A Comparison of Changes in Pulmonary Flow Resistance in Healthy Volunteers Acutely Exposed to SO₂ by Mouth and by Nose*

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On separate occasions, healthy male volunteers were exposed either by nose or by mouth to one of two concentrations of sulphur dioxide, 15 and 28 p.p.m. Exposure to SO₂ lasted 10 minutes. Pulmonary flow resistance (Rl) was measured by the oesophageal catheter method, and the lung volume was measured by a modification of the gas-compression method; when SO₂ was administered by nose, nasal flow resistance (Rn) was measured by means of a catheter placed in the posterior pharynx. The increase in Rl was greater when SO₂ was administered by mouth than when it was administered by nose. Similarly, irritative symptoms of the posterior pharynx and chest were more common during exposure by mouth. These findings suggest that the mouth is less effective than the nose as an absorptive surface for SO₂.

In the experimental animals, the mechanical response of the lungs to sulphur dioxide (SO₂) is influenced by the level at which the gas is introduced into the airways. In guinea-pigs (Amdur, 1959) and in dogs (Frank and Speizer, to be published), the increase in pulmonary flow resistance is greater when SO₂ is given by tracheal cannula than when it is given through the intact upper airways. Similarly, greater mechanical changes are evoked by administering SO₂ to the lungs through a tracheal cannula than by limiting exposure only to an isolated segment of the upper trachea (Balchum, Dybicki, and Meneely, 1960a; Frank and Speizer, to be published). Whether breathing the gas by nose or by mouth might also impose differences in response, particularly in human subjects, has not previously been determined. Our purpose was to provide this information and to record the changes in nasal flow resistance (Rn) as well as the changes in pulmonary flow resistance (Rl) when the subjects were breathing SO₂ by nose.

Differences in response, in terms of the changes in Rl, might be expected if the nose and mouth were unequal in their capacity to absorb SO₂ or if either pathway contained (more) receptor tissue capable of initiating reflex changes in bronchomotor tone. Although no attempt was made to measure the up-

take of SO₂ in these experiments, it was thought that a rough estimate of the relative absorptive efficiencies of the mouth and nose could be made by comparing the frequency of throat and chest symptoms occurring in the two circumstances.

Method

Eight healthy male volunteers were studied. The subject sat in a volume-displacement body plethysmograph† during all the exposures by mouth and in half the exposures by nose; in the remainder, the subject sat outside the plethysmograph, the latter serving both as the source of gas and as the volume recorder (Mead, 1960).

Tidal volume was measured with a seven-litre Krogh spirometer mounted on the plethysmograph (Mead, 1960). Flow rate was obtained by electrical differentiation of the volume signal. Oesophageal pressure was used as an index of pleural pressure and was measured with a polyethylene catheter (PE 200) placed in the lower third of the oesophagus (Mead and Whittenberger, 1953). The catheter was passed through the nose for the oral exposures and through the mouth for the nasal exposures. The lower end of the catheter was covered with a thin-walled latex balloon 12 cm. in length, having a maximal circumference of 3.5 cm.; the balloon contained 1 ml. of air. Pharyngeal pressure was measured with an identical catheter covered at the end by a balloon 2.5 cm. long. The two catheters were tied together so that when the oesophageal catheter was in place the pharyngeal catheter lay against the posterior pharyngeal wall at the level of the tonsillar fauces. The distance between the tip of the pharyngeal balloon and the lips was usually 11 to 12 cm. The volume of air in the

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pharyngeal balloon, once in place, was determined as follows. The subject was asked to collapse the balloon by briefly raising the pressure in the oropharynx. The balloon was then reinflated in increments of 0.1 ml. With each increment, the subject paused for several seconds at the end of normal expiration while pressure in the catheter was recorded. Generally, the range of volume over which catheter-pressure remained atmospheric during this pause was 0.3 to 0.6 ml. Thereafter, for all measurements, the volume of the balloon was kept constant within this range.

