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Mechanical consequences of airway smooth muscle relaxation

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BOUHUYS, AREND, AND KAREL P. VAN DE WOESTIJNE. *Mechanical consequences of airway smooth muscle relaxation.* J. Appl. Physiol. 30(5): 670–676. 1971.—We measured lung volumes, airway conductance (Gaw), maximum expiratory flow-volume (MEFV) curves, isovolume pressure-flow (IVPF) curves, and static lung recoil curves in healthy volunteers before and after inhalation of a bronchodilator drug. On the average, Gaw at 50% VC increased 34.7%, Gaw/TGV ratio increased 33.9% , maximum expiratory flow at 50% VC 9.0%, and $FEV_{1.0}$ 3.6%. TLC, VC, peak expiratory flow, and static lung recoil pressure did not change significantly. In a few subjects, maximum flows on IVPF curves decreased slightly after bronchodilation. These results fit the hypothesis that bronchodilation renders large airways more compressible in man in vivo. This limits flow increase during forced expiration and may even result in decreased flows. The increased Gaw during panting reflects increased airway caliber which results from relaxation of tone when transmural stresses are low. Our results suggest that normal airway smooth muscle tone in man may help large airways to withstand dynamic compression during forced expirations.

bronchodilation; airway conductance; maximum expiratory flow-volume curves; isovolume pressure-flow curves; static lung recoil pressure; airway compressibility

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THE PHYSIOLOGICAL FUNCTION of airway smooth muscle is unknown. Widdicombe and Nadel (20) have suggested that its tone helps to adjust dead space and airway resistance to optimal values at which the mechanical work of breathing is minimal. In small airways, muscle tone may help to keep unequal gas distribution at a minimum (6). In large airways, muscle tone increases airway wall rigidity (13, 14). This may reduce airway collapse during forced expirations. This paper reports indirect evidence that such a mechanism may indeed operate in man.

METHODS AND SUBJECTS

Methods. Total lung capacity (TLC) was obtained from measurements of thoracic gas volume (TGV) in the body plethysmograph, followed by a maximal inspiration. The average of three to five technically satisfactory readings was taken as the result. Airway conductance (Gaw) was measured during panting at different lung volume levels. Each Gaw measurement was preceded and followed by a maximal inspiration to TLC; the lung volume level during panting was measured relative to TLC. Maximum expiratory flow-volume (MEFV) curves were recorded on a storage oscilloscope, with lung volume changes (from the body plethysmograph) on the abscissa and expiratory flow rate (from a Fleisch flowmeter at the mouth) on the ordinate. The plethysmographic procedures for TLC, Gaw, and MEFV curves have been described in detail elsewhere (2, 7). After the plethysmographic measurements, the forced expiratory volume ($FEV_{1.0}$) and, in most subjects, the vital capacity (VC) were measured with a direct-reading spirometer as in previous studies (7). In other subjects, VC was obtained from the plethysmographic volume traces. The complete set of measurements was repeated, in the same sequence, after bronchodilation.

Isovolume pressure-flow (IVPF) curves were obtained, before and after bronchodilation, in a separate session. The methods have been described elsewhere in detail (18). Briefly, lung volume changes (from the body plethysmograph), esophageal pressure, and airflow rate at the mouth were recorded on magnetic tape, during maximal expirations at widely different rates of flow, each starting at TLC. During these expirations, the subject monitored his flow rates by watching a flow-volume display on a storage oscilloscope screen; he was requested to fill the surface area of the expiratory flow-volume loop. This ensured that the full range of expiratory flow rates was included in the measurements.

The IVPF data were played back on a direct-writing recorder, using time expansion for adequate description of events at high flow rates. From these recordings, isovolume pressure-flow points were plotted at different lung volume levels. The slopes of the ascending portion of the IVPF curves were obtained from lines of visual best fit, drawn by an independent observer who was not aware of the purpose of the study. This observer was asked to draw a tangent to each IVPF curve at flow zero. This initial slope of the IVPF curve represents airway conductance at low rates of flow.

To study maximum flow rates on the IVPF curves, we also played the taped data back as flow-volume curves on an *XY* recorder, using time expansion. Three flow-volume loops from forced expirations were used for each subject; these always included the curve with the highest peak flow rate. Nineteen to thirty-eight values of flow and corresponding lung volume were measured on each of the curves, between 40 and 70% of total lung capacity (TLC). We checked that each of these points were within the range of flow values on plateaus of the corresponding IVPF curves.

