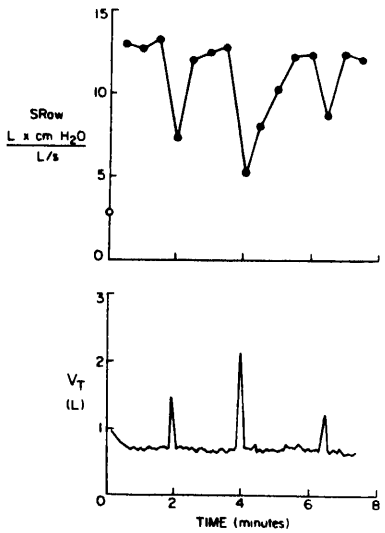

Fig. 6. Specific airway resistance (SRaw) (*upper graph*) and tidal volume (VT) (*lower graph*) after inhalation of 1.00 ppm of SO_2 during voluntary eucapnic hyperventilation in 1 subject. (O = the baseline SRaw for this subject before inhalation of SO_2.) The subject was instructed to take 3 large breaths, and SRaw decreased after each breath.

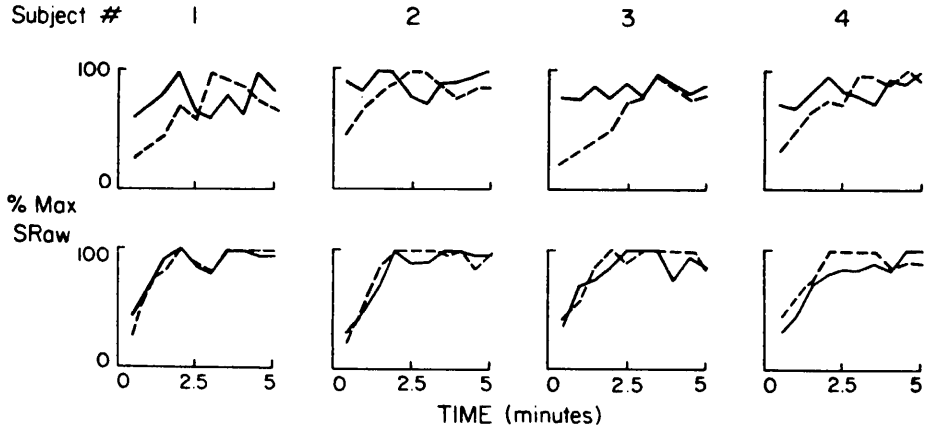

Fig. 7. Individual data for per cent of maximal specific resistance (% max SRaw) plotted at 30-s intervals after voluntary eucapnic hyperventilation with 1.00 ppm of SO_2 (*solid lines*) and after exercise while breathing 1.00 ppm of SO_2 (*broken lines*) in 4 subjects with asthma. In one series of experiments (*top*), the pattern of breathing after exposure to SO_2 was not controlled. In another series of experiments (*bottom*), the largest inspired volume during each 30-s interval was the same after hyperventilation as after exercise.

tion during exercise is not merely a function of the increased minute volume of ventilation during exercise.

Nadel and Tierney (7) have shown that a single deep breath to total lung capacity (TLC) can reverse bronchoconstriction induced by histamine, cigarette smoke, or SO_2 in normal subjects. Although there are no published studies on the effects of smaller breaths on induced bronchoconstriction in humans, evidence from animal studies (15) and *in vitro* studies of the characteristics of smooth muscle (16) suggest that breaths to lung volumes well below TLC might have a similar effect on induced bronchoconstricton. In many asthmatic subjects without induced bronchoconstriction, deep breaths to TLC can cause bronchoconstriction (17, 18), but the only published report of the effect of breaths to TLC on induced bronchoconstriction in subjects with asthma was inconclusive (19). Our results suggested that deep breaths, with inspired volumes of as little as 1.25 L, can largely reverse the bronchoconstriction induced by SO_2 in some subjects with asthma.

One major difference between exercise and eucapnic hyperventilation is that after a subject exercises, the tidal volume remains increased over baseline values for some minutes, whereas after eucapnic hyperventilation, tidal volume returns rapidly to near baseline values. Our finding, in 1 subject, that breaths similar in volume to those taken during the first few minutes after exercising transiently reversed SO_2-induced bronchoconstriction (figure 6) suggested that the delay in bronchoconstriction after SO_2 was inhaled during exercise might be due to large tidal volume breaths. Furthermore, in 4 subjects who inhaled SO_2 during voluntary hyperventilation, we were able to reproduce the time course of bronchoconstriction seen after the same subjects exercised while breathing SO_2 by having the subjects imitate the inspired volumes they achieved after exercise. This finding suggested that the difference between the time course of bronchoconstriction after breathing SO_2 during exercise and that after voluntary hyperventilation with SO_2 is a result of the difference between the tidal volume of ventilation after exercise and that after voluntary hyperventilation.

Studies of the effects of maximal exercise on airway mechanics in subjects with asthma have also demonstrated delayed bronchoconstriction (20). In these studies, maximal bronchoconstriction occurred after a delay of 3 to 5 min, longer than the 2 to 4 min we observed, but the significantly higher exercise work rates used in these studies might have caused a longer period of increased ventilation after exercise. We therefore speculate that the delay in the bronchoconstriction caused by maximal exercise may also be caused by large tidal volume breaths.

Our findings are relevant to both workplace and environmental exposure to SO_2. Because presently approved standards (21) allow brief exposure to SO_2 concentrations more than 10 times the concentration that caused symptomatic bronchoconstriction in this study (0.50 ppm), SO_2 may be a significant cause of work-related exacerbations of asthma. Furthermore, since the concentrations we studied are sometimes equaled or exceeded in polluted urban air, our findings supported the contention that SO_2 is at least partially responsible for the observed association between air pollution and increased morbidity from asthma (1-3, 22). Current standards for occupational exposure to SO_2 set limits for the 8-h average concentration only. Our studies indicated that mildly asthmatic subjects develop clinically significant bronchoconstriction from very short exposures to low concentrations of SO_2. These findings suggested that the peak, rather than average, concentration of SO_2 may be most important to monitor. In this study, subjects breathed through a mouthpiece, however, whereas at these exercise loads, normal persons use oronasal breathing. Because a greater percentage of SO_2 is probably removed from air inspired through the nose than that inspired through the mouth (5), it is conceivable that somewhat higher concentrations might be required in polluted air to produce comparable amounts of bronchoconstriction during this amount of exercise. Careful studies of the distribution of inspired air between the nose and mouth under various circumstances (e.g., rest versus exercise) in different populations (e.g., normal versus asthmatic subjects) are needed. Exposures during mouth breathing are probably most pertinent to exercise, where the percentage of air inhaled through the mouth increases with progressive increases in work rates, and to asthmatic subjects, whose nasal allergies prevent normal ingress of air through the nose.

Acknowledgment

The writers thank Dr. N. Robert Frank for his valuable advice and Ms. Patty Snell for her assistance in preparing this manuscript.

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Effect of the Oronasal Breathing Route on Sulfur Dioxide-Induced Bronchoconstriction in Exercising Asthmatic Subjects[1-3]

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SUMMARY We undertook a study to determine how the oronasal breathing route affects the bronchoconstrictor response to sulfur dioxide (SO_2) inhaled by asthmatic subjects during exercise. In 6 subjects, we compared the changes in specific airway resistance (SRaw) caused by breathing humidified air through a mouthpiece during 5 min of exercise on a bicycle ergometer (550 kpm/min) to the changes caused by breathing humidified air plus 0.5 ppm of SO_2, (a) through a mouthpiece (oral breathing), (b) by facemask (oronasal breathing), and (c) by facemask with the mouth occluded (nasal breathing) during exercise. Breathing humidified air plus 0.5 ppm of SO_2 through a mouthpiece or by facemask during exercise significantly increased SRaw in all 6 subjects, and breathing humidified air plus 0.5 PPM of SO_2 by facemask with the mouth occluded significantly increased SRaw in 5 of 6 subjects. The increase in SRaw caused by breathing humidified air plus 0.5 PPM of SO_2 through a mouthpiece was not significantly different from the increase caused by breathing SO_2 by facemask ($p > 0.05$), but was significantly greater than the increase caused by breathing SO_2 by facemask with the mouth occluded ($p < 0.05$). These results indicate that although nasal breathing partially protected against SO_2-induced bronchoconstriction in our subjects, both oral and oronasal breathing of low concentrations of SO_2 during exercise can cause significant bronchoconstriction in people with asthma.

AM REV RESPIR DIS 1982; 125:627-631

Introduction

Recent studies have shown that asthmatic subjects develop bronchoconstriction after breathing sulfur dioxide (SO_2) in concentrations as low as 1 ppm at rest, and as low as 0.1 ppm during moderate exercise (1, 2). These and other studies in which subjects inhaled pollutants through a mouthpiece have been criticized because this method of exposure bypasses the possible protective effects of breathing through the nose (3). Indeed, SO_2 is a highly water-soluble gas that is rapidly absorbed by mucous membranes, and several previous studies in both animals and humans have documented the ability of the nose and upper respiratory tract to remove SO_2 from air passing through these structures at low flow rates (4–9). However, there are no studies to assess the ability of the nose and upper respiratory tract to protect people with hyperreactive airways from the bronchoconstrictor effects of SO_2 when inspiratory airflow is high, as it is during exercise. Therefore, the purpose of this study was to determine whether the bronchoconstrictor effects of low concentrations of SO_2 in asthmatic subjects vary during exercise when they breathe SO_2 by (a) mouthpiece (oral breathing), (b) facemask (oronasal breathing), or (c) facemask with the mouth occluded (nasal breathing).

Methods

Subjects. We studied 6 nonsmoking adult asthmatic subjects (4 men, 2 women between 21 and 28 yr of age), each of whom had a history of episodic cough, wheezing, and dyspnea, and either airway hyperreactivity demonstrated by histamine bronchoprovocation (5 subjects) or reversible airflow obstruction demonstrated by spirometry (1 subject). No subject required chronic medication for asthma and no subject had had symptoms of a respiratory infection within 4 wk of the beginning of the study. We recorded a respiratory history and performed a physical examination on each subject. Four subjects (Nos. 2, 3, 5, 6) had a history of chronic rhinitis (as defined by perennial or seasonal sneezing, rhinorrhea, lacrimation, and conjunctival pruritis) and 3 had an abnormal nasal examination—1 had nasal polyps (No. 4), 1 had a deviated anterior nasal septum (No. 5), and 1 had partial occlusion of one nasal passage due to an enlarged middle turbinate (No. 2). Four subjects had normal pulmonary function tests (consisting of spirometry, flow-volume loop, lung volumes, single-breath diffusing capacity for carbon monoxide, and single-breath oxygen test). One subject (No. 1) had normal pulmonary function except for mild maldistribution of ventilation, and 1 subject (No. 2) had moderate airflow obstruction evidenced by an FEV_1/FVC of 52%. Each subject gave informed consent and received financial remuneration.

Apparatus and measurement techniques. We measured airway resistance (Raw) and thoracic gas volume (Vtg) while each subject sat in a constant-volume whole-body plethysmograph (10) and breathed through a heated No. 2 Fleisch pneumotachograph. Box and mouth pressures were measured by differential pressure transducers (Validyne Model MP 45-1-871 and DP7-30, respectively), and the electrical signals from the pneumotachograph and pressure transducers were passed through preamplifiers (Validyne CD-19) and displayed on an X–Y plot on the screen of a storage oscilloscope (Tektronix 5115). A protractor attached to the oscilloscope face was aligned with the slope of the curve generated, and the angle was electronically measured. The electrical signal obtained was passed through an analog-to-digital converter (ADAC 600-11) to a digital computer (Digital PDP 11/34A), which calculated Vtg, Raw, and their product, specific airway resistance (SRaw).

We measured each subject's inspired minute volume of ventilation, tidal volume, respiratory frequency, and maximal mid-inspiratory flow rate with a respiratory inductive plethysmograph (Respitrace) (11).

The air delivery system was constructed as follows: dry air at a flow of 3.6 L/s was passed through 2 filters (MSA Air Line No. 81857), humidified by being bubbled through heated, deionized water, passed through a

(*Received in original form September 4, 1981 and in revised form January 7, 1982*)

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[2] Supported in part by Program Project Grant No. HL-24136 from the U.S. Public Health Service, and by California Air Resources Board Contract No. A9-115-30.

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HEPA filter (MSA Ultra Aire No. 86444) to remove any water droplets, and then passed to a 3-L glass mixing chamber. The mixing chamber was connected to either a facemask or a glass mouthpiece by Teflon tubing (4 cm diameter). Desired SO_2 concentrations were achieved by adding the appropriate flow of 500 ppm SO_2 to the airstream in the glass mixing chamber.