The subject, when breathing by the nose, wore a close-fitting oronasal hard plastic mask having two ports, one for the air supply and the other for the passage of the pressure-recording catheters. A side tap was used to measure pressure inside the mask. The mask had an inflatable rubber cuff and rested against the bridge of the nose, the cheeks, and the chin. Care was taken to avoid contact between the mask and the alae nasi. The changes in pressure between the inside of the mask and the posterior pharynx (transnasal pressure) and between the posterior pharynx and the oesophagus (transpulmonary pressure minus mouth pressure) were measured simultaneously with differential transducers. A detailed account of the technique for measuring R_n has already been published (Speizer and Frank, 1964). All measurements were recorded on a direct-writing polygraph. Flow rate and nasal pressure drop were photographed from an X-Y oscilloscope. Each of the values for R_n shown in 'Results' represents a mean of inspiratory and expiratory flow resistance, based on five consecutive breaths, and was calculated at a flow of 0.5 l./sec. The values for R_I are means of inspiratory and expiratory flow resistance (isovolumes) in the mid-tidal range of breathing, based on 10 breaths (Frank, Amdur, Worcester, and Whittenberger, 1962).

The functional residual capacity (F.R.C.) was measured with a modification of the technique of DuBois, Botelho, Bedell, Marshall, and Comroe (1956). The F.R.C. was determined routinely in the subjects breathing by mouth. In the six subjects exposed to about 28 p.p.m. of SO_2 by nose, who were seated inside the plethysmograph with their heads emerging above the apparatus, an attempt was made to measure the F.R.C. in the following way. The subject was instructed to occlude the nasal passage by lifting the soft palate, to keep the glottis open, and to make inspiratory and expiratory efforts against the occluded airway. Airway pressure was recorded with the pharyngeal catheter; the ratio of the change in enclosed gas volume to the change in airway pressure was used to solve the F.R.C. End-expiratory pressure was recorded during spontaneous breathing; changes in this pressure were used as indices of changes in lung volume when the F.R.C. could not be obtained.

The experimental procedure was to collect two to three sets of control measurements, start the SO_2 , and repeat the measurements after one to two, five, and 10 minutes of uninterrupted exposure, then to discontinue the SO_2 and again repeat the measurements after five, 10, and 15 minutes of breathing room air (designated Recovery). At least one month elapsed before the

subject was re-exposed to the gas. The sequence of exposures (nose and mouth) was random. The SO_2 concentrations were prepared by metering 1% SO_2 and filtered room air into a mixing chamber about 3 cu. feet in volume. The gas was transferred from the chamber to the subject through large-bore Tygon tubing. The concentration of SO_2 was measured several times in each experiment by the electroconductivity method of Thomas and Abersold (1929).

Results

Groups of six individuals were exposed by mouth, and on separate occasions by nose, to two average levels of SO_2 , 15 and 28 p.p.m. There was a total of 24 experiments.

Changes in R_I R_I increased significantly in nine out of 12 experiments when SO_2 was administered by mouth; often these changes were not sustained throughout the exposure (Table I). The magnitude of the change in R_I was on the average greater at 28 p.p.m. than at 15 p.p.m. of SO_2 .

During exposure to the same two levels of SO_2 by nose, R_I increased significantly in only three out of 12 experiments and decreased in one experiment (F.E.S. 15 p.p.m.; $P < 0.05$). A comparison of the average changes in R_I in the two circumstances is made in Figure 1.

In the period following administration of SO_2 by mouth, R_I remained significantly raised in five of the 12 experiments, four of which followed exposure to 28 p.p.m. of gas. Following administration of the gas by nose, R_I was often higher during the recovery period than it had been during exposure: in three experiments, R_I rose significantly for the first time during recovery (J.R.S. and J.M.E., 15 p.p.m.; J.R.S., 28 p.p.m.); in two others, the rise in R_I was greater during recovery than it had been during exposure (N.R.F., 15 p.p.m.; H.M.E., 28 p.p.m.).

Lung Volume Approximately half the subjects breathing SO_2 by mouth had no measurable change in F.R.C.; the remainder showed increases ranging between 0.3 and 0.7 litres. The F.R.C. could be measured in only four of the six subjects who were exposed to 28 p.p.m. of SO_2 by nose and showed no consistent change in these subjects. The transpulmonary pressure (oesophagus-to-mouth) at end-expiration (which might be expected to increase if the lung volume increased) did not change consistently in any of the subjects exposed to the gas by nose.

