Maximum Expiratory Flow Rates in Induced Bronchoconstriction in Man

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ABSTRACT We evaluated changes of maximum expiratory flow-volume (MEFV) curves and of partial expiratory flow-volume (PEFV) curves caused by bronchoconstrictor drugs and dust, and compared these to the reverse changes induced by a bronchodilator drug in previously bronchoconstricted subjects. Measurements of maximum flow at constant lung inflation (i.e. liters thoracic gas volume) showed larger changes, both after constriction and after dilation, than measurements of peak expiratory flow rate, 1 sec forced expiratory volume and the slope of the effort-independent portion of MEFV curves. Changes of flow rates on PEFV curves (made after inspiration to mid-vital capacity) were usually larger than those of flow rates on MEFV curves (made after inspiration to total lung capacity). The decreased maximum flow rates after constrictor agents are not caused by changes in lung static recoil force and are attributed to narrowing of small airways, i.e., airways which are uncompressed during forced expirations. Changes of maximum expiratory flow rates at constant lung inflation (e.g. 60% of the control total lung capacity) provide an objective and sensitive measurement of changes in airway caliber which remains valid if total lung capacity is altered during treatment.

INTRODUCTION

During forced expirations, the rate of air flow cannot increase beyond certain maximum values. At large lung volumes, these maxima are mainly set by the amount of expiratory effort. At lower lung volumes, dynamic compression of intrathoracic airways by high intrapleural pressures is the principal limiting factor. Since the degree of lung inflation is a main determinant in both flow-limiting mechanisms, maximum expiratory flow rates are best studied as a function of lung volume. For this purpose, Fry and Hyatt (1) introduced the maximum expiratory flow-volume (MEFV) curve, which has been a useful tool in a number of physiological and clinical (2–4) studies.

We believe that MEFV curves deserve more general use as a clinical pulmonary function test. Until now, their acceptance as such has been limited for various reasons, probably including (*a*) lack of agreement on quantitation of MEFV curves, and (*b*) the objection that the maximum inspiration which precedes the forced expiratory maneuver may alter pressure-flow relations (5, 6). The purpose of this paper is to examine these and other problems related to the use of MEFV curves in pulmonary function testing. Our conclusions are mainly derived from acute experiments on induced bronchoconstriction in a small number of healthy subjects. Since each subject serves as his own control, this approach avoids some of the difficulties inherent to a comparison of data from healthy persons with data from patients. We have also studied the effect of the depth of the previous inspiration on maximum expiratory flow rates, by comparing such flow rates (*a*) on curves which began after a maximum inspiration to total lung capacity (TLC), and (*b*) on curves which were preceded by a partial inspiration to about 50% vital capacity.

METHODS

Subjects. Experiments with inhaled bronchoconstrictive drugs were done in three healthy nonsmoking laboratory workers. Average control data for a number of measurements in these subjects are shown in Table I. Another healthy nonsmoking subject (D) and a patient with bysinosis (E, patient 13 in reference 7) participated in experiments with cotton dust exposure. The patient, a 45 year old male, had worked in cotton cardrooms for 15 yr and smoked 30 cigarettes per day.

MEFV curves were also obtained in five patients with bronchial asthma, who had slight to moderate dyspnea at the time of study, and who improved clinically after inhala-

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TABLE I
Control Measurements

Subject	A, ♀	B, ♂	C, ♂
Age, *yr*	41	39	35
VC, *liters*	4.37 ±0.14 (19)	4.23 ±0.07 (16)	5.40 ±0.12 (13)
TLC, *liters*	6.21 ±0.29 (17)	5.72 ±0.27 (16)	7.48 ±0.46 (13)
RV, *liters*	1.82 ±0.23 (17)	1.49 ±0.27 (16)	2.08 ±0.43 (13)
$FEV_{1.0}$, *liters*	2.84 ±0.10 (16)	3.18 ±0.05 (11)	4.26 ±0.05 (12)
$\dot{V}_{max}$ at 60% TLC, *liters/sec*			
on MEFV curves	2.04 ±0.20 (20)	3.76 ±0.45 (14)	4.22 ±0.43 (12)
on PEFV curves	2.31 ±0.23 (15)	3.92 ±0.68 (13)	4.07 ±0.40 (11)

Values shown are average ±1 SD; No. of observations in parenthesis.

tion of an isoproterenol-phenylephrine aerosol (Medihaler-Duo[1]). These data were used to compare the changes of MEFV curves after bronchodilation with those obtained in the other subjects after bronchoconstriction. Data obtained in another patient (F) will be described separately.

Methods. The subjects were seated in an air-conditioned volume-displacement body plethysmograph with Krogh-spirometer (J. H. Emerson Co., Cambridge, Mass.). The plethysmograph mouthpiece was connected to a breathing assembly consisting of a shutter, a side-tap for mouth pressure measurements, and a Fleisch pneumotachograph (No. 4). Flow volume curves were recorded while the subjects breathed room air through the mouthpiece-shutter-pneumotachograph assembly. Lung volume changes (from the Krogh-spirometer) and expiratory flow rates were displayed on the axes of an XY storage oscilloscope (Tektronix, Inc., Portland, Oreg., model 564). Flow-volume loops were photographed or traced on paper. Thoracic gas volume (TGV) was measured with a modification of the method of DuBois et al. (8) during panting against the closed shutter. A direct-writing recorder was used to obtain a continuous record of lung volume events vs. time. This allowed the calculation of total lung capacity (TLC) and residual volume (RV) from the TGV measurements (9).

