

Site of Airway Obstruction in Asthma as Determined by Measuring Maximal Expiratory Flow Breathing Air and a Helium-Oxygen Mixture

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ABSTRACT Because maximum expiratory flow-volume rates in normal subjects are dependent on gas density, the resistance between alveoli and the point at which dynamic compression begins (R_{us}) is mostly due to convective acceleration and turbulence. We measured maximum expiratory flow-volume (MEFV) curves in asthmatics and chronic bronchitics breathing air and He-O₂. In the latter and in some asthmatics, MEFV curves did not change, indicating that R_{us} is mostly due to laminar flow. Therefore, the point at which dynamic compression begins must be further upstream than in normal subjects and the site of obstruction must be in small airways. In other asthmatics, flow increased normally indicating obstruction in larger airways. The response to He-O₂ did not correlate with initial values of pulmonary resistance, the initial MEFV curves or the response to bronchodilators. We conclude that the site of airway obstruction varies among asthmatics and that the site of obstruction is not detectable by measurement of the usual parameters of lung mechanics.

INTRODUCTION

The site of airway obstruction in most patients with chronic obstructive lung disease is in airways less than 2–3 mm in diameter (1). Less is known about the site of airway obstruction in asthmatics. Bronchography indicates that central airways may be constricted (2–4) during an acute attack, while in remission there is evidence that considerable obstruction may affect peripheral airways (5–7).

Examination of the effects of altered gas density on the maximum expiratory flow-volume (MEFV)¹ curve

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¹Abbreviations used in this paper: A_{EPP} , cross-sectional area at EPP; EPP, equal pressure points; FRC, functional

may be a simple way of defining the site of airway obstruction in asthmatics. According to Mead maximum expiratory flow rate at a particular lung volume is determined by the elastic recoil pressure of the lung at that volume and the resistance of the airways between the alveoli and the points where the lateral intraluminal pressure equals pleural pressure (equal pressure points, EPP). This resistance is defined as the upstream resistance (R_{us}) (8). If EPP are in large airways most of R_{us} will be due to convective acceleration and turbulence. Because pressure losses due to both of these are dependent on gas density, changes in gas density will alter R_{us} and thus maximum expiratory flow. This is the case in normal subjects: EPP are in large airways at lung volumes above 40% vital capacity (VC) (9) and maximum expiratory flow rates over these lung volumes are density dependent (10–12). In the presence of airway obstruction in small airways, EPP will be further upstream (toward the alveoli) than in normal subjects and maximum expiratory flow will be less density dependent than normal to the extent that the resistance to laminar flow (which is independent of gas density) makes up a greater portion of the total resistance upstream from EPP. Obstruction in larger airways might have a lesser influence on the normal response to a change in gas density.

Previous studies in patients with airway obstruction reveal a marked variation in the changes in dynamic lung function that occur when gas density is altered (13–16). The variation is not obviously related to the

residual capacity; MEFV, maximum expiratory flow-volume; P_{ca} , pressure drop due to convective acceleration; $P_{st}(l)$, elastic recoil pressure of the lung; R_{ca} , resistance due to convective acceleration; R_{fr} , frictional resistance to airflow; R_L , pulmonary resistance; R_{us} , upstream resistance; RV, residual volume; TLC, total lung capacity; VC, vital capacity; V_{max50} , maximum expiratory flow at 50% vital capacity.