A polynomial regression, $\dot{V} = aV + bV^2 + cV^3 + dV^4 + e$ (where $\dot{V}$ = flow, V = volume, and *a*, *b*, *c*, *d*, and *e* are regression coefficients), was fitted on the flow-volume data for each subject. The effect of the bronchodilator drug was determined by analysis of covariance.

The IVPF data included slow expirations, which were used to plot static lung recoil curves. For these, the subjects were requested to breathe out as slowly as possible, starting at TLC, and maintaining flow rate constant by visual monitoring on the oscilloscope screen. In most instances, flows were less than 0.5 liter/sec; in none did flow exceed 1 liter/sec at large volumes or 0.7 liter/sec at low volumes.

Bronchodilation. After completion of the control measurements, the subject inhaled an aerosol of isoproterenol and phenylephrine from a commercially available pocket nebulizer (Medihaler-Duo). All inhalations were made during a deep inspiration, followed by a few seconds breath holding; inhalations where aerosol escaped around the subject's mouth were not counted. Four to eight doses were inhaled, over a 30-min period; the postdilator measurements began 20 min after the first dose. None of the subjects experienced any side effects other than slight palpitations.

Subjects. Twenty-two subjects (21 male, 1 female; ages 9–42 yr) took part in the study; IVPF data were obtained in seventeen of these. All were healthy; none had a history of significant respiratory disease, except *subject 10*, who had bronchial asthma previously but was symptom-free for several years prior to study. Data from two additional subjects were excluded because we were unable to obtain consistent airway conductance values in them. Only five subjects (adults) were regular smokers. VC and $FEV_{1.0}$ were larger than 80% of the predicted values in all subjects; TLC was also close to predicted values or somewhat larger (Table 1). Presumably, therefore, all subjects had normal control ventilatory lung function. The control data for airway conductance and for maximum expiratory flow rate at 50% of VC are similar to the results of Zapletal et al. (22). In the 9- to 16-year-old subjects, Gaw at 50% VC averaged 0.094 TLC/sec per cm H_2O; this was 0.115 TLC/sec per cm H_2O in the 20- to 42-year-old men. Maximum flow rate ($\dot{V}_{max}$) at 50% was 0.852 TLC/sec for the 9- to 16-year-old group, and 0.675 TLC/sec in the 20- to 42-year olds.

RESULTS

Airway conductance and MEFV curves. Representative examples of Gaw-TGV graphs and MEFV curves before and after bronchodilation are shown in Fig. 1. After the bronchodilator inhalations airway conductance increases markedly, while flow rates on the MEFV curve either do not change (*subj 8*) or increase minimally (*subj 5*).

Several points on the Gaw-TGV graph were obtained during each observation period. To avoid alinear portions of the Gaw-TGV graph, we used only points between 20 and 80% of the control VC, and we drew a line of visual best fit through these. Gaw at 50% VC was read from this line; we also calculated the average Gaw/TGV ratio. From the MEFV curves, we read three points: peak expiratory flow rate (PEFR), and maximum expiratory flow at 50% ($\dot{V}_{max(50)}$) and at 20% ($\dot{V}_{max(20)}$) of VC. We used the highest values from the two or three curves obtained on each occasion. PEFR did not increase significantly after dilator, and $\dot{V}_{max(20)}$ showed increases similar to those of $\dot{V}_{max(50)}$ (Table 2). We therefore limit this part of the discussion to flow rates measured at 50% VC.