Two types of expiratory flow-volume loops were obtained (Fig. 1). One is the curve recorded when the subject expires as rapidly as possible. He first expires to RV, then inspires to TLC, and the maximum expiratory flow-volume (MEFV) curve is recorded while he next expires as rapidly as possible down to RV. For the other type of curve the subject first expires to RV and then inspires to about 50% of his vital capacity (VC). At this point, the operator closes the shutter at the mouth, and the subject pants briefly for a measurement of TGV. The subject is then warned that the shutter will be opened and is instructed to expire immediately, as fast as possible, to RV. We have called this second type of curve the partial expiratory flow-volume (PEFV) curve. During each experiment and in each condition, two or three PEFV curves were first recorded, and these were followed by two or three MEFV curves. The largest of each of the two types of curves was analyzed.

Forced expiratory volume ($FEV_{1.0}$) was determined separately, with a direct-reading spirometer with electronic timer, as in previous studies (7). Residual volume (RV) was calculated as TLC minus FVC. All VC data refer to forced expiratory vital capacities (FVC) and were measured from the MEFV curves.

The sensitivity of the subjects to the pharmacological agents (histamine [H], carbachol [C], methacholine [M], and acetylcholine [ACh]) was determined in trial experiments at low drug concentrations. Serotonin (5-hydroxytryptamine creatinine sulphate, up to 10 mg base/ml) was used in subjects B and C only. A Dautrebande D30 generator (20 lb. air pressure; 0.5 ml liquid nebulized/min) was used for all aerosol inhalations. Aerosols were inhaled for 2 min from the inspiratory line of a separate valved breathing circuit. In the final experiments, increasing dose levels (i.e. drug concentrations in the nebulized liquid) were used to obtain a graded response. The cotton dust exposures were performed in a plastic exposure tent, in which a dust cloud was produced by blowing pressurized air through a perforated bag containing cotton dust and trash collected in a cotton ginnery. 2 hr of exposure was sufficient to produce a measurable response in the three subjects of these experiments. Since we were principally interested in observing effects of the dust on the men, no attempt was made to measure dust levels in the tent. Visually, the atmosphere was very dusty. To avoid negative results because of tachyphylaxis on repeated exposures (10), serial experiments in subjects D and E were made at intervals of not less than 3 days.

RESULTS

MEFV and PEFV curves. Both types of flow-volume curve reach a peak flow shortly after initiation of the forced expiratory maneuver; from that point on flow rates decrease towards zero at RV. Fig. 1 shows representative results with histamine inhalation. The general configuration of the curves is not altered after administration of this drug, but the magnitude of the flow rates decreases. This decrease is more pronounced for the PEFV curves than for the MEFV curves. In the experiment of Fig. 1, the lowest histamine dose (6 mg/ml) did not alter the MEFV curve perceptibly, while flow rates on the PEFV curve decreased. One can express the alterations of the curves quantitatively by measuring the maximum flow rate at a given constant lung volume before and after drug administration, and both on MEFV and on PEFV curves. In this way, one can compare the response of flow rates during both expiratory maneuvers at the same degree of lung inflation. Fig. 1 indicates the volume level chosen in the present study, i.e., 60% of the control TLC. Flow rate at this volume

[1] Riker Laboratories, Inc., Northridge, Calif.

TABLE II

Changes of Total Lung Capacity (Liters) during Exposure to Bronchoconstrictor Drugs and Cotton Dust

Subject	A*	B*	C*	D‡	E‡
n	15	17	13	6	7
Control, *liters*	6.23 ±0.27	5.70 ±0.27	7.48 ±0.46	7.95 ±0.39	7.99 ±0.36
After exposure, *liters*	6.39 ±0.38	5.62 ±0.30	7.41 ±0.41	8.23 ±0.38	8.34 ±0.52
t	3.167	1.618	1.074	2.996	2.855
P	<0.01	NS	NS	<0.05	<0.05

Values shown are average ±1 SD; n = No. of paired observations; *t* = values derived from Fisher's *t* distribution for paired variates.

* Exposures to bronchoconstrictor drugs.

‡ Exposures to cotton dust.