The mask used in these experiments was a full facemask with transparent face plate (MSA No. BM-130-17), which when properly fitted, provided an airtight seal enclosing the mouth, nose, and eyes, and allowing nasal breathing, mouth breathing, or both. We sprayed the interior of the mask with an inert, chemically pure TFE fluoropolymer compound (Fluoroglide CP) to prevent adsorption of SO_2 to the rubber of the mask. In the 2 subjects in whom we measured the concentration of SO_2 inside the facemask, we found it was identical to the concentration measured at the inlet port of the mask.

We measured SO_2 concentrations in the airstream by continuously passing samples taken from the inlet port of the mask (or mouthpiece) to a pulsed, fluorescent SO_2 analyzer (No. 43, Thermo Electron Corp.), which was calibrated at the beginning of the study by the California Air and Industrial Hygiene Laboratory (AIHL), Berkeley, using a standard tube permeation technique (12). To assure the accuracy of the SO_2 analyzer during the study, we checked it with an SO_2 span gas of known concentration (certified by AIHL) before each experiment. We measured the dew point and temperature of the delivered air by passing air continuously from the inlet port of the facemask (or mouthpiece) to a digital humidity analyzer (Dew All Model 911, E.G. & G). We calculated relative humidity from the dew point and temperature using standard tables.

Experimental protocol. For each experiment, the subject first sat in a body plethysmograph while we measured baseline Vtg and Raw every 30 s for 10 min. The subject then exercised on a cycle ergometer (Elma-Schonander, Stockholm, Sweden) at 550 kpm/min for 5 min while breathing either humidified air from a mouthpiece while wearing a noseclip, or humidified air plus 0.5 ppm SO_2 by either (a) a mouthpiece while wearing a noseclip (oral breathing), (b) a facemask (oronasal breathing), or (c) a facemask while the mouth was occluded by adhesive tape (nasal breathing). Although we did not measure oxygen consumption in our subjects during the experimental studies, the average oxygen consumption in 3 different subjects during the same exercise protocol was 22.4 ml/min/kg, a level of oxygen consumption corresponding to such activities as playing tennis, splitting wood, cycling at 11 mph, or shoveling snow (13). We then measured each subject's Vtg and Raw every 30 s for 10 min beginning 2 min after the end of exercise. The SRaw measurements from a representative experiment are plotted in figure 1. Each subject performed all 4 experimental maneuvers in random order on separate days, but no subject breathed SO_2 more than once in any 48-h period. Subjects were not told whether they were breathing SO_2 or humidified air. We questioned each subject about nasal and chest symptoms after each experiment. After each experiment involving breathing from a facemask, the subject was questioned about the oronasal breathing route during exercise.

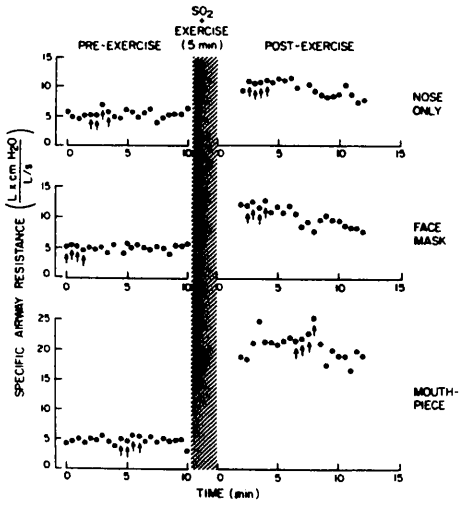

Fig. 1. Values for specific airway resistance from one subject (No. 6) before and after exercising for 5 min while breathing 0.5 ppm SO_2 by facemask with the mouth occluded (nose only, upper graph), by facemask (oronasal breathing, middle graph), and through a mouthpiece (oral breathing, lower graph). Each plotted point represents a single measurement. Arrows indicate values used for statistical comparisons.

To verify that the bronchoconstrictor response to SO_2 was related to the concentration inhaled, regardless of the route of inhalation, we constructed SO_2 dose-response curves from data on 2 subjects who breathed 3 different concentrations of SO_2 both through a mouthpiece and by facemask during exercise.

The experimental protocol used in this study was approved by the Committee on Human Research of the University of California, San Francisco.

Statistical analysis of data. We compared each subject's 4 highest consecutive baseline values of SRaw to the 4 highest consecutive postexercise values in each experiment by the unpaired *t* test. We chose to use the 4 highest consecutive SRaw values for statistical comparison because we were interested in comparing the *peak* postexercise values for SRaw to the preexercise values. Because the time of the peak postexercise values for SRaw varied between subjects, the SRaw values obtained from a specified postexercise time interval would not coincide with the peak postexercise response in all subjects. Conversely, the average of *all* postexercise SRaw measurements would also not yield a peak value because the postexercise SRaw values in some subjects were decreasing by 8 to 10 min postexercise. We then compared the group's baseline to postexercise SRaw by the Wilcoxon paired-sample *t* test (14). We compared the increases in SRaw caused by breathing SO_2 by mouthpiece, facemask, and facemask with mouth occluded to each other, and to the increase caused by breathing humidified air by mouthpiece, first by the Kruskal-Wallis single-factor analysis of variance by ranks, and then by a nonparametric multiple-comparisons test based on the Newman-Keuls test (14). The level of significance was chosen to be 0.05.

To determine whether minute volume of ventilation, respiratory frequency, tidal volume, or the relative humidity and temperature of the delivered air differed significantly between experiments, we analyzed each variable by a single-factor analysis of variance.

Results

Specific airway resistance was significantly increased in all 6 subjects after moderate exercise performed while breathing 0.5 ppm of SO_2 in humidified air either through a mouthpiece (oral breathing) or by facemask (oronasal breathing) and in 5 of the 6 subjects after breathing the same gas mixture from a facemask with the mouth occluded (nasal breathing) (table 1). Although the increase in SRaw was greater when subjects breathed SO_2 through a mouthpiece than when they breathed SO_2 from a facemask, the difference for the group did not achieve significance ($p > 0.05$, figure 2). The increase in SRaw caused by breathing SO_2 through a mouthpiece was significantly greater than the increase caused by breathing humidified air through a mouthpiece ($p < 0.01$). Likewise, the increases in SRaw caused by breathing SO_2 either through a mouthpiece or by facemask were significantly greater than that caused by breathing humidified air through a mouthpiece, ($p < 0.01$ for breathing SO_2 by mouthpiece versus breathing air by mouthpiece, and $p < 0.005$ for breathing SO_2 by facemask versus breathing air by mouthpiece). The increase in SRaw caused by breathing SO_2 through a facemask with the mouth occluded was significantly greater than that caused by breathing humidified air through a mouthpiece ($p < 0.01$) but was significantly less than that caused by breathing SO_2 through a mouthpiece (p

TABLE 1

SPECIFIC AIRWAY RESISTANCE BEFORE AND AFTER EXERCISE IN SIX ASTHMATIC SUBJECTS BREATHING HUMIDIFIED AIR AND HUMIDIFIED AIR PLUS SO_2 BY VARIOUS ROUTES

		SRaw (L × cm H_2O/L/s)			
		Without SO_2	SO_2 (0.5 ppm)		
Subject	Time of Measurement	Mouthpiece (oral breathing)	Mouthpiece (oral breathing)	Facemask (oronasal breathing)	Facemask with Mouth Occluded (nasal breathing)
1	Baseline	3.55	3.95	4.92	5.52
	Postexercise	4.46	11.28†	9.92†	17.39†
2	Baseline	19.57	14.73	13.74	11.13
	Postexercise	21.82*	32.07†	23.93†	15.80†
3	Baseline	3.51	3.85	4.27	3.14
	Postexercise	3.62	12.36†	7.89†	4.02†
4	Baseline	6.44	6.83	6.86	6.10
	Postexercise	7.55	11.60†	8.74†	7.13*
5	Baseline	5.27	6.19	9.21	6.97
	Postexercise	6.11	8.72†	11.83†	8.30
6	Baseline	4.65	5.32	5.12	5.65
	Postexercise	6.08†	22.61†	12.34†	10.80†
Group Mean	Baseline	7.17	6.81	7.36	6.42
	Postexercise	8.27*	16.44*	12.45*	10.58*

* Significantly greater than baseline value ($p < 0.05$).
† Significantly greater than baseline value ($p < 0.01$).

< 0.05). Although the increase in SRaw caused by breathing SO_2 by facemask was greater than the increase caused by breathing SO_2 by facemask with the mouth occluded, the differences did not reach significance ($p > 0.05$). For the group, the increase in SRaw caused by exercising while breathing humidified air through a mouthpiece was significant ($p < 0.05$) but very small (table 1).

One subject (No. 1) had a greater increase in SRaw after breathing SO_2 by facemask with the mouth occluded than after breathing SO_2 either through a mouthpiece (oral breathing), or by facemask (oronasal breathing). However, when she again breathed SO_2 by facemask with the mouth occluded 1 wk later, her SRaw did not increase significantly (baseline SRaw = 5.11, postexercise SRaw = 6.15) and the mechanism of the large response after her first experiment remains unexplained.

Each SRaw measurement, made before and after exercise in all 3 experimental conditions in 1 subject (No. 6) is plotted in figure 1. These data represent the typical time-course of the increase in SRaw caused by breathing SO_2 during exercise. In most subjects the peak values for SRaw were seen 2–5 min postexercise, although 1 subject's (No. 4) peak response did not occur until 7–8 min postexercise. The duration of the bronchoconstrictor response to SO_2 was in general proportional to the magnitude of the peak response. We did not routinely record SRaw values beyond 12 min postexercise, but in those subjects in whom we recorded SRaw values for longer periods, the value generally returned to normal in 20–30 min.

The minute volume of ventilation of the subjects and the temperature and relative humidity of the delivered air did not differ significantly between experiments (table 2). While breathing SO_2 through the nose only during exercise, the group's maximal mid-inspira-

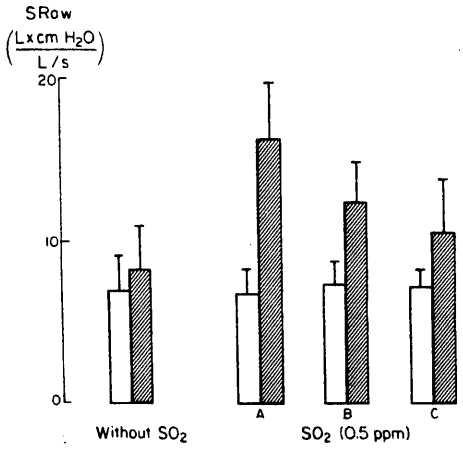

Fig. 2. Group mean values for specific airway resistance (SRaw) in six asthmatic subjects after exercising while breathing humidified air through a mouthpiece (oral breathing), and humidified air plus 0.5 ppm of SO_2 through a mouthpiece (oral breathing, A), by facemask (oronasal breathing, B), or by facemask with the mouth occluded (nasal breathing, C). Values represent mean ± SE. (□ baseline, ■ postexercise)

TABLE 2

MINUTE VOLUME OF INSPIRED VENTILATION ($\dot{V}_I$) RESPIRATORY FREQUENCY (f), AND TIDAL VOLUME (V_T) OF SUBJECTS DURING EXERCISE AND RELATIVE HUMIDITY AND TEMPERATURE OF INSPIRED AIR IN EACH EXPERIMENTAL CONDITION

	Without SO_2	SO_2 (0.5 ppm)		
	Mouthpiece (oral breathing)	Mouthpiece (oral breathing)	Facemask (oronasal breathing)	Facemask with Mouth Occluded (nasal breathing)
$\dot{V}_I$ (L/min)	43.8 ± 6.9*†	41.1 ± 5.0	41.9 ± 5.8	42.6 ± 5.8
f (breaths/min)	23.6 ± 8.7	22.3 ± 7.9	22.1 ± 7.7	20.6 ± 6.6
V_T (L)	1.99 ± 0.49	2.02 ± 0.55	2.06 ± 0.68	2.19 ± 0.52
Relative Humidity (%)	72.8 ± 2.2	73.9 ± 1.9	74.6 ± 2.5	72.8 ± 3.0
Temperature (°C)	23.2 ± 0.4	23.0 ± 0.8	22.8 ± 0.6	23.6 ± 0.4

* All values represent mean ± SD.
† $p > 0.20$ between groups for each variable by ANOV.

tory flow rate was 2.16 ± 0.21 L/s (mean ± SD).