TABLE 1. *Age, height, and control pulmonary function*

Subj	Age, yr	Ht, cm	Smoking History*	TLC†		VC†		$FEV_{1.0}$†		Gaw at 50% VC		$\dot{V}_{max}$ at 50% VC	
				liters	%	liters	%	liters	%	liters/sec per cm H_2O	TLC/sec per cm H_2O	liters/sec	TLC/sec
1	9	139	0	2.82	96	2.13	93	1.96	98	0.304	0.108	3.4	1.206
2	11	144	0	3.16	98	2.64	104	2.12	96	0.228	0.072	2.6	0.823
3	10	142	0	3.57	116	3.02	124	2.53	119	0.348	0.097	3.3	0.924
4	15	159	0	4.26	98	3.48	102	2.88	98	0.430	0.101	3.2	0.751
5(♀)	13	173	0	4.28	88	3.80	102	—	—	0.350	0.082	4.3	1.005
6	15	163	0	4.46	94	3.58	97	3.18	101	0.460	0.103	4.1	0.919
7	15	167	0	5.55	108	4.14	104	3.38	99	0.495	0.089	4.3	0.775
8	21	170	0	6.04	102	4.42	91	4.05	99	0.810	0.134	4.8	0.803
9	16	178	0	6.10	94	5.40	110	3.88	93	0.509	0.083	3.0	0.492
10	42	179	CP	6.98	105	4.37	90	3.44	89	1.200	0.172	2.5	0.358
11	24	184	0	7.01	100	5.26	95	4.00	88	1.180	0.168	6.8	0.970
12	22	180	0	7.03	104	5.82	109	3.62	81	0.580	0.083	2.6	0.370
13	20	178	0	7.19	109	5.65	107	5.12	115	0.610	0.085	8.9	1.238
14	34	170	0	7.38	124	5.33	117	4.33	115	0.915	0.124	3.8	0.515
15	22	180	0	7.57	112	6.20	116	4.94	111	0.840	0.111	6.8	0.898
16	22	193	15	7.62	98	6.36	106	5.34	108	1.260	0.165	8.2	1.076
17	16	181	0	8.03	117	6.40	124	5.26	119	0.870	0.108	6.2	0.772
18	27	185	0	8.55	120	5.69	104	3.88	86	0.920	0.108	4.4	0.515
19	22	191	10	9.18	121	5.98	101	4.74	98	0.825	0.090	3.6	0.392
20	22	190	CP	9.26	123	6.90	118	5.68	118	0.885	0.096	6.0	0.648
21	38	191	0	9.88	130	6.49	117	5.23	119	0.725	0.073	3.0	0.304
22	23	184	3	10.55	150	7.45	135	6.16	134	0.960	0.091	7.3	0.692

* 0 = nonsmoker; CP = cigar or pipe smoker. For cigarette smokers, no. of cigarettes/day given. † % = percent of predicted value according to Zapletal et al. (22) for subjects, 9–16 yr, and according to Boren et al. (1) for 20- to 42-yr-old subjects.

After bronchodilator, Gaw increased much more than $\dot{V}_{max}$ (both at 50% VC) in most experiments (Fig. 2). In several subjects, Gaw increased 30–60%, while $\dot{V}_{max(50)}$ increased less than 10% or not at all. The percentage change of Gaw at 50% VC was usually similar to the change of the Gaw/TGV ratio, and the average changes of these two were also similar (Table 2). Although the increases of $\dot{V}_{max(50)}$ were small, they occurred systematically and were therefore statistically significant. $FEV_{1.0}$, which is an integral of flow during the first second of maximal expiration, increased slightly but significantly. Lung volume (TLC and VC, and hence residual volume) did not change (Table 2).

IVPF curves. Average data obtained from the IVPF curves are shown in Fig. 3, and individual examples are in Figs. 4–7.

The initial slope of an IVPF curve represents a conductance at low flow rates. This conductance increased after bronchodilation, and analysis of variance showed that this increase was significant at the 1% level (Fig. 3*A*). The average maximum expiratory flow rates from the IVPF data also increased significantly after bronchodilation (Fig. 3*B*). The data of Fig. 3, *A* and *B*, confirm the conclusions drawn from the measurements of airway conductance during panting and from the directly recorded MEFV curves: airway conductance is increased more by bronchodilation than maximum expiratory flow rates. Maximum flow rates at 50% VC increased, on the average, 11.8% when measured from IVPF curves and 6.9% when measured from MEFV curves in the same 17 subjects.

The IVPF data of Fig. 4 are representative for the majority of our subjects. Conductance increases, while maximum flow changes little, after bronchodilation. In a few

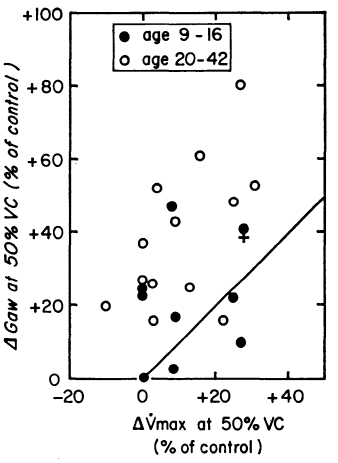

FIG. 2. Change of Gaw (*ordinate*) vs. change of $\dot{V}_{max(50)}$ (*abscissa*) after dilator drug. Line of equal change drawn at 45° from zero point. ♀ = female *subject 5*.