Changes in R_n (Table II) The pressure-flow relations for the nose were curvilinear; they showed no systematic differences between inspiration and

TABLE I

COMPARISON OF CHANGES IN PULMONARY FLOW RESISTANCE (cm. H₂O/l./sec.) DURING AND AFTER EXPOSURE TO SO₂ BY MOUTH AND BY NOSE

Subject	SO ₂ Conc. (p.p.m.)	Mouth-breathing							SO ₂ Conc. (p.p.m.)	Nose-breathing						
		Control	Exposure (min.)			Recovery (min.)				Control	Exposure (min.)			Recovery (min.)		
			2	5	10	5	10	15			2	5	10	5	10	15
N.R.F.	13	1.88	—	1.52	1.75	1.99	2.02	1.86	14	1.34	1.79	2.13†	2.14†	2.21†	2.50†	2.28†
J.M.T.	16	1.59	—	2.43*	2.71†	1.92	1.55	1.83	16	1.99	2.32	1.58	1.99	1.92	2.22	2.33
F.E.S.	15	2.13	—	2.24	2.30	2.25	2.82†	3.47‡	15	2.64	2.25	2.39	1.54*	1.97	1.64	1.41*
H.M.E.	17	1.66	—	1.91*	1.92*	1.67	1.87	1.90	16	1.17	1.16	1.37	1.35	1.26	1.62*	1.24
J.L.W.	14	1.32	—	2.23†	1.48	1.47	1.36	1.47	14	1.36	1.13	1.60	1.23	1.08	1.03	0.89
J.R.S.	14	2.36	—	2.96*	2.36	2.33	2.41	2.35	16	2.71	—	2.91	3.11	2.90	3.19	3.86†
Mean	15	1.82	—	2.22	2.09	1.94	2.00	2.15	15	1.87	1.73	1.99	1.89	1.89	2.03	1.98
% change from control			—	+22	+15	+7	+10	+18			-7	+6	+1	+1	+9	+6
E.P.R.	30	1.18	1.84†	1.29	1.44	1.28	1.11	1.44	29	1.24	1.65	1.82	1.85	1.41	1.46	1.26
J.M.T.	28	1.56	1.50	1.46	1.95	1.42	1.46	1.31	28	2.20	2.25	2.02	1.82	2.42	1.92	1.62
H.M.E.	26	1.12	1.69†	1.48†	1.55	1.48†	1.05	1.50†	31	1.01	1.16	1.18*	1.14	0.98	1.17*	1.35*
J.R.S.	27	1.87	2.42†	2.32†	3.09†	1.93	2.33†	1.82	27	2.05	2.04	2.58	2.49	2.70†	2.93‡	3.04‡
M.M.O.	27	1.60	2.30†	2.59†	3.72†	2.40†	1.90*	1.74	29	1.62	1.89	1.71	1.24	2.00	1.36	1.75
N.R.F.	27	1.52	2.11*	2.20†	2.59†	2.31‡	1.91*	1.71	30	1.27	1.23	1.54*	1.39	1.37	1.39	1.10*
Mean	27	1.47	1.98	1.89	2.39	1.80	1.63	1.59	29	1.56	1.70	1.81	1.66	1.81	1.70	1.69
% change from control			+35	+29	+63	+22	+11	+8			+9	+16	+6	+16	+9	+8

Change from control is significant at * = P < 0.05; † = P < 0.01; ‡ = P < 0.001.

TABLE II

CHANGES IN NASAL FLOW RESISTANCE (cm. H₂O/l./sec.) DURING AND AFTER EXPOSURE TO SO₂ BY NOSE

Subject	SO ₂ Conc. (p.p.m.)	Exposure (min.)				Recovery (min.)		
		Control	2	5	10	5	10	15
N.R.F.	14	1.74	2.62‡	1.88	2.60‡	2.06*	1.82	2.04*
J.M.T.	16	2.14	2.74	2.57†	2.29	1.83	1.79	1.74*
F.E.S.	15	2.07	1.94	1.98	2.28*	3.07‡	2.66†	2.06
H.M.E.	16	2.28	2.26	2.27	2.41	2.27	2.26	2.32
J.L.W.	14	0.95	0.89	1.09*	1.10*	1.00	1.04	0.99
J.R.S.	16	2.11	—	2.70‡	2.74‡	2.17	2.96‡	2.86‡
Mean	15	1.88	2.00	2.08	2.24	2.07	2.09	2.00
% change from control		—	+6	+11	+19	+10	+11	+6
E.P.R.	29	1.78	1.80	1.67†	1.71*	1.79	1.90‡	1.72*
J.M.T.	28	3.38	2.49†	2.55‡	3.99†	3.36	2.39‡	2.38‡
H.M.E.	31	1.86	2.30†	1.93	1.84	2.37†	2.28†	1.90
J.R.S.	27	4.87	7.33‡	5.54	4.91	4.59	4.82	4.08
M.M.O.	29	5.76	5.06	4.56*	4.22†	4.09†	4.41*	4.37*
N.R.F.	30	3.60	4.05†	4.73‡	4.82‡	4.50†	4.49†	4.66‡
Mean	29	3.54	3.84	3.50	3.58	3.45	3.05	3.18
% change from control		—	+8	-1	+1	-3	-14	-10