All subjects reported that they breathed oronasally during exercise while wearing the facemask, and we directly observed all subjects to breathe with their mouths open while exercising with the mask on. At the completion of the study, 5 subjects reported that the facemask allowed them to breathe with a normal oronasal pattern, and 1 subject (No. 3) felt the mask "slightly favored" oral breathing.

No subject reported any symptoms after breathing humidified air from a mouthpiece during exercise. However, after exercising while breathing 0.5 ppm SO_2 from a mouthpiece, 5 subjects reported shortness of breath and the remaining subject (No. 5) reported throat irritation but no shortness of breath. Three subjects (Nos. 2, 3, and 4) coughed only while breathing SO_2 through a mouthpiece, and 1 subject (No. 6) coughed while breathing SO_2 through a mouthpiece and by facemask. After breathing SO_2 by facemask during exercise, 4 subjects reported both shortness of breath and nose and throat irritation, and 2 (Nos. 2, and 4) had no symptoms. After breathing SO_2 by nose only, 1 subject (No. 1) reported shortness of breath, 2 subjects (Nos. 5, and 3) reported nose and throat irritation, and 1 (No. 6) reported eye irritation.

Sulfur dioxide dose-response curves constructed from data on 2 subjects (Nos. 3, and 5) indicated that the change in SRaw increased as the concentration of SO_2 breathed during exercise increased, whether the SO_2 was breathed through a mouthpiece (oral breathing) or from a facemask (oronasal breathing) (figure 3).

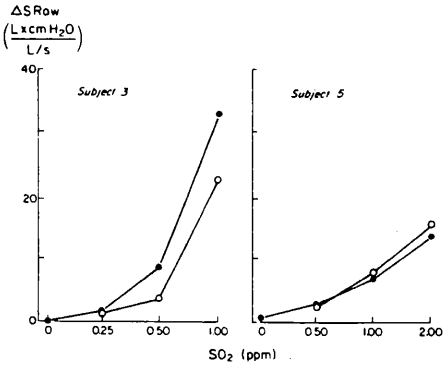

Fig. 3. SO_2 dose-response curves in two subjects during exercise showing the change in specific airway resistance (ΔSRaw) caused by breathing different concentrations of SO_2 by either mouthpiece (oral breathing, ●) or facemask (oronasal breathing, o). Each plotted point represents the result of one experiment.

Discussion

This study shows that exercising moderately while breathing 0.5 ppm of SO_2 with humidified air through a mouthpiece, by facemask, or through the nose causes significantly more bronchoconstriction in asthmatic subjects we studied than exercising moderately while breathing humidified air through a mouthpiece. Although exercising while breathing humidified air through a mouthpiece caused bronchoconstriction in our subjects, the amount of bronchoconstriction was small in all subjects, and was presumably caused by respiratory heat loss, because the temperature of the inspired air was less than 37° C and the water saturation less than 100%. That SO_2 was responsible for augmenting the bronchoconstrictor effects of exercise in our subjects is confirmed by the two SO_2 dose-response curves (figure 3), which show that the change in SRaw increased as the inspired concentration of SO_2 increased, whether the SO_2 was breathed orally or oronasally.

Nasal breathing of SO_2 partially protected most of our subjects from the bronchoconstrictor effects of the gas. This result is consistent with the results of previous studies in both animals and humans that report that the nose and upper respiratory tract remove a large fraction of SO_2 from an inspired airstream (4–9). These previous studies showed that when SO_2 was passed through the nose and upper respiratory tract at very low flow rates (< 0.1 L/s), less than 10% of the delivered concentration of SO_2 reached the lower airways, even when the concentration of SO_2 in the delivered gas was as high as 300 ppm (5). However, when SO_2 was passed at a higher flow rate (0.58 L/s) through the noses of dogs, the fraction of SO_2 that reached the lower airways increased (8). Because the fraction of SO_2 that reaches the lower airways increases as the flow rate of the delivered gas increases, the actual amount of SO_2 that penetrates to the lower airways, per unit of time, may increase by several orders of magnitude (15). Therefore, we reasoned that at the higher inspiratory flows that occur during exercise, the amount of SO_2 reaching the larynx and trachea, even during nasal breathing, might be sufficient to cause significant bronchoconstriction in asthmatic subjects. Although SO_2 breathed nasally did cause significant bronchoconstriction in our subjects, this bronchoconstriction was significantly less than that caused by SO_2 breathed orally, and less (but not significantly less) than SO_2 breathed oronasally. Therefore, nasal breathing partially protected our subjects from the bronchoconstrictor effects of SO_2, even though our subjects' nasal inspiratory flows during exercise were close to the maximum inspiratory flow that can be achieved when breathing through the nose (16) and greater than the nasal inspiratory airflow rate usually achieved before switching from nasal to oronasal breathing (17, 18).

Mouth breathing, on the other hand, allows higher concentrations of SO_2 to penetrate to the lower airways. Animal studies have shown that a much greater fraction of inspired SO_2 penetrates to the trachea when the SO_2 is passed through the mouth than when it is passed through the nose (4, 5, 8). Again, an increase in flow rate of the gas delivered through the mouth allowed a much greater fraction of SO_2 to penetrate to the trachea (8). Also, studies in normal human subjects at rest have consistently reported greater changes in pulmonary function variables when SO_2 is inhaled orally than when the gas is inhaled either nasally, or oronasally (19, 20). Likewise, the bronchoconstrictor effect of SO_2 in our subjects was greatest when the gas was inhaled orally, less (but not significantly less) when inhaled oronasally, and least when inhaled nasally. Therefore, the oronasal breathing pattern of an asthmatic is probably an important determinant of the risk of SO_2-induced bronchoconstriction.

Most normal human subjects without nasal pathology breathe entirely through the nose at rest, and switch to oronasal breathing at an average minute ventilation of approximately 35 L/min (17). Thereafter, as minute ventilation increases, oral ventilation increases faster than nasal ventilation (17). Factors that have been proposed to determine the switching point from nasal to oronasal breathing include collapse of the anterior nares (16), nasal airway resistance, sensation of breathlessness, nasal work of breathing, and rating of perceived exertion of breathing (i.e., the perception of the amount

of effort required for breathing) (17). The oronasal breathing route during exercise in asthmatic subjects has not been described. However, because nasal disorders that may interfere with nasal breathing are prevalent in an asthmatic population (21, 22), people with asthma might be more likely to breathe oronasally at rest and/or to switch to oronasal breathing at a lower minute ventilation than normal people, or both. For example, one of our subjects (No. 5), who had a deviated anterior nasal septum, stated that he always breathed through his mouth because nasal breathing was difficult. Nasal breathing during exercise (which he found very difficult because of his high nasal resistance) prevented SO_2-induced bronchoconstriction in this subject (table 1). However, oral and oronasal breathing of SO_2 at three different concentrations caused similar amounts of bronchoconstriction (figure 2), suggesting that most of this subject's inspiratory airflow was through his mouth and demonstrating that, at least in some subjects with asthma, the bronchoconstrictor response to SO_2 inhaled oronasally is as great as the response to SO_2 inhaled orally. Another reason why people with asthma might switch to oronasal breathing at a lower minute volume of ventilation than normal people is the sensation of breathlessness that often accompanies exercise-induced bronchoconstriction in these people.

We conclude that asthmatic subjects are at significant risk of developing bronchoconstriction when breathing even low concentrations of SO_2 during moderate exercise. Although nasal breathing appears to partially protect many asthmatic subjects from SO_2-induced bronchoconstriction, most will presumably switch to oronasal breathing during moderate and perhaps, light, exercise, thus increasing their risk of SO_2-induced bronchoconstriction. In addition, an unknown number of asthmatic subjects may breathe oronasally even at rest. Therefore, we believe the results of this and previous studies that demonstrate the sensitivity of asthmatic subjects to the bronchoconstrictor effects of even low concentrations of SO_2 are relevant to the determination of air pollution standards.

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EFFECT OF EXERCISE LEVEL AND ROUTE OF INHALATION ON THE BRONCHOMOTOR RESPONSE TO 0.5 PPM SULFUR DIOXIDE IN ASTHMATIC SUBJECTS. R.A. Bethel, D.J. Erle, J. Epstein, D. Sheppard, J.A. Nadel, and H.A. Boushey, CVRI, UCSF, San Francisco, CA

We studied the influence of the level of exercise and of the route of inhalation (oral vs. oronasal) on sulfur dioxide (SO_2)-induced bronchoconstriction in 9 subjects with mild asthma. In the first phase of the study, we measured the rise in specific airway resistance (SRaw) produced by 5 min of exercise on a cycle ergometer at low, moderate, and high work rates [250, 500, and 750 kilopond meters/min (kpm/min)] while subjects breathed through a mouthpiece (oral breathing). Subjects performed each level of exercise on two consecutive experimental days, once while breathing humidified, filtered air and once while breathing similarly treated air containing 0.5 ppm SO_2. We randomized the order of exercise levels and delivered the SO_2 in a double blind manner. In the second phase of the study, subjects repeated this protocol breathing through a facemask (oronasal breathing) which separated and permitted independent measurement of oral and nasal airflow. Exercise alone induced bronchoconstriction in only 1 subject. Mean increase in SRaw ± S.D. (L x cmH_2O/L/sec) on breathing SO_2, above that due to exercise alone, was:

	250 kpm	500 kpm	750 kpm
Mouthpiece	1.3 ± 2.2	9.8 ± 8.8[a]	12.2 ± 8.9[b]
Facemask	0.6 ± 1.9	1.6 ± 3.3	8.5 ± 8.2[a]

a) significant change, $p<0.02$; b) $p<0.005$

Inhaled by mouthpiece, SO_2 caused bronchoconstriction at moderate and high, but not at low, exercise levels. Inhaled oronasally, SO_2 caused bronchoconstriction only at the high exercise level. These findings demonstrate that SO_2-induced bronchoconstriction is exercise-dependent, and that oronasal breathing is partially but not entirely effective in preventing this response. (Supported by USPHS Grants HL-24136, HL-07185 and a grant from the California Air Resources Board)

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Effect of Exercise Rate and Route of Inhalation on Sulfur-Dioxide-induced Bronchoconstriction in Asthmatic Subjects[1-3]

ROBERT A. BETHEL,[4] DAVID J. ERLE, JOHANNA EPSTEIN, DEAN SHEPPARD, JAY A. NADEL, and HOMER A. BOUSHEY

SUMMARY Nine asthmatic subjects exercised at low, moderate, and high work rates on a cycle ergometer while breathing filtered, humidified air with or without 0.5 ppm of sulfur dioxide (SO_2) in a double-blind study. Subjects first performed these experiments breathing through a mouthpiece while wearing a noseclip (oral breathing) and then repeated the experiments breathing through a facemask that separated and permitted independent measurement of oral and nasal air flow (oronasal breathing). We determined specific airway resistance before and after exercise by body plethysmography. Inhaled by mouthpiece, 0.5 ppm So_2 caused bronchoconstriction at moderate and high but not at low work rates. There was a dose-response relationship between the work rate performed and the degree of bronchoconstriction induced. Inhaled oronasally, 0.5 ppm SO_2 caused bronchoconstriction only at the high work rate. These findings demonstrate that So_2-induced bronchoconstriction is dependent on the work rate of exercise during exposure, that oronasal breathing is only partially effective in preventing the bronchoconstriction observed with oral breathing, and that oronasal breathing is less effective in preventing bronchoconstriction with high than with moderate exercise at this concentration of SO_2.

AM REV RESPIR DIS 1983; 128:592-596

Introduction

Previous studies have shown that subjects with asthma are more sensitive to the bronchoconstrictor effects of inhaled sulfur dioxide (SO_2) than are subjects without asthma (1). Additionally, they are sensitive to low concentrations of SO_2 when exposed during exercise (2). Inhaled by mouthpiece, SO_2 causes bronchoconstriction in asthmatics in concentrations as low as 1 ppm at rest and as low as 0.25 ppm, or possibly lower, during moderate exercise.

Studies on the effects of SO_2 inhaled by mouthpiece, however, may overestimate the effects that identical concentrations would have on freely breathing asthmatic subjects. Inhaled by mouthpiece, air bypasses the nose, which during free breathing protects the lower airways by efficiently absorbing SO_2 (3). The mouth also absorbs SO_2 but does so less efficiently than the nose (4, 5) and may do so even less efficiently when its configuration is altered by a mouthpiece (6).

On the other hand, asthmatics frequently have congestive rhinitis, and thus little air may pass through the nose during free breathing. Moreover, during high exercise work rates, a greater proportion of ventilation is likely to occur breathing by mouth. Thus, asthmatics may respond to SO_2 during free breathing, especially during exercise, much as they do when breathing through a mouthpiece.