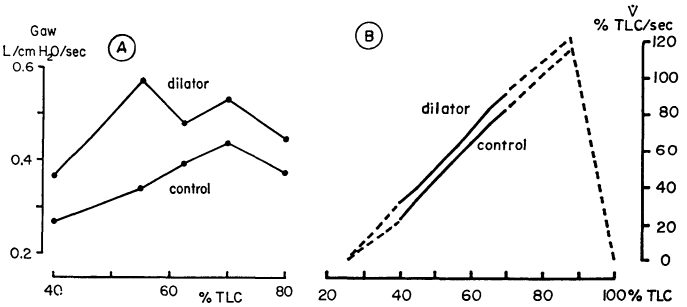

FIG. 3. *A:* conductance measured from initial slope of IVPF curves. Increase of conductance after dilator significant at 1% level. *B:* average maximum flow rates from IVPF data, analyzed between 40 and 70% of TLC. Dashed lines join data on which a regression was fitted (the drawn lines) with points representing TLC, PEFR, and RV. Increase of flow rates after dilator significant at 0.1% level.

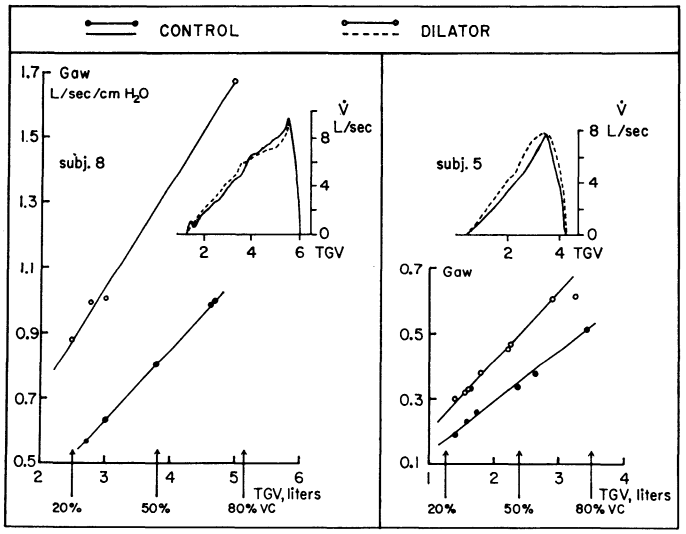

FIG. 1. Gaw-TGV graphs and MEFV curves before and after dilator drug in two subjects. See text for discussion, and Table 1 for numerical data on subjects.

TABLE 2. *Average changes of pulmonary function after bronchodilator treatment*

	TLC, liters	VC, liters	$FEV_{1.0}$, liters	PEFR		$\dot{V}_{max(50)}$		$\dot{V}_{max(20)}$		Gaw at 50% VC		Gaw/TGV Ratio
				liters/sec	TLC/sec	liters/sec	TLC/sec	liters/sec	TLC/sec	liters/sec per cm H_2O	TLC/sec per cm H_2O	
Avg control	6.66	5.02	4.13	7.83	1.24	4.69	0.75	1.78	0.28	0.714	0.106	0.174
Avg after dilator	6.68	5.09	4.28	8.03	1.27	5.11	0.81	1.94	0.31	0.962	0.141	0.233
Difference	+0.02	+0.07	+0.15	+0.20	+0.03	+0.42	+0.06	+0.16	+0.03	+0.248	+0.035	+0.059
% Change	+0.3	+1.4	+3.6	+2.6	+2.4	+9.0	+8.0	+9.0	+10.7	+34.7	+33.0	+33.9
t	0.517	1.500	4.879	1.772	1.881	3.968	3.778	1.418	1.763	6.087	6.591	7.005
P	NS	NS	<0.001	NS	NS	<0.001	<0.002	NS	NS	<0.001	<0.001	<0.001

Data from 22 subjects ($FEV_{1.0}$ in 19 only). TLC = total lung capacity; VC = vital capacity; $FEV_{1.0}$ = forced expiratory volume in 1 sec; PEFR = peak expiratory flow rate; $\dot{V}_{max(50)}$ and $\dot{V}_{max(20)}$: maximum expiratory flow rates at 50 and 20% VC, respectively; Gaw = airway conductance; Gaw/TGV = conductance-thoracic gas volume ratio. *t* = Fisher's *t* for paired variables. *P* = probability that observed *t* value is due to chance. NS = not significant.