TABLE III

Changes of Selected Measurements after Inhalation of Bronchoconstrictor Aerosols

		VC			$FEV_{1.0}/VC$			V_{max} at 50% VC			$\dot{V}_{max}$ at RV + 1 liter			t‡		
Subject	Dose	(1)*	(2)*	Δ(%)*	(1)	(2)	Δ	(1)	(2)	Δ(%)	(1)	(2)	Δ(%)	(1)	(2)	Δ(%)
	mg base/ml	*liters*			%			*liters/sec*			*liters/sec*			*sec*		
Histamine																
A	6	4.3	4.2	(−2)	65	65	0	2.6	2.7	(+4)	0.9	0.9	0	0.70	0.59	(−16)
	12	4.7	4.5	(−4)	61	65	+4	2.5	2.3	(−8)	0.8	0.7	(−12)	0.84	0.75	(−11)
	18	4.3	3.9	(−9)	69	60	−9	2.5	1.6	(−36)	0.9	0.5	(−44)	0.71	0.89	(+25)
B§	6	4.3	4.1	(−5)	76	76	0	5.3	4.4	(−17)	1.5	1.3	(−13)	0.35	0.34	(−3)
	12		3.9	(−9)	72	80	+8		3.8	(−28)		1.2	(−20)		0.41	(+17)
C	6	5.6	5.4	(−4)	77	81	+4	4.8	4.8	(0)	1.1	1.5	(+36)	0.48	0.54	(+12)
	12	5.6	5.3	(−5)	77	78	+1	4.8	4.2	(−12)	1.1	1.7	(+54)	0.48	0.70	(+46)
	18	5.3	5.3	(0)	82	72	−10	5.1	3.4	(−33)	1.5	1.0	(−33)	0.46	0.70	(+52)
Carbachol																
A	7.5	4.4	4.3	(−2)	64	60	−4	2.3	2.2	(−4)	0.8	0.8	(0)	0.76	0.86	(+12)
	15	4.4	4.3	(−2)	67	59	−8	2.5	2.3	(−8)	0.8	0.9	(+12)	0.75	0.85	(+13)
	20	4.5	4.4	(−2)				2.6	1.9	(−27)	1.0	0.8	(−20)	0.70	0.83	(+19)
B	3.8	4.3	4.2	(−2)	75	77	+2	4.5	4.3	(−3)	1.5	1.3	(−13)	0.38	0.36	(−5)
	7.5	4.2	4.1	(−2)	76	77	+1	4.4	4.2	(−4)	1.3	1.6	(+23)	0.35	0.40	(+14)
	15	4.2	4.1	(−2)	75	76	+1	4.8	4.5	(−6)	1.6	1.5	(−6)	0.38	0.40	(−5)
	30	4.2	4.0	(−5)	78	74	−4	4.4	3.8	(−14)	1.7	1.5	(−12)	0.34	0.33	(−3)
	45	4.2	3.6	(−14)	77	72	−5	4.1	3.2	(−22)	1.5	1.1	(−27)	0.29	0.30	(+3)
Methacholine																
A	3	4.5	4.4	(−2)	61	62	+1	2.4	2.8	(+17)	0.7	0.9	(+29)	0.69	0.61	(−12)
	6	4.3	4.3	(0)	64	61	−3	2.4	2.4	(0)	0.8	1.0	(+25)	0.67	0.71	(+6)
	12	4.3	3.6	(−16)	60	58	−2	2.3	2.0	(−13)	0.8	1.0	(+25)	0.75	1.00	(+33)
Acetylcholine																
A	18	4.6	4.5	(−2)	61	63	+2	2.7	2.6	(−4)	0.9	1.0	(−11)	0.72	0.73	(+1)
	30	4.5	4.3	(−4)	65	60	−5	2.7	2.3	(−15)	0.8	0.7	(−12)	0.65	0.77	(+18)
	36	4.4	4.6	(+4)	65	61	−4	2.7	1.9	(−30)	0.8	0.6	(−25)	0.65	0.88	(+35)
C‖	18	5.4	5.4	(0)	79	78	−1	4.7	5.0	(+6)	1.8	2.0	(+11)	0.59	0.45	(−24)
	36	5.4	5.4	(0)	78	78	0	4.5	4.5	(0)	1.6	1.3	(−19)	0.56	0.50	(−11)
	54	5.3	5.5	(+4)	79	76	−3	4.1	4.0	(−2)	1.0	0.8	(−20)	0.54	0.54	(0)

* (1) = data before exposure; (2) = data after exposure; Δ = difference.

‡ t = time constant (reference 4).

§ Both experiments on same day; one control used for both.

‖ With local anesthesia.

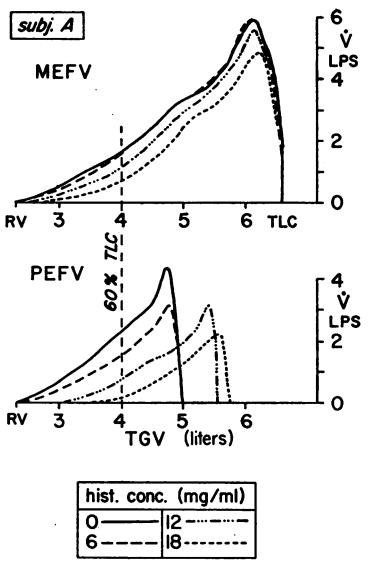


FIGURE 1 Histamine inhalations in subject A. *Ordinate:* expiratory flow rate; *abscissa:* thoracic gas volume (TGV). *Upper curves:* MEFV curves; *lower curves:* PEFV curves. For the MEFV curves, TLC is taken as constant since its average change was zero in these experiments.

($\dot{V}_{max}$ at 60% TLC) decreases progressively with increasing doses of inhaled histamine on both MEFV and PEFV curves, but the changes are greater on the PEFV curve.

Lung volumes. Average data for total lung capacity (TLC) are given in Table II. Small, but systematic and statistically significant, increases of TLC were found in subject A after bronchoconstrictor drugs, and in subjects D and E after cotton dust exposure (Table II). The decrease of expiratory flow rates at small lung volumes is accompanied by an increase of RV, i.e., the lung volume at which flow reaches zero increases. This increase of RV is larger than any increase of TLC and therefore occurs mostly at the expense of the vital capacity.