Kirkpatrick and coworkers (7) have found that during moderate exercise, oronasal breathing decreased but did not eliminate the bronchoconstriction caused by 0.5 ppm SO_2 breathed by mouthpiece. Linn and coworkers (8) reported, however, that 0.5 ppm SO_2 breathed in an exposure chamber did not cause bronchoconstriction in asthmatic subjects exercising at a lower work rate.

The apparent disparity between these studies may be explained if the degree of bronchoconstriction induced by SO_2 is dependent on the work rate of exercise performed during exposure. Exercise may increase the dose of SO_2 delivered beyond the upper airways to the lungs by several mechanisms. First, the increase in minute ventilation associated with the increase in exercise will cause a greater quantity of SO_2 to be inhaled. Second, the mouth will absorb a smaller proportion of SO_2 from the inhaled air when the flow rate increases because of exercise (4). Third, the shift from nasal to oronasal breathing will decrease the proportion of SO_2 absorbed in the upper airways because the mouth is less effective in absorbing SO_2 than the nose.

The purposes of this study were to determine the influence of work rate on the bronchoconstriction induced by SO_2 and to determine whether the degree of protection given by oronasal breathing against SO_2-induced bronchoconstriction is dependent on work rate.

Methods

Subjects

The subjects were 9 nonsmoking volunteers, 6 women and 3 men 20 to 37 yr of age, who were told of the risks of the experimental protocol and who signed consent forms approved by the Committee on Human Experimentation of the University of California, San Francisco. All 9 subjects had a history of recurrent wheezing or chest tightness since childhood, reversible bronchoconstriction previously documented by a physician, multiple allergies and recurrent

(Received in original form August 27, 1982 and in revised form April 15, 1983)

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[2] Supported in part by Program Project Grant No. HL-24136 from the U.S. Public Health Service and by Contract No. A9-115-30 from the California Air Resources Board.

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[4] Recipient of Pulmonary Faculty Training Grant No. HL-07159 from the National Institutes of Health.

allergic rhinitis, and had increased responsiveness of the airways to histamine inhaled from a deVilbiss 646 nebulizer (specific airway resistance doubled after inhalation of 10 breaths of an aerosolized solution of 4 mg/ml or less of histamine). In addition, subjects were able to perform 750 kpm/m on a cycle ergometer for 5 min. Characteristics of the subjects are listed in table 1.

Two of the 9 subjects were known from previous experimental work to develop bronchoconstriction after inhalation of low concentrations of SO_2. The other 7 subjects were selected from 10 volunteers who met the above criteria for asthma. These 7 developed a rise in specific airway resistance of 4.75 L × cm H_2O/L/s or greater after 5 min of exercise at 750 kpm/min while breathing 0.5 ppm of SO_2 through a mouthpiece. The other 3 developed lesser degrees of bronchoconstriction and were not included.

Screening tests of pulmonary function (spirometry, single-breath carbon monoxide diffusing capacity, single-breath oxygen test of gas distribution, and maximal expiratory flow-volume curve) were normal in 6 subjects. The other 3 subjects had mild airway obstruction at the time of testing, as indicated by ratios of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) of 74, 74, and 73%, and by decreased maximal expiratory flow at low lung volumes. No subject required chronic bronchodilator therapy or had taken any medication for 48 h before any experiment.

Experimental Design

To determine if the degree of bronchoconstriction induced by SO_2 is dependent on exercise work rate, we performed an experiment on each subject on 6 different experimental days. On each day, we first measured the subject's baseline airway resistance and thoracic gas volume every 30 s for 8 min in a constant-volume whole-body plethysmograph. Specific airway resistance was calculated as the product of airway resistance and thoracic gas volume. The subject then exercised for 5 min on a cycle ergometer (Elema-Schonander, Stockholm, Sweden) at 1 of 3 exercise work rates: 250, 500, or 750 kpm/min. While breathing through a mouthpiece and wearing a noseclip, each subject exercised at the same work rate on 2 successive experimental days—on one day breathing filtered, humidified air and on the other day breathing similarly treated air containing 0.5 ppm SO_2. The order of exercise work rates and the order of administration of SO_2 or filtered air were randomized. Neither the subject nor the investigator performing the plethysmographic measurements knew on which days SO_2 was given. Two minutes after the end of exercise, the subject returned to the body plethysmograph where specific airway resistance again was determined every 30 s for 8 min.

To determine whether SO_2 induces less bronchoconstriction when breathed oronasally than when breathed by mouthpiece, and if so, whether the diminution in bronchoconstriction is present at all 3 work rates, we then repeated the series of 6 experiments as outlined above with the subject breathing through a facemask instead of through a mouthpiece.

We thus determined the change in specific airway resistance after the subject exercised while breathing filtered air and after he or she exercised while breathing 0.5 ppm SO_2 at low, moderate, and heavy work rates. The bronchoconstriction induced by SO_2 while the subject breathed orally by mouthpiece was compared with the bronchoconstriction induced when the subject breathed oronasally by facemask.

Methods and Apparatus

The method of delivery of SO_2 has been described previously (2, 7). Briefly, compressed air was filtered and passed through a bubble humidifier to obtain a humidity of 80%. Particulate water was removed by passing the air flow through another filter. Sulfur dioxide was added in a 3-L glass mixing chamber and the mixed gas was delivered to subjects through Teflon tubing.

Sulfur dioxide concentrations in the air stream were measured continuously by passing samples from the inspiratory air stream to a pulsed, fluorescent SO_2 analyzer No. 43; (Thermo-Electron Corp.) The dew point and temperature of the delivered air were measured by passing air from the inspiratory air stream to a digital humidity analyzer Dew All Model 911; (E.G. and G.). Relative humidity was calculated from the dew point and temperature using standard tables. Mean variables (± SD) of the inhaled air for all experiments were temperature, 22.9° C (± 0.8) relative humidity, 80% (± 0.6); SO_2 during SO_2 trials, 0.52 ppm (± 0.03) SO_2 during SO_2-free trials, 0.00 ppm.

The mouthpiece was attached to a Koegel Y valve to assure unidirectional flow in the inspiratory limb of the system. Small, medium, and large facemasks were made from Mine Safety Appliances "Comfo II" masks (465825, 460968, 466486). The masks fitted snugly around the nose and mouth. We constructed a septum within the mask between the nose and mouth to separate nasal and oral air flow and cut inspiratory and expiratory ports for both chambers. Koegel valves in the inspiratory ports and Rudolph valves in the expiratory ports assured unidirectional flow. Significant air leaks into the mask were excluded in each subject by demonstrating that expired nitrogen concentration fell to less than 3% while the subject exercised on a cycle ergometer for 7 min while breathing 100% oxygen through the mask. Several subjects required placement of a rapidly setting alginate impression material, "Caulk Jeltrate" (L.D. Caulk Co.), at the bridge of the nose to establish an airtight mask. The mask was sprayed with an inert, chemically pure, TFE fluoropolymer compound (Fluoroglide CP) to prevent absorption of SO_2 by the rubber of the mask.

We measured minute ventilation via the mouthpiece and via both the nose and mouth chambers of the facemask by integrating the output from pneumotachygraphs in the inspiratory circuits.

Data Analysis

For purposes of statistical analysis, we chose the highest mean of 4 consecutive measurements of specific airway resistance during the 8-min measuring period (7). The postexercise minus the pre-exercise specific airway resistance was considered the change in specific airway resistance. The change in specific airway resistance caused by SO_2 was the change in specific airway resistance while breathing SO_2 minus that while breathing filtered air.

To determine whether the increase in specific airway resistance caused by SO_2 was significant, we performed a randomized block analysis of variance (9). The variable in question was the change in specific airway resistance from before to after exercise (table 2). Each subject performed 12 experiments that varied from one another in exercise work rate (3 levels), presence or absence of 0.5 ppm SO_2 in the inhaled air, and route of inhalation (mouthpiece versus facemask). The 12 experiments performed

TABLE 1

CHARACTERISTICS OF THE SUBJECTS

Subject No.	Age (yr)	Sex	Height (cm)	Weight (kg)	Initial SRaw (L × cm H_2O/L/s)	FEV_1 (L)	FEV_1/FVC (%)
1	20	M	168.0	63.0	1.74	3.9	87
2	28	F	171.0	98.0	5.24	3.5	85
3	25	M	166.0	65.5	5.09	4.0	74
4	25	F	152.5	56.0	2.13	2.5	74
5	26	F	166.0	65.0	7.18	3.2	73
6	24	M	174.5	78.0	3.75	4.7	81
7	37	F	168.0	56.0	4.68	3.3	88
8	22	F	168.0	60.5	3.87	4.3	93
9	27	F	165.5	63.9	5.52	4.0	86

Definition of abbreviations: SRaw = specific airway resistance; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.

TABLE 2

THE CHANGE IN SPECIFIC AIRWAY RESISTANCE (ΔSRAW) (L × CM H_2O/L/S) FROM BEFORE TO AFTER EXERCISE IN 9 ASTHMATIC SUBJECTS EXERCISING FOR 5 MIN AT 250, 500, AND 750 KPM/MIN WHILE BREATHING FILTERED AIR OR 0.5 PPM SO_2, FIRST THROUGH A MOUTHPIECE AND LATER THROUGH A FACEMASK

Subject No.	ΔSRaw 250 kpm/min		500 kpm/min		750 kpm/min	
	No SO_2	SO_2	No SO_2	SO_2	No SO_2	SO_2
Mouthpiece experiments						
1	−1.98	1.58	1.00	5.70	−1.24	13.86
2	1.00	−1.24	−2.44	12.88	1.03	13.42
3	−1.31	−0.79	−0.06	1.40	−1.22	9.59
4	0.39	0.09	1.99	5.99	14.19	21.86
5	−1.10	0.66	−2.11	19.35	−4.01	17.19
6	−0.47	2.88	−0.12	22.63	−1.32	28.76
7	−0.17	4.40	0.51	15.93	0.68	3.20
8	0.55	0.03	1.21	2.49	0.40	5.61
9	−1.15	−0.36	1.99	4.29	1.15	6.06
Mean	−0.47	0.81	0.22	10.07*	1.07	13.28*
SD	0.99	1.84	1.61	7.81	5.18	8.33
Facemask experiments						
1	−1.40	−0.42	−0.70	0.16	−1.21	1.44
2	−4.02	0.68	−0.13	3.64	−0.49	6.68
3	−1.64	−1.08	−0.76	−0.09	0.58	12.08
4	−0.01	0.33	8.00	4.17	13.29	15.38
5	−3.90	−1.50	−0.46	5.10	−1.99	16.47
6	0.27	0.15	0.11	0.55	0.22	24.73
7	−0.11	−0.85	−0.40	6.48	−1.21	−0.15
8	−0.46	0.17	0.00	0.84	0.28	2.18
9	1.46	0.05	0.31	−0.59	0.54	7.07
Mean	−1.09	−0.27	0.66	2.25	1.11	9.54*
SD	1.86	0.73	2.78	2.61	4.46	8.27

* Significant increase $p < 0.001$.

by each subject comprised a block and the between-block differences were therefore due to interindividual variation. The null hypothesis was rejected, indicating that the increases in specific airway resistance caused by the 12 different experimental conditions differed significantly. To determine which experimental conditions caused significantly different increases in specific airway resistance at the 0.05 level of significance, we performed a Newman-Keuls multiple range test.

In a similar manner, to determine whether the percentage of ventilation while breathing orally (table 3) varied during different experimental conditions, we again performed a randomized block analysis of variance. Here, the variable in question was the percentage of total ventilation while breathing orally during experiments in which subjects breathed from a facemask. The experimental conditions varied from one another in exercise work rates (3 levels) and in the presence or absence of 0.5 ppm SO_2 in the inhaled air. The 6 experiments performed by each subject comprised a block. The null hypothesis was accepted, indicating that the percentage of ventilation while breathing orally during the 6 experimental conditions did not vary significantly.

Results

In experiments in which subjects breathed through a mouthpiece, 0.5 ppm SO_2 did not cause bronchoconstriction during light exercise but did cause bronchoconstriction during moderate exercise ($p < 0.001$) and an even greater degree of bronchoconstriction during heavy exercise ($p < 0.001$) (table 2 and figure 1). Although the degree of bronchoconstriction induced by SO_2 during moderate and heavy exercise was not significantly different, there was a dose-response relationship between exercise work rate performed and the mean bronchoconstriction induced by SO_2.