Change from control is significant at * = P < 0.05; † = P < 0.01; ‡ = P < 0.001.

expiration (Lilly, 1950; Ferris, Mead, and Opie, 1964; Speizer and Frank, 1964). Because of this curvilinearity, all values of R_n were taken at a flow rate of 0.5 l./sec. The response of R_n to exposure to SO₂ was variable: in eight of the 12 experiments R_n increased at some point during exposure; in three experiments there was a decrease in R_n, and in one subject (J.M.T.) it fell and then rose in the same exposure. The subjects experienced no diffi-

culty in breathing by nose in the instances when R_n increased.

Symptoms When exposed by mouth, most of the subjects coughed several times during the first few minutes and had slight burning sensations of the throat and substernal area for at least five minutes. When exposed by nose, there was little coughing and no chest symptoms; some subjects

FIG. 1. The average changes in RI are shown for the periods during and after exposure to SO_2 , by mouth and by nose. The responses to 15 and 28 p.p.m. of SO_2 (see Table I) have been combined.

did experience irritation of the posterior pharynx which lasted a few minutes.

Discussion

The administration of SO_2 by mouth to healthy subjects caused a greater rise in RI and more frequent coughing and discomfort of the posterior pharyngeal and substernal areas than when it was administered by nose. These findings suggest that the mouth may be less effective than the nose in removing SO_2 from the inspired air. Direct measurements in human subjects have shown that the uptake of SO_2 by the nasopharynx is virtually complete (Frank, 1964); there are no analogous data for the mouth. Dalhamn and Strandberg (1961) found in rabbits that the nasopharynx removed slightly more SO_2 than did the oropharynx but that the absorptive rates of both pathways generally exceeded 90% of the inspired concentration (100 to 300 p.p.m. of SO_2 for 30 minutes).

To the extent that these changes in RI can be

ascribed to excitation of subepithelial receptors in the larynx, trachea, and bronchi (Widdicombe, 1963), it appears that quite low levels of SO_2 —perhaps even traces of the gas—provide an adequate stimulus. It follows that any circumstance that might favour penetration of the gas, even slightly, as for example the high flow rates associated with exercise, might also lead to an additional increase in RI. There is also the possibility that the reflex changes in bronchomotor tone caused by SO_2 , and ultimately mediated by the vagal nerves (Nadel, Salem, Tamplin, and Tokiwa, 1965), may act in part through other receptors. One possible site for these receptors is the nose. A nasobronchial reflex (resulting in increased bronchomotor tone) has been described in response to irritant stimuli (Ellis, 1938; Rall, Gilbert, and Trump, 1945); more recently, Nadel and Widdicombe (1962) were unable to elicit this reflex in cats with either mechanical or chemical stimuli. Our observation that SO_2 could affect the nose sufficiently to increase Rn while causing little or no change in RI may be taken as evidence that the nasobronchial reflex is not readily evoked in healthy subjects. Another mode of response is suggested by the finding that some of the SO_2 that is absorbed by the nasopharynx and that enters the blood is then excreted as a gas into the lungs (Frank, Yoder, Yokoyama, and Speizer, 1964). A way is thereby provided for the smaller airways to be exposed 'from below'. Whether this type of exposure is responsible for changes in bronchomotor tone is not known.

Two other results deserve mention. One is that the combined increase in Rn and RI during exposure to SO_2 by nose did in some subjects exceed the increase in RI that accompanied exposure by mouth. Secondly, the average changes in RI associated with exposure by mouth were smaller than those reported by this laboratory in a previous study (Frank *et al.* 1962); the techniques and some of the subjects were identical in both studies, and the reason for this difference in response is not apparent.

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