The pronounced decrease of flow rates, as seen on the PEFV curves, and the concomitant increase of RV is partially reversed by a single maximum inspiration. Immediately after performing the PEFV curve maneuvers, the subject inspired to TLC and performed an MEFV curve. In the example of Fig. 1, RV was 3.5 liters after completion of the PEFV curve corresponding to the highest histamine dose. During the subse-

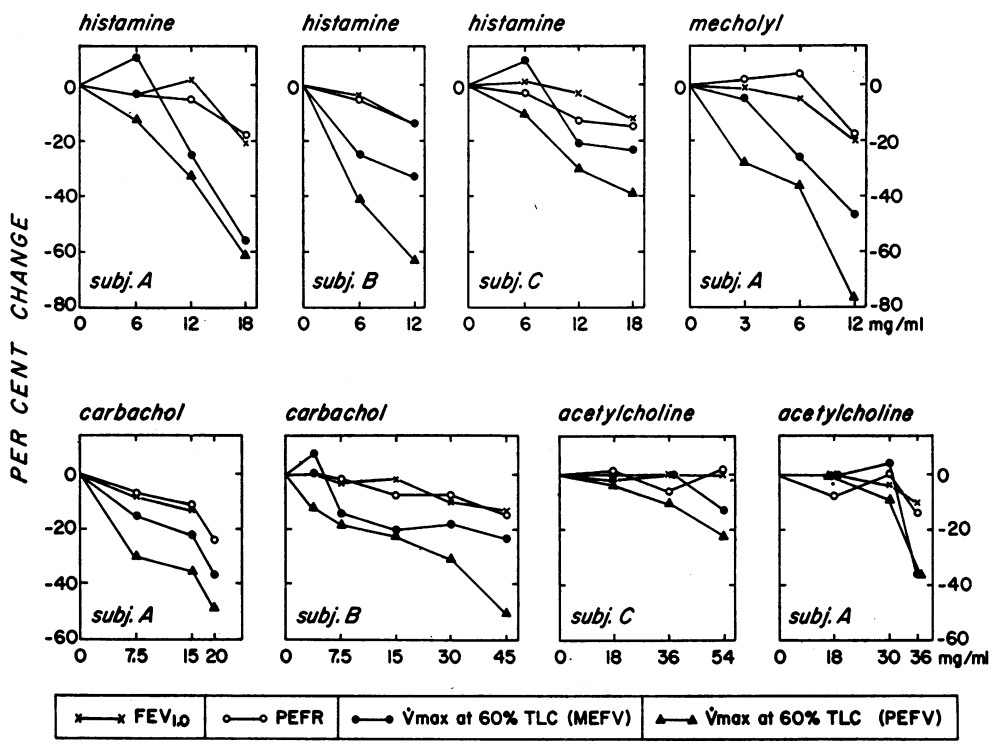


FIGURE 2 Dose-response relationships in individual subjects and for different drugs. *Abscissa:* drug concentration (mg base/ml) in nebulized liquid; *ordinate:* per cent change of measurements (control values = 0).

quent MEFV curve, measurable expiratory flow occurred down to a lower RV level (2.9 liters).

Comparison of measurements from MEFV and PEFV curves. Fig. 2 summarizes the dose-response relationships for $\dot{V}_{max}$ at 60% of TLC on PEFV as well as MEFV curves. Further data from the same experiments are shown in Table III. In all instances, the percentage changes of $FEV_{1.0}$ and peak expiratory flow rate (PEFR, Fig. 2) as well as those of VC (Table III) were less than those of $\dot{V}_{max}$ at 60% TLC. In most instances, the $\dot{V}_{max}$ value on the PEFV curve showed a larger change than the $\dot{V}_{max}$ value on the MEFV curve, at the same volume.

Table III includes several additional measurements made on the MEFV curves. These are: (*a*) maximum flow rate at 50% VC; (*b*) maximum flow rate at a lung volume 1 liter above RV (11), and (*c*) the ratio $\Delta V/\Delta \dot{V}$ over the volume range 50–75% of VC. This ratio (4) has the dimension of time. It represents the reciprocal of the MEFV curve slope over the volume interval chosen and has been considered a measurement of the time constant of lung emptying (4). The value of $\dot{V}_{max}$ at RV + 1 liter describes the average slope of the last portion of the MEFV curve, since it is determined by the zero end point of the curve and by a point situated 1 liter above that point. These measurements are schematically shown in Fig. 3. The two measures (*b* and *c*) which reflect the slope of the MEFV curve show small changes and inconsistent dose-response relations in several experiments (Table III), compared with the changes of $\dot{V}_{max}$ at 60% TLC (Fig. 2). On the other hand, $\dot{V}_{max}$ at 50% VC decreases with increasing doses of the three drugs in all series.

Comparative effects of bronchoconstrictor drugs. Histamine, methacholine, and carbachol aerosols caused similar effects, both subjectively and objectively. The dose-response relations for the various measurements on MEFV and PEFV curves followed similar patterns (Fig. 2, Table III). Subjectively, the subjects felt moderate dyspnea, chest tightness, and wheezing at the highest dose level of each drug. These symptoms developed gradually during the 2 min of aerosol inhalation. A dry cough occurred only in subject C during methacholine inhalation. Subjects B and C did not react subjectively to methacholine, except for cough in C; their expiratory flow rates and other measurements were unchanged. Subject C did not respond to carbachol aerosol either (up to 45 mg/ml). Serotonin (10 mg base/ml) caused no subjective symptoms nor changes of any of the expiratory flow measurements, including $\dot{V}_{max}$ at 60% TLC on MEFV and PEFV curves, in subjects B and C.