In experiments in which subjects breathed through a facemask, the results were somewhat different. Sulfur dioxide did not cause bronchoconstriction during light or moderate exercise but did cause bronchoconstriction during heavy exercise ($p < 0.001$) (table 2 and figure 1). The bronchoconstriction induced by SO_2 during heavy exercise and breathing through a facemask was less than that induced while breathing through a mouthpiece. Thus, at high exercise work rates, oronasal breathing diminished but did not prevent the bronchoconstriction induced by SO_2 in mouthpiece experiments.

The subjects varied greatly in the degree of bronchoconstriction induced by SO_2. During heavy exercise and mouthpiece breathing, Subject 6 developed the greatest degree of bronchoconstriction caused by SO_2 observed in this study (30.08 L × cmH_2O/L/s) (figure 2). Under the same experimental conditions, Subject 7 developed considerably less bronchoconstriction caused by SO_2 (2.52 L× cm H_2O/L/s). The remaining subjects developed intermediate degrees of bronchoconstriction.

Mean minute ventilation during the fifth minute of exercise for all experiments was 26.9, 40.7, and 60.8 L/s during exercise at 250, 500, and 750 kpm/min, respectively. During facemask experiments, both oral and nasal ventilation increased incrementally as exercise work rate increased (table 3). Although the proportion of total venti-

TABLE 3

MINUTE VENTILATION (MV) (L/MIN) AND THE PERCENT VENTILATION BREATHED ORALLY DURING THE FIFTH MINUTE OF EXERCISE AT WORK RATES OF 250, 500, AND 750 KPM/MIN IN 9 ASTHMATIC SUBJECTS BREATHING THROUGH A FACEMASK, INHALING FILTERED AIR WITH OR WITHOUT ADDED SO_2

Subject No.	250 kpm/min				500 kpm/min				750 kpm/min			
	No SO_2		SO_2		No SO_2		SO_2		No SO_2		SO_2	
	MV	% Oral	MV	% Oral	MV	% Oral	MV	% Oral	MV	% Oral	MV	% Oral
1	26.4	66	28.8	64	38.1	47	40.7	49	55.6	45	54.3	45
2	33.1	55	34.3	47	52.3	57	55.6	57	61.6	55	75.1	57
3	27.5	81	25.6	70	33.2	95	36.3	62	50.9	89	52.9	82
4	28.2	44	26.8	31	37.4	44	36.4	39	50.7	57	53.2	52
5	27.2	49	28.8	51	43.1	51	44.8	52	72.1	55	69.3	61
6	25.8	71	—	—	42.3	57	38.9	59	66.4	61	75.7	55
7	22.2	0	21.2	0	37.1	23	39.1	33	63.4	56	61.9	47
8	21.5	82	24.4	67	45.1	56	45.1	60	76.7	64	62.8	79
9	22.9	55	26.0	45	39.1	50	35.4	54	—	—	49.8	75
Mean	26.1	56	27.0	50	40.9	53	41.4	52	62.2	62	61.7	61
SD	3.6	25	3.8	23	5.6	19	6.4	10	9.5	13	9.9	14

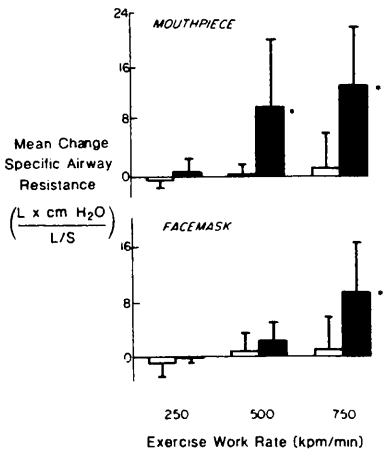

Fig. 1. Mean change in specific airway resistance from before to after exercise in 9 asthmatic subjects breathing SO_2-free air (□) or 0.5 ppm SO_2 (■) through a mouthpiece and through a facemask during exercise at 250, 500, and 750 kpm/min. The bar extensions are standard deviations; * = significant increase ($p < 0.001$).

lation breathed by mouth was greater during heavy than during light or moderate exercise, this difference was not statistically significant.

The pattern of oral and nasal distribution of ventilation differed greatly among subjects. Some (e.g., Subject 7) breathed chiefly or entirely through the nose during light exercise. As work rate increased, nasal ventilation also increased, but the proportion of total ventilation breathed by nose decreased because of the marked increase in oral ventilation. Other subjects (e.g., Subject 1) followed a different pattern. The proportion of total ventilation breathed nasally was least at the low exercise work rate and increased as work rate increased. The frequency of allergic rhinitis and the daily variation in nasal congestion in these subjects may have contributed to the variation in the pattern of oral-nasal distribution of ventilation.

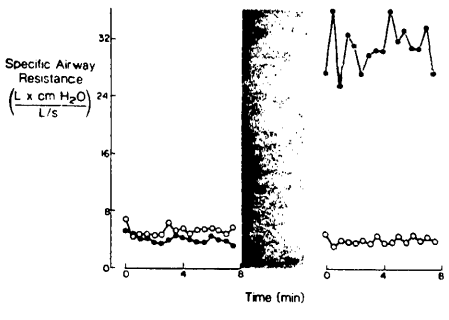

Fig. 2. Effect of exercise at 750 kpm/min (*shaded area*) while breathing filtered, humidified air (○) or 0.5 ppm SO_2 (●) from a mouthpiece on specific airway resistance in Subject 6.

Discussion

This study demonstrates that the degree of bronchoconstriction induced by SO_2 in subjects with asthma depends on the work rate of exercise performed as they breathe SO_2. Higher work rates result in greater bronchoconstriction, presumably because of the increased rate at which the dose of SO_2 is delivered to the lungs with increased ventilation.

This study also confirms the finding of Kirkpatrick and coworkers (7) that nasal or oronasal breathing during exercise only partially prevents the bronchoconstriction induced by SO_2 breathed by mouthpiece. In this study, oronasal breathing prevented the response to 0.5 ppm SO_2 during moderate exercise. During heavy exercise, however, oronasal breathing only partially diminished the bronchoconstriction observed after mouthpiece breathing of SO_2. Therefore, oronasal breathing is less effective at preventing SO_2-induced bronchoconstriction at high than at moderate exercise work rates, at least when subjects breathe 0.5 ppm.

In a previous study from this laboratory, Kirkpatrick and coworkers (7) found that 0.5 ppm SO_2 caused significant bronchoconstriction in subjects with asthma breathing through a facemask during exercise at the moderate work rate of 550 kpm/min. In the present study, we found that 0.5 ppm SO_2 did not cause significant bronchoconstriction during similar experimental conditions. This apparent discrepancy, however, may be easily resolved. The 2 subjects common to both studies (Subjects 2 and 3 of this study were Subjects 1 and 4 of the previous study) had similar minute ventilations in the 2 studies and also developed similar degrees of bronchoconstriction. Moreover, the remaining 4 subjects in the study of Kirkpatrick and coworkers had a high prevalence of nasal disorders (1 subject had a deviated septum, 2 had severe rhinitis with nasal congestion). It is likely, therefore, that although the exercise work rates were similar, the group mean oral ventilation at these similar exercise levels was greater in their study than in the present study. Greater oral ventilation may well have caused greater bronchoconstriction. Rather than defining a specific exercise work rate at which oronasal ventilation ceases to protect the airways from SO_2-induced bronchoconstriction, these studies demonstrate the principle that, for asthmatics, as the exercise work rate increases, a point is reached at which oronasal ventilation is no longer effective in preventing SO_2-induced bronchoconstriction, although it still may mitigate the response. Whatever contributes to an increased oral airflow rate—whether it be work rate of exercise or nasal obstruction—is likely to contribute to an increased bronchoconstrictor effect.

In this study, the distribution of airflow between the nose and the mouth, as subjects increased their exercise work rate, varied greatly among subjects. We had predicted that with increasing work rate, subjects would breathe a greater proportion of their total ventilation through the mouth. A consequence of this predicted change would be that proportionately more SO_2 would reach the lungs. Some subjects (e.g., Subject 7) did follow the predicted pattern but other subjects (e.g., Subject 1) breathed proportionately less through the mouth as they exercised at higher work rates. As exercise is an effective nasal decongestant (10), some subjects, especially those with rhinitis and nasal congestion, may have benefited greatly from exercise-induced decongestion. Regardless of the relative proportions of ventilation through the nose and the mouth, absolute ventilation through both the nose and the mouth increased incrementally with increase in exercise work rate in almost all instances. Thus, as exercise increased, a greater dose of SO_2 was delivered to the larynx and lower airways through both the nose and the mouth.

Niinimaa and associates (11) found that the mean minute ventilation at which healthy subjects switched from purely nasal to oronasal breathing was 35.3 L/min. In the present study, 8 of 9 subjects breathed oronasally during the low exercise work rate during which mean minute ventilation was 26.9 L/min. We think that this altered pattern of ventilation was due to the frequency of rhinitis in our subjects but that our subject group was more typical of persons with asthma.

Perhaps the unexpected pattern of ventilation in these subjects was due to nasal congestion, but it is possible that the facemask may have altered the oronasal distribution of breathing during exercise. The facemask, which fitted snugly about the nose and mouth, may have caused subjects to breathe oronasally at exercise work rates at which they would have breathed only nasally

during free breathing. The resultant increase in oral ventilation would have increased the dose of SO_2 to lungs causing greater degrees of bronchoconstriction. On the other hand, the facemask might have prevented a subject from opening his mouth as widely as he would have during free breathing. The resultant narrowing of the mouth opening and increase in nasal ventilation would have caused a more efficient absorption of SO_2 and thus less bronchoconstriction. Studies performed in an exposure chamber with subjects breathing freely would more reliably determine the bronchoconstrictor effects of ambient SO_2 on subjects with asthma but could not determine the oronasal distribution of air flow.

This study demonstrates that there is a dose-response relationship between the exercise work rate performed and the degree of bronchoconstriction induced by SO_2 in persons with asthma. It confirms the study of Kirkpatrick and coworkers (7), which showed that oronasal breathing only partially prevents the bronchoconstriction induced by SO_2 after mouthpiece breathing. It demonstrates that nasal or oronasal breathing is less effective at preventing SO_2-induced bronchoconstriction during heavy than during moderate exercise.

Acknowledgment

We wish to thank Beth Cost and Patty Snell for their assistance in preparing the manuscript.

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ENVIRONMENTAL RESEARCH 30, 412–419 (1983)

Tolerance to Sulfur Dioxide-Induced Bronchoconstriction in Subjects with Asthma

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Received May 2, 1982

A study to determine whether the bronchoconstriction induced by low concentration of sulfur dioxide in subjects with asthma decreases with repeated exposure was undertaken. Eight subjects with asthma performed 3 min of voluntary eucapnic hyperpnea with 0.5 ppm of SO_2 in humidified filtered air three times at 30-min intervals and we measured specific airway resistance (SR_{aw}) before and after each period of hyperpnea. Specific airway resistance increased significantly more after the first exposure to SO_2 [(from 7.6 ± 1.7 to 15.5 ± 2.0 L × cm H_2O/liter/sec (mean ± SEM)] than after the second (from 8.1 ± 1.3 to 10.8 ± 1.6) or third (from 7.6 ± 1.6 to 10.1 ± 1.9) exposures ($P < 0.025$). When seven subjects repeated hyperpnea with SO_2 24 hr and 7 days later, SR_{aw} increased as much as it had after the first exposure (from 8.2 ± 2.5 to 15.5 ± 4.5 at 24 hr and from 6.6 ± 1.4 to 15.4 ± 2.1 at 7 days). In four subjects repeated exposure to SO_2 caused short-term inhibition of the bronchomotor response to SO_2 but did not inhibit the bronchomotor response to histamine aerosol. It was concluded that repeated exposures to a low concentration of SO_2 over a short period (on 1 day) can induce tolerance to the bronchomotor effects of SO_2 in subjects with asthma. Tolerance to the bronchomotor effects of SO_2 is not caused by decreased responsiveness of airway smooth muscle or a generalized decrease in the responsiveness of vagal reflex pathways since the bronchomotor response to histamine is preserved.