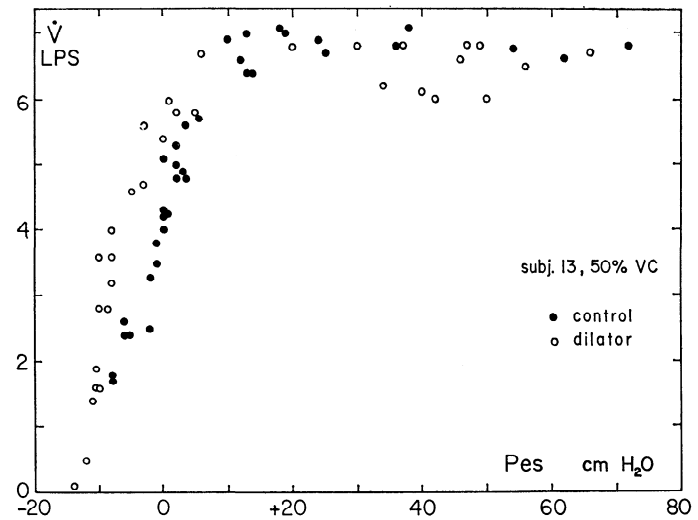

FIG. 4. Expiratory IVPF points at 50% VC in *subject 13*. Pes = esophageal (= pleural) pressure. After dilator, less pressure is required to drive flow from 0 to about 5 liters/sec, i.e., conductance increases.

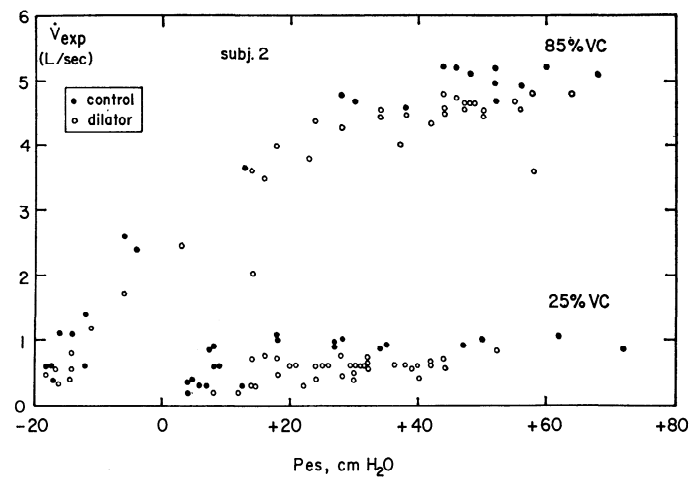

FIG. 5. Expiratory IVPF points in *subject 2*, at 85% and 25% VC. After dilator, maximum flow rate decreases at both lung volumes.

subjects maximum flow rates decreased slightly. In *subject 2* (Fig. 5) flow rates decreased at all volume levels. In this subject, the initial slope of the IVPF curve did not change after bronchodilation; his panting conductance did not increase either. In *subject 21* (Fig. 6), maximum flow rates also decreased after dilator, but only at small lung volumes. In the subject with a previous history of bronchial asthma, a large flow rate increase occurred after dilator (Fig. 7). In some IVPF curves, maximum flow rates were reached at lower pressures after dilator. In the curve of Fig. 7, for example, maximum flows are reached at an esophageal pressure of about + 7 cm H_2O before dilator, and at a pressure of about + 2 cm H_2O after dilator. In many curves, the inflection point could not be determined accurately enough, even though many experimental points were obtained.

Static lung recoil pressure. No systematic changes of static recoil pressures were found in any subject. Average data for all 17 subjects are shown in Fig. 8.

DISCUSSION

Isoproterenol stimulates β-adrenergic receptors and this leads to relaxation of airway smooth muscle. We believe that all responses seen in the present study can be explained by this action of isoproterenol.

After dilator, airway conductance nearly always increased. This was true when conductance was measured during panting (Fig. 1, Table 2) and also when conductance was measured from the initial slope of IVPF curves (Figs. 3, 4). In a few subjects, conductance remained unchanged (Figs. 5, 6), but the average increases were statistically significant with both methods. The relation between panting conductance and lung volume was similar to that described by others (8). The relation between conductance, measured