The results with acetylcholine aerosols were somewhat different from those with the other drugs. Data from

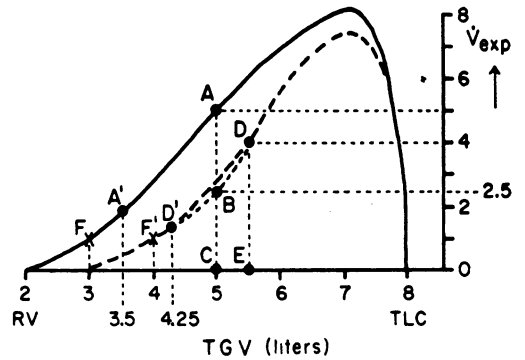
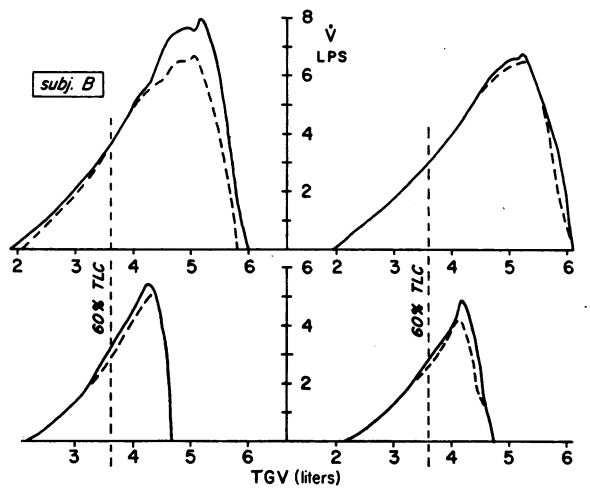


FIGURE 3 Schematic MEFV curves before (——) and after (– – – –) a bronchoconstrictor drug. *AC* and *DE:* $\dot{V}_{max}$ at 50% VC. *AC* and *BC:* $\dot{V}_{max}$ at TGV = 5 liters. *AA'* and *DD':* average MEFV-curve slope over 50–75% of expired VC. *F* and *F':* flow at RV + 1 liter.

subject B are shown in Fig. 4. Inhalation of an 18 mg/ml acetylcholine aerosol resulted in violent cough, starting after the first aerosol breath, and symptoms of chest tightness and dyspnea. Immediately after 2 min inhalation the PEFV curve was minimally altered, whereas the MEFV curve showed lower flow rates only at large lung volumes (near peak flow). When superimposed on the absolute volume scale, as in Fig. 4, the curves showed little change of flow rates at lung vol-



ACh conc. mg/ml	Δ F.E.V.$_{1.0}$ (liters)	Δ V.C. (liters)		ACh conc. mg/ml	Δ F.E.V.$_{1.0}$ (liters)	Δ V.C. (liters)	
0	-	-	——	0	-	-	——
18	-0.38	-0.4	– – –	54	-0.10	0	– – –

NO ANESTHESIA LOCAL ANESTHESIA

FIGURE 4 Acetylcholine (ACh) inhalations in subject B. *Abscissa:* thoracic gas volume (liters); *ordinate:* expiratory flow rate (liters per sec). *Upper curves:* MEFV curves; *lower curves:* PEFV curves. The table shows the drug concentrations in the nebulized liquid and the changes of $FEV_{1.0}$ and VC during each exposure.

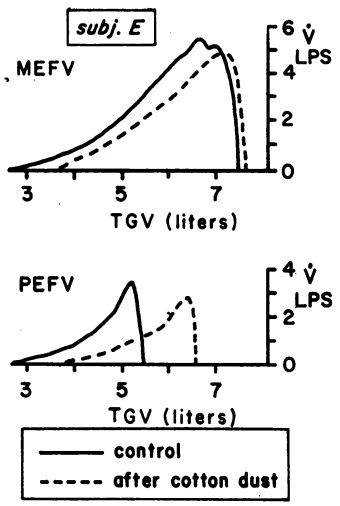


FIGURE 5 Cotton dust exposure in subject E. *Abscissa:* thoracic gas volume (liters); *ordinate:* expiratory flow rate (liters per sec).

umes less than about 70% of TLC. After local anesthesia of the pharynx with 2% xylocaine, subject B tolerated 54 mg/ml acetylcholine without developing cough or other symptoms, while both his PEFV and MEFV curves remained unchanged (Fig. 4). Local anesthesia also prevented acetylcholine-induced cough in subject C. In contrast to the results in subject B, his flow rates decreased when he inhaled 54 mg/ml acetylcholine after anesthesia (Fig. 2).

Effects of cotton dust exposure. This produced changes of MEFV and PEFV curves which were similar to those induced by bronchoconstrictor drugs (Fig. 5, Table IV). Again, the values of $\dot{V}_{max}$ at 60% TLC underwent a larger percentage change than any of the other measurements. The two healthy subjects reacted, in most respects, to the same extent as the patient with byssinosis. All three subjects coughed and felt dyspneic and tight in the chest at the end of the 2 hr exposure and for several hours thereafter.