INTRODUCTION

Inhalation of low concentrations of sulfur dioxide causes significant bronchoconstriction in people with asthma (Sheppard *et al.*, 1980, Sheppard, 1981b, Sheppard, 1981a; Koenig *et al.*, 1981). Sulfur dioxide-induced bronchoconstriction is potentiated by increased minute ventilation so that concentrations of SO_2 of 0.5 ppm or less, as may be encountered in polluted urban air, can cause symptomatic bronchoconstriction when inhaled during exercise or voluntary eucapnic hyperpnea (Sheppard, 1981b; Koenig *et al.*, 1981). In normal subjects, repeated exposure to high concentrations of SO_2 (9–21 ppm) has been reported to cause tolerance to SO_2-induced bronchoconstriction in that these subjects developed less bronchoconstriction after the second of a pair of successive exposure to SO_2 than they did after the first (Frank, 1964). The duration of tolerance to the bronchomotor effects of SO_2 and the mechanism by which it is induced, however, are unknown. It is also unknown whether tolerance occurs in subjects with asthma

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0013-9351/83/020412-08$03.00/0
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who are repeatedly exposed to low concentrations of SO_2. We therefore undertook this study to determine whether subjects with asthma develop tolerance to SO_2-induced bronchoconstriction and, if they do, how long this tolerance persists. In addition, we assessed the specificity of tolerance to SO_2-induced bronchoconstriction by studying whether or not decreased bronchomotor responsiveness to SO_2 is associated with decreased bronchomotor responsiveness to inhaled histamine.

METHODS

The subjects were 10 nonsmoking volunteers who were informed of the risks of the experimental protocol and signed consent forms approved by the Committee on Human Experimentation of the University of California, San Francisco. All 10 subjects had asthma as defined by a history of recurrent episodes of wheezing, chest tightness, and reversible airway obstruction previously documented by a physician. No subject took antihistaminic drugs within 48 hr, theophylline drugs within 12 hr, or sympathomimetic drugs within 8 hr of any study. Anthropometric data and results of screening pulmonary function tests are shown in Table 1. All subjects had been previously found to increase specific airway resistance (SR_{aw}) by more than 100% after performing voluntary eucapnic hyperpnea with 0.5 ppm of SO_2 as described below.

Each subject breathed SO_2 from a mouthpiece attached to a two-way valve. We delivered SO_2 at a metered flow from a calibrated tank of SO_2 (500 ppm) to a 3-liter glass mixing chamber where it was mixed with air delivered from a compressed air source at 3 liters/sec. Before entering the mixing chamber, the air was filtered through a HEPA filter and two vapor filters (Mine Safety Appliances, No. 8185), then humidified by a bubble humidifier, and, finally, filtered again through a second HEPA filter (Mine Safety Appliances, No. Cu-86444) to remove any water particles added during humidification. The subject controlled her/his respiration rate by following a metronome and controlled her/his tidal volume by watching a signal proportional to inspired volume displayed on a screen mounted above the mouthpiece. We measured the expired CO_2 concentration from a point in the

TABLE 1
ANTHROPOMORPHIC DATA AND SPIROMETRIC VALUES IN EIGHT SUBJECTS WITH ASTHMA

Subject	Age (years)	Sex	Height (cm)	Weight (kg)	FEV_1[a] (liters)	FVC[b] (liters)
1	24	M	175	78	4.7	5.4
2	28	F	162	54	1.7	2.9
3	36	F	177	87	2.2	4.3
4	28	F	171	88	3.5	4.1
5	26	M	181	71	3.4	4.7
6	22	F	168	61	4.3	4.7
7	25	M	166	66	4.0	5.4
8	24	M	168	65	3.0	3.8

[a] Forced expired volume in 1 s.
[b] Forced vital capacity.

expiratory tubing just distal to the mouthpiece with a CO_2 analyzer (Beckman, No. LB-1), and maintained end-tidal CO_2 at resting levels by adding a metered flow of 100% CO_2 to the inspiratory tubing. We measured the inspired SO_2 concentration continuously from a needle just proximal to the mouthpiece with a pulsed fluorescent SO_2 analyzer (Model 43, Thermo-Electron Corp., Bohemia, N.Y.). We also measured the temperature and dew point of the inspired gas continuously with a digital humidity analyzer equipped with a mirrored dew point hygrometer and a platinum temperature probe (Model 911, E.G. and G., Waltham, Mass.), and calculated relative humidity from standard tables. To obtain a record of minute ventilation during hyperpnea, we measured inspired airflow with a pneumotachygraph (Model 3, Fleisch, Lausanne, Switzerland) and a differential pressure transducer (Model DP-45, Validyne Co., Northridge, Calif.), and electrically integrated this signal to obtain a volume signal.

We prepared histamine solution daily in normal saline and generated histamine aerosol from a nebulizer (DeVilbiss, No. 646) filled with 3 ml of solution and equipped with a Rosenthal French dosimeter (Lab for Applied Immunology) which was powered by compressed oxygen at 20 psi. We instructed the subject to inhale slowly from functional residual capacity to total lung capacity. The output of the nebulizer was 11.1 ± 0.6 μl (mean ± SD) per breath.

In the first part of our study, we determined whether repeated inhalation of low concentrations of SO_2 altered the magnitude of SO_2-induced bronchoconstriction. In each subject, we first measured airway resistance (R_{aw}) and thoracic gas volume (V_{tg}) in a constant-volume, whole-body plethysmograph (DuBois, *et al.*, 1956) every 30 sec for 2.5 min and multiplied R_{aw} by V_{tg} to obtain SR_{aw}. The subject then performed voluntary eucapnic hyperpnea with 0.5 ppm of SO_2 in partially humidified, ambient-temperature air for 3 min at a minute ventilation that had previously resulted in significant bronchoconstriction in that subject. Two minutes later, we again measured SR_{aw} every 30 sec for 2.5 min. We chose this timing on the basis of our previously reported data on the time course of SO_2-induced bronchoconstriction (Sheppard, 1981b). In seven subjects, this initial period of hyperpnea with SO_2 increased SR_{aw} by more than 60% over baseline. In the other three subjects (Nos. 4, 7, and 8), we immediately repeated hyperpnea with SO_2 for 3 min at a higher minute ventilation. It was necessary to have one subject (No. 4) perform hyperpnea with SO_2 at yet a third minute ventilation in order to produce an increase in SR_{aw} of greater than 60% over baseline. Once we had increased SR_{aw} by 60% or more, we waited 30 min and again measured SR_{aw} every 30 sec for 2.5 min. If SR_{aw} remained more than 2 liter × cm H_2O/liter/sec above baseline (as it did in two subjects), we did not continue the experiment. In both of these subjects, SR_{aw} was still more than 50% above baseline 45 min after exposure. We had the remaining eight subjects repeat hyperpnea with SO_2 in an identical fashion to that used in their initial exposure (i.e., at one level of minute ventilation in five subjects, at two levels in two subjects, and at three levels in one subject). We again measured SR_{aw} every 30 sec for 2.5 min beginning 2 min after each period of hyperpnea. Finally, we waited another 30 min and then had each subject perform hyperpnea with SO_2 again.

To determine whether inhalation of 0.5 ppm of SO_2 caused a longlasting alter-

ation in SO_2-induced bronchoconstriction, the subjects returned and again performed hyperpnea with SO_2 24 hr and 7 days after their initial exposure. Seven subjects returned at 24 hr and seven subjects at 7 days. On a separate day, each subject performed voluntary eucapnic hyperpnea as described above but with filtered humidified air without SO_2.

When we found that our subjects did develop tolerance to the bronchoconstriction caused by hyperpnea with 0.5 ppm of SO_2, we went on to determine whether or not this tolerance was specific for SO_2-induced bronchoconstriction by studying the effects of tolerance to SO_2 on the bronchoconstriction caused by inhaled histamine. In four subjects, we first constructed dose–response curves to inhaled histamine by measuring SR_{aw} before and after inhalation of doubling concentrations of histamine aerosol. Thirty minutes later, we measured SR_{aw} before and beginning 2 min after voluntary eucapnic hyperpnea with 0.5 ppm of SO_2 for 3 min. Thirty minutes after that, we had the subjects repeat hyperpnea with SO_2 to document that we had induced tolerance to SO_2. Finally, after an additional 30 min, we repeated the histamine dose–response curve.

We compared the changes in SR_{aw} caused by each period of hyperpnea with SO_2 and the hyperpnea with SO_2-free air with an analysis of variance and the Neuman–Keuls multiple range test. For the purpose of this analysis, for subjects who performed hyperpnea at more than one minute ventilation, we considered the change in SR_{aw} as the difference between the baseline value and that obtained after hyperpnea at the highest minute ventilation. We also compared SR_{aw} before and after hyperpnea with SO_2-free air with Student's t test for paired data.

RESULTS

When our subjects performed voluntary eucapnic hyperpnea with 0.5 ppm of SO_2 three times in succession at 30-min intervals, the first exposure to SO_2 caused significantly more bronchoconstriction than did the second or third exposure (Table 2, Fig. 1). Twenty-four hours and 7 days later, the magnitude of SO_2-induced bronchoconstriction was the same as it had been initially. Voluntary eucapnic hyperpnea with partially humidified, ambient-temperature air without SO_2 did not cause bronchoconstriction in our subjects (Table 1, Fig. 1). The relative humidity and temperature (and, therefore, water content) of inspired air were constant during all experiments: 81.7 ± 1.4% and 22.6 ± 0.4°C, respectively (mean ± SD). The SO_2 concentration was 0.51 ± 0.02 ppm (mean ± SD).

In four subjects, we assessed the effects of repeated exposures to SO_2 on the bronchomotor response to inhaled histamine aerosol. In each subject, the second period of hyperpnea with SO_2 caused less bronchoconstriction than the first (Fig. 2). Despite this adaptation to the bronchomotor effects of SO_2, the bronchomotor response to inhaled histamine was not inhibited in any subject (Fig. 2).

DISCUSSION

This study shows that the bronchoconstriction caused by hyperpnea with 0.5 ppm of SO_2 in subjects with asthma decreases with repeated exposures at 30-min intervals; in other words, these subjects develop tolerance to the bronchomotor effects of SO_2. This decreased responsiveness (tolerance) to SO_2 persists for at

TABLE 2

SPECIFIC AIRWAY RESISTANCE BEFORE AND AFTER HYPERPNEA WITH 0.5 ppm OF SO_2, AND BEFORE AND AFTER HYPERPNEA WITH PARTIALLY HUMIDIFIED AIR WITHOUT SO_2 IN EIGHT SUBJECTS WITH ASTHMA

	SO_2											
	First		Second		Third		After 24 hr		After 7 days		Air	
Subject	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	6.3[a]	14.3	7.6	9.9	5.6	5.8	—	—	5.0	13.8	4.3	4.3
2	11.6	19.4	10.9	16.0	10.9	13.9	18.2	40.0	11.7	24.3	9.3	8.6
3	14.9	24.3	14.6	18.1	16.6	18.5	16.4	21.4	13.8	21.5	14.8	14.5
4	3.4	9.2	4.5	5.7	3.0	3.9	3.6	5.4	7.2	14.6	3.4	4.4
5	9.8	21.3	9.9	10.9	9.1	11.2	8.6	12.9	7.7	13.3	7.6	6.4
6	3.2	11.7	3.3	7.0	3.3	4.7	2.4	6.8	3.0	7.3	3.0	4.2
7	3.3	8.1	5.3	6.8	4.2	7.6	3.8	7.8	3.6	22.1	5.7	6.0
8	8.2	15.8	8.8	12.5	8.1	13.3	4.4	10.9	—	—	5.3	5.2
Mean	7.6	15.5	8.1	10.9	7.6	9.9	8.2	15.0	7.3	16.7	6.7	6.7
SEM	1.5	2.1	1.3	1.6	1.6	1.8	2.5	4.6	1.5	2.3	1.4	1.2
	(4.3)	(5.8)	(3.7)	(4.5)	(4.6)	(5.2)	(6.6)	(12.2)	(4.1)	(6.1)	(3.9)	(3.5)

Note. Hyperpnea with SO_2 was performed three times in succession at 30-min intervals, and again 24 hr and then 7 days later.

[a] Units of specific airway resistance are liters × cm H_2O/liter/sec.

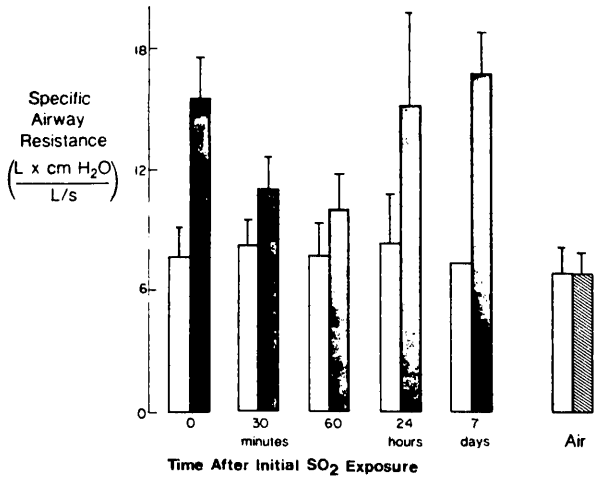

FIG. 1. Specific airway resistance (SR_{aw}) before (□) and after voluntary eucapnic hyperpnea with 0.5 ppm of SO_2 (■) and with partially humidified air without SO_2 (▨) in eight subjects with asthma. Hyperpnea with SO_2 was performed three times in succession, and then 24 hr and 7 days later. Values are means ± SEM. $^*P < 0.025$.

least 30 min but for less than 24 hr. Tolerance to inhaled SO_2 is not associated with decreased bronchomotor responsiveness to inhaled histamine.