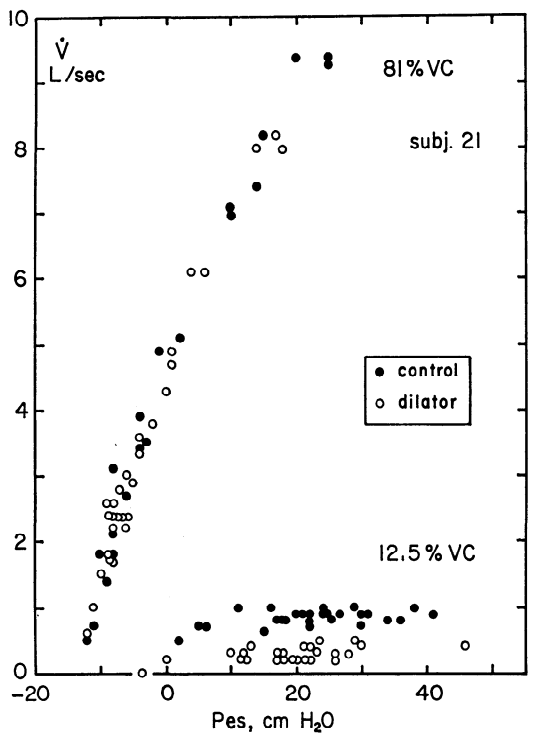

FIG. 6. Expiratory IVPF points in *subject 21*, at 81% and 12.5% VC. Decrease of maximum flow rate after dilator only at small lung volumes.

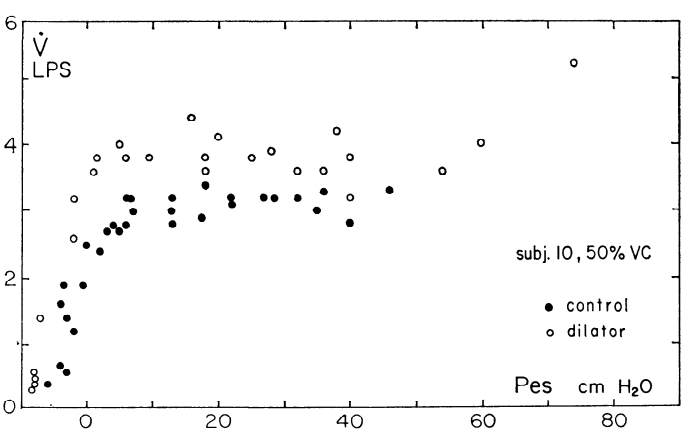

FIG. 7. Expiratory IVPF points in *subject 10* (with history of asthma). Increase of maximum flow rates after dilator drug.

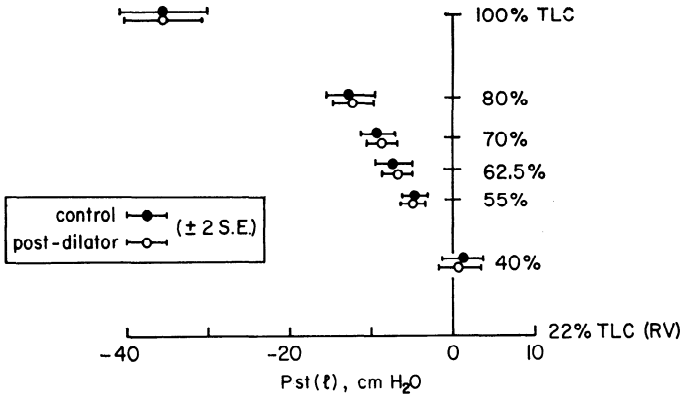

FIG. 8. Average static recoil pressures (Pst(l)) in 17 subjects at percentages of TLC indicated on *ordinate*.

from IVPF curves, and lung volume was similar to that described by Macklem for lower pulmonary conductance in dogs (Fig. 7-3 in ref. 10). In contrast with conductance, maximum expiratory flow rates increased only slightly in most subjects; in some they decreased after the dilator drug. The small average increase of maximum flows at mid vital capacity was similar when measured from directly recorded MEFV curves and from plateau flow rates on IVPF curves. However, the latter method is better suited to detect the small flow decreases seen in some subjects (Figs. 5, 6).

Discrepancies between results of airway conductance and maximum expiratory flow rate measurements have been noted in previous studies (7, 8, 11). We found that isoproterenol was more effective in increasing conductance than in increasing flow rates when we used the drug to reverse bronchoconstriction induced by hemp dust inhalation, and we suggested that this could be explained by assuming that isoproterenol made large intrathoracic airways more compressible (17). More recently, McFadden et al. (11) reported that isoproterenol decreased static lung recoil pressure in five healthy subjects; they felt that this was the most important reason why maximum flows increased less than airway conductance. In other studies, intravenous atropine increased static esophageal pressures, but this might be due to increased esophageal tone rather than to decreased lung elastic recoil (19).