DISCUSSION

The pressure-flow-volume events during expiratory air flow are represented most completely in a set of pressure-flow curves at different lung volumes (isovolume pressure-flow, IVPF, curves, 1). Flow rates on MEFV or PEFV curves represent one important characteristic of IVPF curves, i.e., their effort-independent flow plateaus at lung volumes less than about 75% of VC. Previous work on IVPF curves in this laboratory (12, and unpublished data) suggested that inhalation of histamine may result in a decrease of maximum expiratory flow rates, while leaving pressure-flow relations at low flow rates unchanged. Others described similar results in animals (13) and in patients with bronchial asthma (14). Observations in patients with emphysema (15) and byssinosis (16) suggest that a similar discrepancy between expiratory flow rates and airway resistance may occur in obstructive lung disease. The probable ex-

TABLE IV

Effects of Cotton Dust, Bronchoconstrictor Drugs, and Isoproterenol on Lung Volumes and Forced Expiratory Flow Rates

	TLC		VC		RV		$FEV_{1.0}$		$\dot{V}_{max}$ 60% TLC MEFV		$\dot{V}_{max}$ 60% TLC PEFV		$\dot{V}_{max}$ at RV + 1 liter		t		PEFR		$\dot{V}_{max}$, 50% VC	
Subject	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
	liters		*liters*		*liters*		*liters*		*liters/sec*				*liters/sec*		*sec*		*liters/sec*		*liters/sec*	
D*	8.0	8.2	5.1	5.1	2.9	3.1	3.82	3.58	2.7	1.9	2.7	1.9	1.4	1.2	0.66	0.68	6.0	6.0	3.7	3.4
E‡	8.0	8.3	4.9	4.5	3.1	3.9	3.12	2.87	1.5	0.6	1.5	0.3	0.7	0.7	0.69	0.77	5.6	5.3	2.7	2.3
B§	5.9	5.7	4.2	4.2	1.7	1.5	3.23	2.80	3.0	3.1	3.6	2.5	1.6	1.1	0.40	0.40	8.0	7.4	4.2	3.7
Average % change	+1		−3		+7		−9		−29		−47		−15		+5		−4		−12	
Drug response‖	−1		−5		+10		−13		−32		−48		−16		+22		−13		−22	
Isoproterenol in bronchial asthma¶	−1 (4)		+8		−10 (4)		+19 (3)		+32				−11		−17		+12		+19	

Subjects D, E and B: cotton dust exposures (2 hr); (1) data before, (2) after exposure.

* Healthy subject; average of six experiments.

‡ Subject with byssinosis; average of seven experiments.

§ Healthy subject; one experiment.

‖ Average % change observed with the highest drug concentration in each of the eight experimental series of Fig. 2 and Table III.

¶ Average % change after isoproterenol inhalation in patients with bronchial asthma (n = 5 except where indicated in parenthesis); PEFV curves not done in these patients.

planation of these findings is that maximum flow rates are set, to a large extent, by the flow-resistive properties of small airways (2), while airway resistance at low flow rates depends principally on the resistance of large conducting airways (17). These observations suggested that MEFV curves might allow a sensitive assessment of the functional status of small airways, i.e., those airways which remain uncompressed during forced expiratory maneuvers. This idea is also supported by the observation that, in byssinosis, maximum flow rates decrease under conditions in which other tests (e.g. nitrogen washout and dynamic lung compliance) suggest narrowing of relatively small airways (10, 16).

However, this suggestion disagrees with the widely held view that measurements of airway conductance during panting (i.e. at low flow rates) are a more sensitive index of bronchoconstrictor effects than measurements of expiratory flow rates. This view is based upon expiratory flow measurements which differ from those which we found to be the most sensitive ones. For instance, Lloyd and Wright (11) used the ratio $FEV_{1.0}$/VC (which did not alter consistently in our experiments, Table III), flow rate at RV + 1 liter (likewise, an insensitive measure in our hands, Table III) and $\dot{V}_{max}$ at 50% VC (which we found less sensitive than $\dot{V}_{max}$ at 60% TLC).

We believe that the maximum expiratory flow rate at a defined, absolute level of lung volume is a more satisfactory measure of expressing changes of MEFV and PEFV curves than the indices proposed by previous authors. Leuallen and Fowler (18) were the first to point out the advantages of flow rate measurements over the middle portion of the VC (maximum mid-expiratory flow). Our method is a refinement of theirs and uses an instantaneous rather than an average flow. Some features of our method have been pointed out by previous authors. Frank et al. (19) suggested that expiratory flow rate measurements after a less than maximum inspiration might be useful, and Hyatt (20) stated that it might be worthwhile to relate maximum flows to TGV. We have shown that $\dot{V}_{max}$ at 60% TLC is more sensitive than other indices to relatively slight degrees of bronchoconstriction by pharmacological agents and cotton dust, and the changes are similar for both types of agents. Table IV includes data on the effect of isoproterenol inhalation in five patients with bronchial asthma. In these patients, the changes were in the opposite direction from those induced in subjects A–E by drugs or dust, and again $\dot{V}_{max}$ at 60% TLC is the measure which shows the largest changes.

Fig. 3 shows several calculations which can be made to express changes of MEFV curves in quantitative fashion. Peak expiratory flow rate (PEFR) changes little after bronchoconstriction, probably because it occurs at a large lung volume and depends on the subject's effort. $\dot{V}_{max}$ at 50% VC changes more, but if