The bronchomotor response to inhaled histamine is dependent both on vagal efferent nerve activity and on the contraction of airway smooth muscle (Holtzman

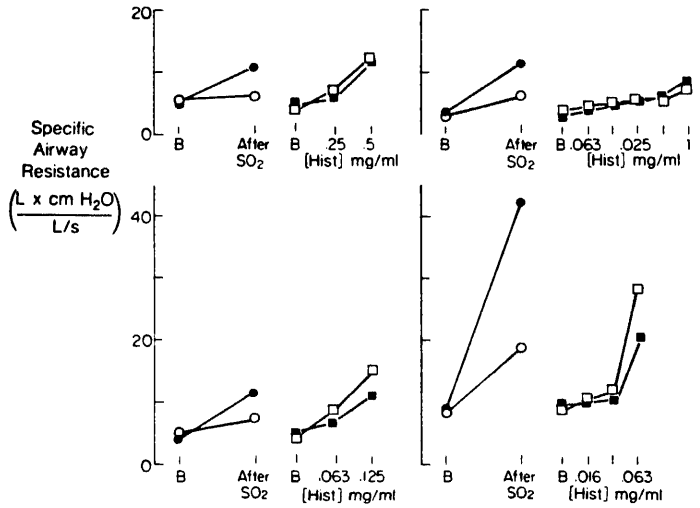

FIG. 2. Left-hand columns plot specific airway resistance (SR_{aw}) before and after the first (●) and second (○) periods of voluntary eucapnic hyperpnea with SO_2 performed 30 min apart in each of four subjects with asthma. Each subject developed tolerance to SO_2. Right-hand columns plot dose–response curves to inhaled histamine aerosol 30 min before the first period of hyperpnea with SO_2 (■) and 30 min after the second period (□). The bronchomotor response to inhaled histamine was unaffected by the development of tolerance to SO_2.

et al., 1980). The preservation of the bronchomotor response to inhaled histamine despite tolerance to inhaled SO_2 in our subjects thus suggests that tolerance to SO_2 is not caused by direct inhibition of vagal efferent activity or of airway smooth muscle contraction.

Since tolerance to the bronchomotor effects of SO_2 is unlikely to be caused by inhibition of the efferent limb of the vagal reflex pathway, it is most likely caused by inhibition of the effects of inhaled SO_2 on airway afferent nerve fibers. This explanation is consistent with the observations that changes in the pattern of breathing ascribed to inhalation of SO_2 did not occur in men who were chronically exposed (Amdur *et al.*, 1953), and that cough and chest discomfort from inhalation of SO_2 tend to diminish after the first 5 min of exposure (Frank *et al.*, 1962) since breathing pattern, cough, and chest discomfort are all primarily mediated through airway afferent fibers.

Both histamine (Vidruk *et al.*, 1977) and SO_2 (Nadel *et al.*, 1965) can cause bronchoconstriction reflexly by increasing activity in airway afferent nerves. These two agents may, however, stimulate different populations of afferent fibers (Widdicombe, 1954). Since SO_2 is highly soluble in water, it is deposited primarily in the oropharynx and larynx (Frank *et al.*, 1969), and whatever gas reaches the tracheobronchial tree is likely to be deposited proximally. Histamine aerosol delivered under the conditions of our study would be expected to deposit more diffusely throughout the airways (Ryan *et al.*, 1981). It is likely, then, that SO_2 and histamine stimulate afferent fibers in different anatomic locations. The preservation of the bronchomotor response to inhaled histamine despite tolerance to the bronchomotor response to SO_2 could thus be explained if prior exposure to SO_2 selectively inhibits activity only in those afferent fibers stimulated by inhaled SO_2. These fibers may differ from the afferent fibers stimulated by inhaled histamine on the basis of fiber type and/or anatomic location.

The clinical significance of our observation that subjects with asthma can develop tolerance to the bronchomotor effects of SO_2 is uncertain. This observation does imply that within a single day repeated episodes of hyperpnea (as with exercise) with a constant concentration of SO_2 would afford some protection against the acute bronchomotor effects of SO_2. However, the severity of the bronchoconstriction in some subjects and its long duration (for greater than 45 min in the two subjects eliminated from this study) make the first episode of hyperpnea potentially hazardous. In addition, since tolerance in this study was short lived, it would not afford protection against effects of SO_2 on subsequent days. Finally, in real-life exposure conditions, SO_2 concentrations change abruptly, as from wind shifts near point sources or from opening a door to walk outside on a polluted day, so people performing exercise in polluted air are unlikely to be exposed repeatedly to the same concentration of SO_2.

ACKNOWLEDGMENTS

The authors wish to thank Patty Snell and Beth Cost for their assistance in preparing this manuscript. This study was supported in part by Program Project Grant HL-24136 from the U.S. Public Health Service and by the California Air Resources Board Contract A9-115-30. R. A. Bethel was supported in part by NIH Training Grant HL-07185.

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INHIBITION OF SULFUR DIOXIDE-INDUCED BRONCHOCONSTRICTION BY DISODIUM CROMOGLYCATE. D. Sheppard*, J.A. Nadel**, and H.A. Boushey, Cardiovascular Research Institute, University of California, San Francisco.

To determine whether disodium cromoglycate (cromolyn) inhibits the bronchoconstriction produced by inhalation of sulfur dioxide (SO_2) in people with asthma, we undertook a study of six asthmatic subjects. Each subject inhaled 40mg of cromolyn on one day and lactose placebo on another day 20 min. before inhaling SO_2 for 10 min. while exercising at a moderate rate (400 KPM/min) on a bicycle ergometer. SO_2 was delivered in humidified air at ambient temperature in concentrations of 0.5 ppm (3 subjects) or 1.0 ppm (3 subjects). Cromolyn and lactose treatments were given to each subject in a randomized sequence and in a double blind manner. On a third day each subject exercised at the same work rate breathing humidified ambient temperature air without SO_2. We measured specific airway resistance (SRaw) in a body plethysmograph every 30s for 10 min. before and after each of the 3 periods of exercise. After treatment with lactose, SO_2 inhalation significantly increased SRaw in all six subjects {from a baseline of 6.5 $\pm$ 0.9 to 19.0 $\pm$ 4.8 L x cmH_2O/L/s (Mean $\pm$ S.E.) after SO_2}. After treatment with cromolyn, SO_2 inhalation caused no increase in SRaw in 4 subjects and a small rise in 2 subjects. The mean increase in SRaw (from a baseline of 7.3 $\pm$ 0.9 to 10.0$\pm$ 1.5 L x cmH_2O/L/s after SO_2) was significantly smaller than after lactose treatment ($p<0.025$). Exercise alone had no effect on SRaw in any subject. Thus, cromolyn inhibits SO_2-induced bronchoconstriction in subjects with asthma. This finding suggests either that SO_2 induces bronchoconstriction by stimulating the release of mediators from mast cells or that cromolyn inhibits bronchoconstriction by a mechanism independent of its effect on mast cells.

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Inhibition of Sulfur Dioxide-Induced Bronchoconstriction by Disodium Cromoglycate in Asthmatic Subjects[1-3]

DEAN SHEPPARD, JAY A. NADEL, and HOMER A. BOUSHEY

SUMMARY To determine whether disodium cromoglycate (cromolyn) inhibits the bronchoconstriction produced by inhalation of sulfur dioxide (SO_2) in people with asthma, we undertook a study of 6 asthmatic subjects. Each subject inhaled 40 mg of cromolyn on one day and lactose placebo on another day 20 min before inhaling SO_2 for 10 min while exercising at a moderate rate (400 kpm/min) on a bicycle ergometer. Sulfur dioxide was delivered in humidified air at ambient temperature in concentrations of 0.5 ppm (3 subjects) or 1.0 ppm (3 subjects). Cromolyn and lactose treatments were given to each subject in a randomized sequence and in a double-blind manner. On a third day, each subject exercised at the same work rate breathing humidified air without SO_2 at ambient temperature. We measured specific airway resistance (SRaw) in a body plethysmograph every 30 s for 10 min before and after each of the 3 periods of exercise. After treatment with lactose, SO_2 inhalation significantly increased SRaw in all 6 subjects (from a baseline of 6.5 ± 0.9 to 19.0 ± 4.8 L × cm H_2O/L/s (mean ± SE) after SO_2). After treatment with cromolyn, SO_2 inhalation caused no increase in SRaw in 4 subjects and a small rise in 2 subjects. The mean increase in SRaw (from a baseline of 7.3 ± 0.9 to 10.0 ± 1.5 L × cm H_2O/L/s after SO_2) was significantly smaller than after lactose treatment ($p < 0.025$). Exercise alone had no effect on SRaw in any subject. Thus, cromolyn inhibits SO_2-induced bronchoconstriction in subjects with asthma. This finding suggests either that SO_2 induces bronchoconstriction by stimulating the release of mediators from mast cells or that cromolyn inhibits bronchoconstriction by a mechanism independent of its effect on mast cells.

AM REV RESPIR DIS 1981; 124:257-259

Introduction

Inhalation of sulfur dioxide (SO_2) causes significant bronchoconstriction in people with asthma (1). Sulfur dioxide-induced bronchoconstriction is mediated by parasympathetic pathways (1, 2), but the mechanism by which these pathways are activated is unknown. Some workers have suggested that SO_2 may initiate reflex bronchoconstriction indirectly by causing mast cells to degranulate and release chemical mediators (3, 4), which, in turn, might activate parasympathetic pathways. Because disodium cromoglycate (cromolyn) is known to inhibit the release of mediators from mast cells, we studied the effect of treatment with cromolyn on the bronchomotor response to SO_2 in subjects with asthma as a first step toward determining whether mast cell degranulation contributes to SO_2-induced bronchoconstriction.

Methods

The subjects were 6 nonsmoking volunteers, 5 men and 1 woman, who were informed of the risks of the experimental protocol and who signed consent forms approved by the Committee on Human Experimentation of the University of California. All 6 subjects had a history of recurrent episodes of wheezing, chest tightness, and reversible airway obstruction previously documented by a physician. Screening tests of pulmonary function—spirometry, single-breath carbon monoxide diffusing capacity, single-breath oxygen test of gas distribution, and maximal expiratory flow-volume curve—were normal in all subjects (for anthropometric data, see table 1). No subject required chronic bronchodilator therapy, and none had taken any medications within 48 h of any study.

All 6 subjects had marked bronchial hyperreactivity to inhaled histamine sulfate aerosol, as demonstrated by a doubling of specific airway resistance (SRaw) after inhaling 10 tidal breaths of a solution of 0.1% concentration or less delivered from a DeVilbiss No. 646 nebulizer with a dosemetering device. In 13 normal subjects in our laboratory, SRaw increased by 62 ± 24% (mean ± SD) after inhalation of 10 breaths of 16 times that concentration (1.6%) (5).

To assess the effect of cromolyn on SO_2-induced bronchoconstriction, we studied each subject on 2 separate days, 1 wk apart. On one day, the subject first inhaled 40 mg of cromolyn from a Spinhaler, and on the other day, the subject inhaled lactose placebo in an identical fashion. These studies were performed in a random sequence and were conducted double blind.

Twenty minutes after inhalation of cromolyn or placebo, the subject sat in a constant-volume body plethysmograph (6), and we measured airway resistance (Raw) and thoracic gas volume (Vtg) every 30 s for 10 min to obtain baseline values. We multiplied Raw by Vtg to obtain SRaw. The subject then inhaled 0.5 or 1.0 ppm of SO_2 for 10 min while exercising on a cycle ergometer at a work rate of 400 kpm/min.

The concentration of SO_2 each subject inhaled was selected to increase SRaw by more than 50% over baseline on the basis of that subject's response to previous exposures; 3 subjects inhaled 0.5 ppm of SO_2 and 3 inhaled 1.0 ppm of SO_2. During each exposure, we continuously recorded the temperature, dew point, and SO_2 concentration of the air delivered to the subject. We also measured expired tidal volume, minute ventilation, and respiratory rate, and averaged the values of each variable during the last 2 min of each exposure. After inhaling SO_2, the subject returned to the body plethysmograph, and we again measured Raw and Vtg every 30 s for 10 min. To determine whether any subject developed exercise-induced bronchoconstriction under the conditions of our study, we repeated the above protocol on a separate day with the subject breathing SO_2-free air.