Since lung elastic recoil pressure is an important component of the driving pressure for expiratory flow (12), changes in this pressure can alter maximum expiratory flow rates. In the studies of McFadden et al. (11) this was clearly an important factor. Their subjects continuously inhaled an aerosol of 1 % isoproterenol (10 mg/ml) during 5 min from a Wright nebulizer. This instrument nebulizes 20 ml liquid/hr (21); therefore, the total delivered dose of isoproterenol was about 17 mg in the experiments of McFadden et al. The responses seen in the present study were obtained with much smaller amounts of isoproterenol (0.2 mg/dose; 4–8 doses = 0.8–1.6 mg/subject); systemic effects were absent or minimal. We did not observe changes in static lung recoil pressures; presumably, the amount of isoproterenol which reached terminal lung units was insufficient to cause detectable smooth muscle relaxation in that region. The lack of change of static recoil pressure in our studies simplifies our discussion, since we need to consider only relaxation of smooth muscle in conducting airways.

Several explanations of the different changes of conductance and maximum expiratory flow rates are possible. The pressure-flow relations in airways can be approximated by Rohrer's equation: $P = K_1 \cdot \dot{V} + K_2 \cdot \dot{V}^2$ (16). Suitable changes of the constants K_1 and K_2, after dilation, could yield discrepancies between changes of conductance at low flow rates, and of maximum flow rates. One might also suppose that regional nonuniformity of mechanical characteristics plays a role: the conductance at low flows might reflect regions with time constants which differ from those of the regions that contribute most to maximum flows. One might also assume that the aerosol was mainly deposited in large airways, which contribute a major part of airway resistance (10), and not in small airways, which determine maximum flow rates to a large extent (12). The last explanation is untenable, since the same aerosol is effective in increasing maximum flows under conditions where they are decreased by bronchoconstrictor agents (7). Yet another explanation would be that isoproterenol decreases resistance only in extrathoracic airways, thus decreasing conductance but leaving maximum flows unchanged. There is no evidence for such an action of the drug, and the decrease of flows in some subjects cannot be explained in this way. In fact, none of these explanations can account in a simple way for the fact that, while conductance nearly always increased after isoproterenol, maximum flows either increased, remained constant, or decreased.

We prefer a different explanation, based on a simple single-compartment model lung, with three airway elements in series (Fig. 9). During quiet breathing, and during panting for Gaw measurements, all airways are wide open (Fig. 9*A*). During forced expirations, the larger intrathoracic airways (*2* in Fig. 9) are being compressed by high transmural pressures. This dynamic compression does not extend to the small, peripheral airways (*1* in Fig. 9), since here intraluminal pressures are high enough to prevent the compression. The point where compression begins (the transition zone between *1* and *2* in Fig. 9) is difficult to determine; it depends on lung volume and its exact location is irrelevant for the present discussion. This problem, and other more formal discussions of the mechanics of dynamic compression of intrathoracic airways are available elsewhere (3, 12, 15). In the following, the terms "small" or "peripheral" airways apply to segment *1*, and the term "large" airways to segment *2*. The extrathoracic airway (*3* in Fig. 9) will be considered a tube with constant properties.

During measurement of airway conductance, either during panting or from IVPF curves, flow rates as well as transmural pressures across the walls of the airways are low. Under these conditions, the model of Fig. 9*A* may apply.

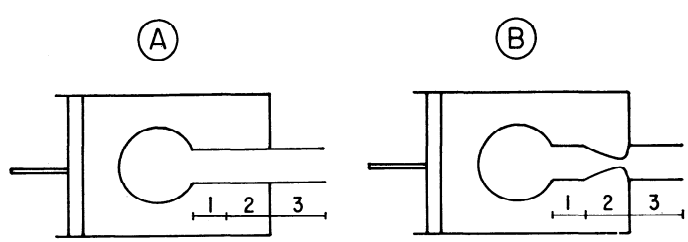

FIG. 9. Model of airways: *A* during quiet breathing, *B* during forced expiration. *1* = uncompressed airway segment; *2* = compressed segment; *3* = extrathoracic airway.

Our data confirm that bronchodilation increases airway conductance (8). Thus, relaxation of airway smooth muscle appears to increase airway caliber when air flow rates and transmural pressures across airway walls are low. At these low transmural pressures, airway wall compliance is increased by bronchodilation, as shown by the increased slope of Gaw-TGV and Gaw-Pst(l) graphs (8; Fig. 1, Table 2). This behavior of human airways is similar to that of canine blood vessels in vitro (9).