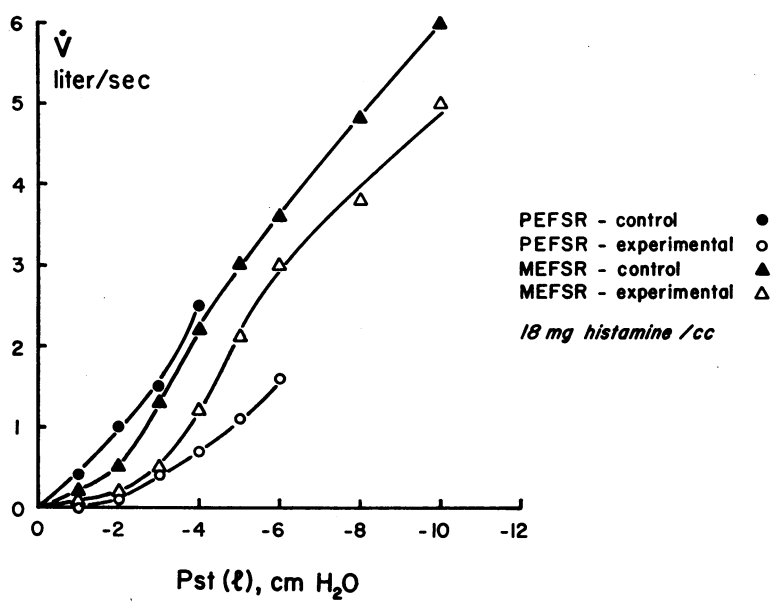


FIGURE 6 Maximum flow–static recoil curves (subject C). *Abscissa:* static lung recoil pressure (cm H_2O); *ordinate:* expiratory flow rate (liters per sec). PEFSR = partial expiratory flow–static recoil curve, corresponding to PEFV maneuver. MEFSR = maximum expiratory flow–static recoil curve, corresponding to MEFV maneuver.

(as in the example of Fig. 3) VC decreases, it reflects flow rates at different lung volumes before and after the exposure. In Fig. 3 $\dot{V}_{max}$ at 50% VC changes from AC to DE, i.e., from a lung volume of 5 liters to one of 5.5 liters. If we measure flow at equal thoracic gas volume, e.g., 5 liters, the flow change is larger, i.e., from AC to BC. Since the mid-vital capacity point is on a steep part of the MEFV curve, the difference between the two measures can be considerable. Measurements of the slope of the effort-independent portion of the MEFV curve are also unsatisfactory for the detection of bronchoconstriction. Many of our curves (e.g. Fig. 1) do not show appreciable changes of the slope after bronchoconstriction; rather, they are displaced towards higher RV levels. The index proposed by Lloyd and Wright (11), i.e., flow rate at RV + 1 liter, ignores the change of RV and only reflects the slope of the very last part of the MEFV curve. This part of the slope is subject to unpredictable changes on account of the difficulty to determine the end-point of a forced vital capacity maneuver (21). The calculation of the average time constant over the volume range 50–75% of VC (4) avoids this difficulty. This measurement is shown in Fig. 3 by the straight lines *AA'* and *DD'*. Since the postexposure MEFV curve is approximately parallel to the control curve, the slope of these lines (i.e. the reciprocal of the time constant) does not alter. Our data show that the changes of this time constant were less than those of the flow rates (compare Fig. 2 and Table III). Finally, the $FEV_{1.0}$ is a relatively insensitive index of change since its measurement, although it includes flow rates at lower volumes, is influenced greatly by the high flow rates which occur near TLC. The acetylcholine experiments in subjects B and C show that decreases of $FEV_{1.0}$ should not be equated with bronchoconstriction without further evidence. In this case, $FEV_{1.0}$ was decreased after the inhalations (Fig. 4, left) although flow rates at lower volumes were unaffected. Our experience with acetylcholine corresponds with that of Tiffeneau (22), who pointed out that spurious decreases of $FEV_{1.0}$ might be found after acetylcholine inhalations, i.e., decreases not attributable to drug-induced bronchoconstriction. Simonsson, Jacobs, and Nadel (23) have pointed out that many bronchoconstrictor agents, when inhaled, also often induce cough, particularly in sensitive patients. They suggest that part of the bronchoconstrictor action of these drugs in such patients may be explained by a reflex which is initiated by stimulation of cough receptors and which has its effector organ in bronchial smooth muscle. On the other hand, in our healthy subjects, the drugs which were most active in causing cough (metha- and acetylcholine) caused less bronchoconstriction than other drugs (histamine, carbachol) which caused little or no cough. Furthermore, prevention of cough by local anesthesia did not prevent bronchoconstriction by acetylcholine in subject C.

A decrease of maximum expiratory flow rates may be caused not only by increased airflow resistance in small airways, but also by a decrease of the driving pressure across these airways. This driving pressure equals the static recoil pressure of the lungs (2). To examine the latter possibility we obtained static pressure-volume curves of the lungs in subjects B and C, before and after inhalation of effective histamine aerosols, and with volume excursions as used for MEFV and PEFV curves. These data enabled us to plot maximum flow as a function of static recoil pressure ($P_{st}[l]$) (Fig. 6). The results for both subjects indicate that $\dot{V}_{max}$, at any given value of $P_{st}(l)$, decreases after histamine inhalation. This decrease is more pronounced during expirations from 50% VC than during expiration from TLC. These data show that flow rate decreases after histamine can not be attributed to a decrease of the driving pressure across small airways.