During each exposure, the subject breathed from a glass mouthpiece. To achieve the desired concentration of SO_2, we mixed a known flow from a calibrated tank of SO_2 (500 ppm) with air delivered at 2.8 L/s from a compressed air source to a 3-L glass mixing chamber. Before entering the mixing

(Received in original form December 5, 1980 and in revised form May 11, 1981)

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[2] Supported in part by U.S. Public Health Service Program Project Grant No. HL-24136 and by California Air Resources Board Contract No. A9-115-30.

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TABLE 1

ANTHROPOMETRIC DATA ON ALL SUBJECTS

Subject No.	Sex	Age	Height (cm)	Weight (kg)	FEV_1 (L)	FVC (L)
1	M	24	166	65	4.0	5.4
2	M	22	176	76	3.6	5.0
3	M	23	162	57	3.6	4.2
4	M	30	186	90	4.4	6.1
5	M	27	183	67	4.3	5.2
6	F	27	165	57	2.8	3.6

chamber, the air was passed through a high-efficiency particulate adsorption (HEPA) filter and 2 vapor filters (Mine Safety Appliances No. 8185), then humidified by a bubble humidifier, and, finally, passed through a second HEPA filter (Mine Safety Appliances No. CU-86444) to remove any water particles added during humidification. All tubing in contact with the gas mixture was made of Teflon®. To document that temperature and relative humidity of the inspired air were relatively constant, we measured temperature and dew point continuously with a digital humidity analyzer equipped with a mirrored dew-point hygrometer and a platinum temperature probe (No. 911; E.G. and G., Waltham, MA) and calculated relative humidity from standard tables. We measured SO_2 concentrations continuously from a needle just proximal to the subject's mouthpiece with a pulsed fluorescent SO_2 analyzer (Model No. 43; Thermo-Electron Corp., Bohemia, N.Y.).

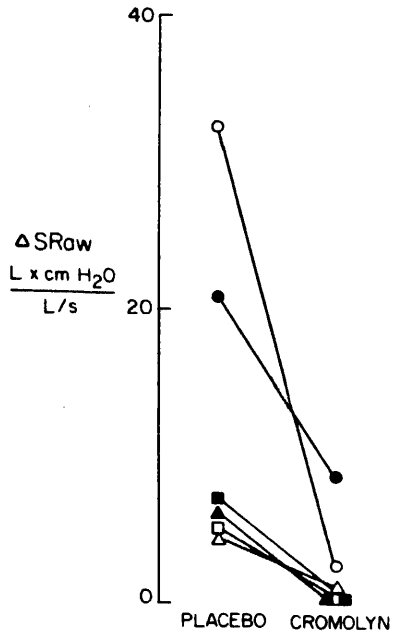

Fig. 1. Effect of cromolyn on the response to inhalation of SO_2 during exercise in 6 asthmatic subjects (□ = control specific airway resistance (SRaw) before exercise and/or SO_2; ▨ = SRaw after exercise alone; ■ = SRaw after exercise and SO_2). All data represent mean ± SD. Exercise alone (*left columns*) did not increase SRaw. Exercise and SO_2 after placebo (*middle columns*) increased SRaw significantly ($p < 0.01$). Exercise and SO_2 after cromolyn (*right columns*) had a significantly smaller effect on SRaw ($p < 0.025$).

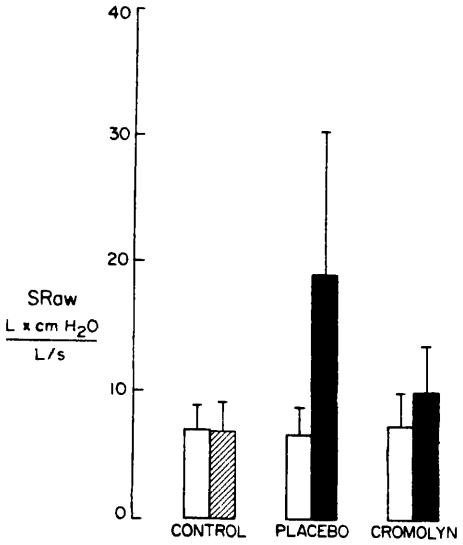

Fig. 2. The change in specific airway resistance (ΔSRaw) produced by inhalation of SO_2 after treatment with cromolyn and with placebo in 6 asthmatic subjects (○, ●, □, ■, △, ▲).

To check for conversion of SO_2 to sulfate in our system, we collected samples of particles on Teflon filters from approximately 6.0 m^3 of humidified air mixed with 1.0 ppm of SO_2. The samples were analyzed for sulfate by the Air Industrial Hygiene Lab micromethod (7), and no sulfate was detected, so there was less than 0.008% conversion of SO_2 to sulfate.

To obtain a record of respiratory rate and minute ventilation during exercise, we measured airflow with a pneumotachygraph (Fleisch No. 3) and a differential pressure transducer (Validyne No. DP-45), electrically subtracting the baseline flow of 2.8 L/s. We then amplified and electrically integrated the flow signal to obtain a volume signal, which we recorded on a rapid writing device (Model No. DR-12; Electronics for Medicine, Pleasantville, NY).

To analyze the effect of each intervention for statistical significance, we compared the 4 highest consecutive baseline values of SRaw to the 4 highest consecutive postintervention values using the *t* test for unpaired data. To analyze the effect of cromolyn on SO_2-induced bronchoconstriction for statistical significance, we compared the change in SRaw produced by SO_2 exposure after treatment with cromolyn with that after placebo using the *t* test for paired data, as well.

Results

Treatment with cromolyn significantly decreased SO_2-induced bronchoconstriction in our study group (figure 1). Furthermore, cromolyn decreased SO_2-induced bronchoconstriction in each individual subject, although the dose we studied did not completely block bronchoconstriction in the 2 subjects with the largest responses to SO_2 (figure 2). The exercise work rate used did not produce bronchoconstriction in any subject under the conditions of temperature and relative humidity we studied (figure 1).

The subjects' minute ventilation was similar during all experiments, as were the relative humidity and temperature of inspired gas (table 2).

Discussion

Sulfur dioxide has been clearly shown to produce bronchoconstriction through parasympathetic pathways (1, 2). The reflex nature of SO_2-induced bronchoconstriction was unequivocally demonstrated by studies in which introduction of SO_2 into the anatomically separated upper airways of cats produced constriction of the lower airways (2). Recently, we showed that SO_2-induced bronchoconstriction is greatly exaggerated in asthmatic subjects and that this exaggerated bronchoconstriction also involves parasympathetic pathways (1). Our results thus suggested that cromolyn can inhibit reflex-mediated bronchoconstriction.

Because the presumed mechanism by which cromolyn inhibits bronchoconstriction is by preventing degranulation of airway mast cells, our results supported the view that SO_2 activates parasympathetic pathways indirectly by causing mast cells to degranulate. Alternatively, cromolyn might interfere with parasympathetically mediated bronchoconstriction by some other mecha-

TABLE 2

EXPERIMENTAL CONDITIONS FOR STUDIES IN 6 ASTHMATIC SUBJECTS

	Without SO_2	SO_2 after Cromolyn	SO_2 after Placebo
Relative humidity of inspired gas, %	70.1 ± 3.3	70.4 ± 1.1	70.6 ± 0.8
Temperature of inspired gas, °C	22.1 ± 3.3	21.8 ± 1.0	22.3 ± 0.7
Minute ventilation, L/min	36.9 ± 7.5	37.2 ± 7.1	38.2 ± 5.2
Respiratory rate, breaths/min	25.6 ± 4.5	24.8 ± 7.3	25.9 ± 5.2

nism, independent of its effects on mast cells. This view is supported by evidence that, in dogs, cromolyn inhibits the bronchoconstriction caused by histamine but not the bronchoconstriction caused by electrical stimulation of the vagus nerves, suggesting that the drug may interfere with the afferent limb of the vagal reflex arc (8).

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LACK OF DOSE DEPENDENCY FOR IPRATROPIUM BROMIDE'S INHIBITORY EFFECT ON SULFUR DIOXIDE-INDUCED BRONCHOSPASM IN ASTHMATIC SUBJECTS. E. Tam, D. Sheppard, J. Epstein, R. Bethel, and H. Boushey, Cardiovascular Research Institute, University of California, San Francisco, CA

To determine if antimuscarinic agents inhibit sulfur dioxide-induced bronchoconstriction in a dose dependent fashion, we studied the effects of different doses of ipratropium bromide in six subjects with mild asthma who develop bronchoconstriction with isocapnic hyperpnea of sulfur dioxide. Each subject inhaled placebo, or 20, 50 or 100 µg of ipratropium bromide delivered in randomized double-blind fashion on 4 separate days. We measured specific airway resistance (SRaw) before and 30 min after inhalation of the blinded drug. Each subject then breathed 1.7 ppm sulfur dioxide at increasing levels of minute ventilation, for 3 min at each level under isocapnic conditions. Sulfur dioxide was delivered in air at room temperature, 80% relative humidity. We measured SRaw 2 min after each level of ventilation. All doses of ipratropium bromide caused a similar fall in baseline SRaw and a slight rightward shift in the dose-response curve to sulfur dioxide. Analysis of the dose-response curves did not reveal dose-dependent inhibition. Furthermore, pretreatment with 200 µg of inhaled ipratropium bromide or with a combination of 1 mg intravenous atropine sulfate and 200 µg of ipratropium bromide did not further inhibit sulfur dioxide-induced bronchoconstriction. The lack of dose dependency for ipratropium bromide's inhibitory effect on the bronchospasm caused by isocapnic hyperpnea with sulfur dioxide in asthmatic subjects suggests that mechanisms other than parasympathetically mediated reflexes must play an important part in the response.
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EFFECTS OF SULFUR DIOXIDE ON VENTILATION IN CONSCIOUS DOGS. H.L. Hahn, K. Sasaki, and J.A. Nadel. Cardiovascular Research Institute, UCSF, San Francisco, CA 94143

We investigated the effects of sulfur dioxide (SO_2) on ventilation in 2 dogs walking on a treadmill (1.4 mph). We applied 25-300 ppm SO_2 for 4 min through a tracheostomy tube while continuously recording ventilatory variables breath by breath. Responses were dose dependent and showed a typical time course with coughing at 0.5 min and peak effects at 2 and 5 min. With 200 ppm, there were significant decreases in: time of inspiration, Ti (1.16 ± 0.07, 0.78 ± 0.09, 0.56 ± 0.06 s, control, 1st and 2nd peak, mean ± SE, n = 10); time of expiration, Te (1.61 ± 0.07, 0.95 ± 0.20, 0.48 ± 0.09), total time of breath, Tt (Ti + Te), tidal volume, V_T (447 ± 17, 303 ± 31, 261 ± 34 ml), and significant increases in: V_T/Ti (0.40 ± 0.02, 0.45 ± 0.04, 0.54 ± 0.02), Ti/Tt (0.42 ± 0.01, 0.48 ± 0.02, 0.56 ± 0.02) and ventilation (10.1 ± 0.7, 13.1 ± 1.9, 18.9 ± 2.0 L/min). The acceleration of breathing at each peak culminated in further brief coughing. Cooling both cervical vagi to +1°C prevented all of these responses which were unaffected by the inhalation of terbutaline (0.2 mg/ml, 10 min). In one experiment in each dog, we introduced a Foley catheter (with its tip cut off above the balloon) through the tracheostomy into the upper trachea. After intubation of the lower trachea, we applied SO_2 alternately to the upper and lower airways. A stream of 4 L/min SO_2 (25 ppm) delivered to the upper airways produced effects similar to 12-14 L/min SO_2 (300 ppm) inhaled into the lower airways. At 2 min, Ti decreased from 1.36 ± 0.16 to 0.90 ± 0.18 s (300 ppm: 1.16 ± 0.36 to 0.70 ± 0.18), Te from 1.81 ± 0.31 to 0.70 ± 0.08 s (1.84 ± 0.66 to 0.72 ± 0.18) and V_T from 536 ± 18 to 389 ± 80 ml (453 ± 120 to 351 ± 21). Coughing was more prominent with upper than with lower airway application (41 ± 1 vs 34 ± 8 coughs/4 min), and it persisted long after the exposure. We conclude that SO_2 delivered to the lungs causes coughing and rapid shallow breathing through vagal afferent pathways, that the reaction is independent of bronchoconstriction and that SO_2 applied to the upper airways produces similar responses at much lower concentrations, suggesting that reflex effects of low concentrations of SO_2 inhaled through the mouth are more likely to be mediated through receptors in the upper than the lower airways.

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Am. Rev. Respir. Dis. 125:320, 1982