During forced expiration, airway geometry alters markedly because of dynamic compression of large airways (Fig. 9*B*). Maximum expiratory flow rates achieved in this system depend on many factors (5, 12, 15); here we discuss only those directly relevant to our problem. Segments *1* and *2* are in series; therefore flow must be equal in both of them (12). Segment *1* approximates Mead et al.'s "upstream airway segment" (i.e., upstream from an equal pressure point), in which maximum flow ($\dot{V}_{max}$) is determined by: $\dot{V}_{max} = Pst(l)/Rus$. As discussed above, static lung recoil pressure (Pst(l)) remained unchanged after dilation. Therefore, changes of $\dot{V}_{max}$ should be inversely proportional to changes of Rus, the resistance of segment *1*. Since we must assume that the inhaled isoproterenol reaches the peripheral airways of segment *1* and exerts its bronchodilator action there (see above), we expect the drug to increase maximum flows consistently. The large flow rate increase in a subject with a history of asthma (Fig. 7) fulfills this expectation. In most subjects, however, the effect on maximum flow of bronchodilation in segment *1* appears to be offset by other factors.

Among these other factors, the mechanical properties of the walls of airways in the compressed segment must be considered. As expiratory force is increased, transmural pressure across the walls of these airways (*2* in Fig. 9) increases. Their tendency to collapse under this increasing transmural stress depends on their compressibility. Olsen et al. (13, 14) have shown that large airways of cats and humans become more rigid and do not buckle under compressing forces when their smooth muscle is contracted. Our data suggest that their findings may apply to the healthy human subject's airway muscle tone. If smooth muscle relaxation makes large airways more compressible, in keeping with Olsen et al.'s findings, the discrepancy between $\dot{V}_{max}$ and Gaw changes can be explained as follows.

By itself, the increased airway caliber (as implied by increased Gaw) would result in increased maximum expiratory flow rates. At the same time, however, large airways become more compliant and collapse at lower transmural pressures. This, by itself, would lower maximum expiratory flow rates. The actually observed $\dot{V}_{max}$ values are the net result of these two opposite effects. This concept allows us not only to reconcile the discrepancies between changes of conductance and of $\dot{V}_{max}$, but also to explain the fact that $\dot{V}_{max}$ may either increase, decrease, or remain unchanged after bronchodilation (Figs. 4–7). In some healthy subjects, the flow-increasing tendency of peripheral airway dilation may predominate (Fig. 7). This is probably true for most subjects with clinically evident airway constriction (asthma, byssinosis); bronchodilator drugs improve maximum expiratory flow rates in such patients (2). In some healthy subjects, on the other hand, the increased compliance of large airways may predominate, and the net result then is a decrease of maximum flow rates after a bronchodilator drug (Figs. 5, 6).

Our concept of the action of bronchodilator drugs in healthy subjects is, of necessity, based on indirect evidence. However, it is supported by the in vitro studies of Olsen et al. (13, 14) which provide more direct evidence. Knudson, Mead, and Sherry (personal communication) have found increased flow transients on MEFV curves after bronchodilation in healthy subjects; this suggests increased large airway compressibility during forced expiration after airway smooth muscle relaxation. Thus, in vitro studies as well as in vivo observations of others support our concept of the bronchodilator action of isoproterenol in man.

In terms of Mead's "equal pressure point" (EPP) theory (12), increased collapsibility of large intrathoracic airways would cause the EPP to stop moving at a point closer to the thoracic inlet. Increased length of the upstream segment would offset the advantage gained by increased caliber of the upstream airways. This explanation differs from ours only in its emphasis on the uncompressed, upstream airway segment. The primary change is increased large airway compressibility; the increased length of the uncompressed airway segment is secondary to alterations in the compressed segment.

Our results suggest that normal airway smooth muscle tone may have physiological significance in allowing large airways to withstand compressing forces during forced expiration. This allows dynamic compression to extend further upstream than would be the case if they were less rigid. In this manner, large airway tone may help to increase the effectiveness of coughing. A less than normal tone might decrease respiratory work against airway resistance during quiet breathing, but at the expense of decreased large airway rigidity during forced ventilation. A slightly more than normal tone decreases maximum flow rates (4) and probably increases respiratory work. Thus, normal airway smooth muscle tone may represent a close to optimal condition in that it allows high expiratory flow rates, while keeping respiratory work during quiet breathing minimal.

The beneficial effects of isoproterenol, in conditions where bronchial smooth muscle spasm causes reversible small airway obstruction, are well known. In other conditions, without this type of airway constriction, the effect of isoproterenol on large airways might preponderate. The significance of increased compressibility of large airways as a clinical side effect of bronchodilator therapy remains to be assessed.

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