Woolcock and Read (24) have reported that total lung capacity (helium-dilution method) may be grossly

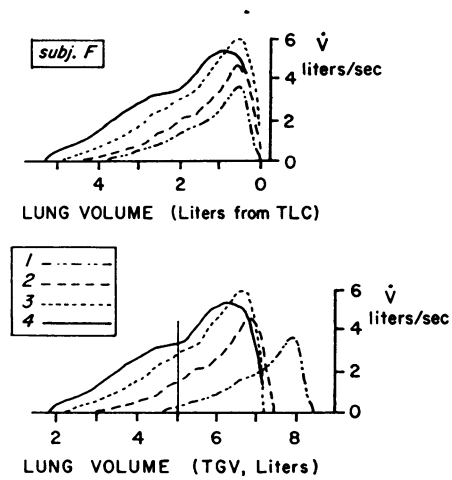


FIGURE 7 MEFV curves in subject F (male, 32 yr). This subject had previously worked in hemp dust but had not been exposed recently. See Table V for quantitative data. When first seen (curve 1), subject F was short of breath and had generalized wheezing in the chest. ½ hr after isoproterenol inhalation he was subjectively improved (curve 2). He continued daily isoproterenol inhalations for 4 wk; further improvement resulted (curves 3 and 4). The improvement is obvious from MEFV curves plotted on the assumption of a constant TLC (*upper graphs*). However, the changes of flow rate at equal thoracic gas volume are larger than this representation suggests. The *lower graphs* are the same MEFV curves, plotted on an absolute volume scale, which shows the decrease of TLC after treatment. This representation is more accurate physiologically and shows that the degree of improvement after treatment is even greater than conventional data suggest (Table V). Vertical line at TGV = 60% of control TLC = 5 liters shows volume level at which $\dot{V}_{max}$ at 60% TLC was measured.

TABLE V

Measurements from MEFV Curves in Subject F (Fig. 7)

Date	Curve	Condition	TLC	VC	$FEV_{1.0}$	$\dot{V}_{max}$ at TGV = 5 liter	$\dot{V}_{max}$ at 50% VC	Gaw/TGV*
			liters	*liters*	*liters*	*liters/sec*	*liters/sec*	
7/28	1	Control	8.5	3.7	1.4	0.2	1.4	0.059
7/28	2	iso.‡	7.5	4.5	2.1	1.5	1.6	0.062
8/24	3	Control	7.2	4.9	2.6	2.9	2.4	0.139
8/24	4	iso.‡	7.2	5.3	3.4	3.4	3.3	0.165

* Gaw/TGV = ratio of airway conductance/thoracic gas volume (panting); units: $(cm\ H_2O \times sec)^{-1}$.
‡ Curves 2 and 4, with corresponding data, were obtained 30 min after inhalation of an isoproterenol-phenylephrine mixture (Medihaler-Duo).

increased in patients with asthma, and that it may decrease when their clinical condition improves. They pointed out that such TLC changes would affect the interpretation of changes in expiratory flow rates and $FEV_{1.0}$. In our study, the reverse change, i.e., increase of TLC after acute administration of bronchoconstrictor agents, was small, and absent in two subjects. Increases of this magnitude might be caused by trapping of air in some lung areas, so that pressures in these areas do not contribute to mouth pressure during panting. Under those conditions, the plethysmograph would see the compressional volume changes (ΔV box) in all lung areas, but the mouth pressure measurement (ΔP) would reflect only pressure changes in areas which communicate with the mouth. Since $TGV = P_{atm} \times (\Delta V/\Delta P)$, this would result in overestimation of TGV. However, such an effect cannot account for TGV increases of more than about 0.2 liters, even when the trapped volume is large. However, we observed one patient (F), with severe but reversible bronchial obstruction, in whom large TLC changes occurred (Fig. 7 and Table V; clinical details in figure legend). TLC decreased 1.3 liter during 4 wk bronchodilator treatment, and most of this change occurred acutely after the first isoproterenol inhalations. All expiratory flow data in patient F reflected the major degree of improvement in his condition. However, the changes of his MEFV curves are most impressive when the curves are plotted on an absolute volume scale (in liters TGV; Fig. 7, lower diagram): $\dot{V}_{max}$ at 60% TLC increases 17-fold, compared with a 2.5-fold increase of $FEV_{1.0}$ and of airway conductance (panting) (Table V). In this patient, the choice of the volume level for flow readings, i.e., 60% of the control TLC, was particularly important. The lower graph in Fig. 7 identifies this level by a vertical line at TGV = 5 liters. The change of $\dot{V}_{max}$ at 50% VC is not as pronounced, since this measurement uses a floating volume level.

In our experiments flow rates on PEFV curves were more sensitive in showing bronchoconstriction than flow rates at comparable volumes on MEFV curves. In part this may reflect inhibition of bronchoconstrictor effects by the deep inspiration required for the MEFV curve (5). An increase of resistance induced by deep expirations (12, 23) may also play a role. Although both the PEFV and MEFV maneuvers were preceded by expiration to RV, such an effect may be abolished by the maximum inspiration of the MEFV maneuver. However, the effects of flow and volume history on maximum expiratory flow rates are complex (12), and how these are affected by bronchial smooth muscle tone, airway wall hysteresis, and stress relaxation is not well understood.

Interpretation of PEFV curves requires measurement of TGV to establish their volume level. For MEFV curves, the absolute volume scale can be obtained from separate measurements of TGV and TLC. This makes MEFV curves simpler to obtain in practice, and the changes of flow rates on MEFV curves are sufficiently pronounced for most clinical purposes. Preliminary normal values for $\dot{V}_{max}$ at 60% TLC are available for healthy children (25), and these have proven useful in studies of children with cystic fibrosis and bronchial asthma (26, and unpublished data). Until sufficient data on healthy adults are available, the measurement of $\dot{V}_{max}$ at 60% TLC may be helpful in detecting changes of MEFV curves during treatment, using the patient as his own control.

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