TABLE I
Physical Characteristics and Lung Function of Patients Studied

Subject	Age	Sex	Height	VC	FRC	RV	TLC	R _L cm H ₂ O/liters per sec	
								Before bronchodilator	After bronchodilator
	yr		cm		% predicted‡				
Asthma responders									
Bou	38	M	154	85	148	193	117	7.5	4.0
				101	126	150	117	6.5	5.0
Mar	35	M	172	83	156	219	119	10.0	4.8
Hec	43	F	167	100	110	139	111	8.0	5.0
Kru	29	M	175	84	108	132	95	12.0	3.0
				100	—	—	—	3.8	—
Pre	54	F	163	91	100	113	100	5.5	3.8
				92	120	153	112	2.3	—
Lew	23	F	161	100	122	128	112	1.9	1.5
Sis	32	M	170	75	126	170	100	5.5	2.0
				77	137	189	108	3.8	1.7
				77	163	252	120	9.8	3.8
Ste	28	M	168	87	90	59	99	3.0	1.5
McC	50	F	165	63	186	260	128	15.0	7.5
				103	—	—	—	6.3	3.7
Hen	15	M	160	91	109	101	99	2.8	2.7
Des	54	M	170	100	114	131	111	6.0	4.0
Sal	25	M	165	86	90	123	103	5.0	1.8
Asthma Nonresponders									
Jac	45	M	170	88	166	220	131	4.1	2.5
Bro	24	M	170	69	163	252	117	12.0	4.5
Loi	35	M	170	100	86	102	97	2.3	2.0
His	67	M	170	86	105	122	106	4.8	2.8
Has	28	M	162	95	93	101	100	5.0	—
				107	110	107	107	2.0	—
Dum	50	F	163	65	211	330	160	9.5	4.0
Hol	59	F	165	78	169	213	129	5.5	4.0
Cup	30	M	177	99	136	180	121	6.0	4.0
				110	118	120	124	4.7	3.0
Dal	46	M	173	86	117	143	106	5.0	3.0
Alt	45	M	178	91	111	128	103	6.0	4.0
Eva	44	F	158	75	178	242	250	7.0	3.8
Bar	35	M	162	100	125	242	139	4.3	2.0
O'K	60	M	167	100	185	224	149	12.0	5.5
				137	170	177	150	3.5	2.6
Irreversible airway obstruction									
*	63.4		166	67	136	180	110	5.80	
Normal									
*	29.7		175	102	101	92	104	1.9	

VC, vital capacity; FRC, functional residual capacity; TLC, total lung capacity; RV, residual volume; R_L, pulmonary resistance.

* Mean values.

‡ Predicted values from Bates, Macklem, and Christie (25).

severity of the airway obstruction or to the type of obstructive lung disease. Barnett (17) suggested that the site of airway obstruction may be an important deter-

minant of the effects of gas density on dynamic lung function. The laws of aerodynamics as they apply to the airways support this suggestion and he showed that with

tracheal obstruction, pulmonary resistance was density dependent but when obstruction was in peripheral airways the resistance was not density dependent (17).

Stimulated by Barnett's observations, we have studied the effects of 20% oxygen in helium on the MEFV curves and pulmonary resistance (R_L) in asthmatics. These effects were compared with those obtained in normal subjects and in patients with irreversible airways obstruction. The mixture's density is only 36% that of air but it is 12% more viscous.

METHODS

We studied 25 asthmatics with significant reversible airway obstruction who had been repeatedly studied in the routine laboratory. Most were symptomatic when we studied them and had a significant reduction in pulmonary resistance immediately following a bronchodilator aerosol (Table I). We also studied seven patients with irreversible airway obstruction. They had chronic bronchitis and dyspnea and showed little change in the degree of airway obstruction over several years. The control group were normal, nonsmoking subjects and included medical and laboratory staff.

While the subjects were breathing air we measured the subdivisions of lung volume, the static deflation pressure volume curve of the lung, pulmonary resistance at functional residual capacity (FRC), and the maximal expiratory flow-volume curves. Change in lung volume was measured by a Krogh spirometer attached to the body plethysmograph. Absolute lung volume was obtained by the gas compression technique based on Boyle's law (18). The static deflation pressure volume curve of the lung was obtained by plotting transpulmonary pressure (as assessed by the difference between mouth and esophageal pressure) during 1-2-sec periods of zero-airflow, against lung volume on deflation to residual volume (RV) after a full inspiration to total lung capacity (TLC). Esophageal pressure was measured by an esophageal balloon catheter (balloon length 10 cm, circumference 3.5 cm, volume 0.5 ml of air, catheter PE 200 tubing 60 cm long) coupled to a Sanborn 267B differential pressure transducer (Sanborn Div., Hewlett-Packard Co., Waltham, Mass.), the other side of which was connected via a catheter to the mouthpiece. Pulmonary resistance during inspiration (R_L) was taken as the ratio of the component of transpulmonary pressure in phase with inspiratory flow to flow during tidal breathing. Flow was measured by a Fleisch pneumotachograph coupled to a Sanborn 270 differential pressure transducer. The component of transpulmonary pressure in phase with flow was measured by subtracting from transpulmonary pressure a signal proportional to lung volume, so that the pressure flow loop, as displayed on the x - y coordinates of a long persistence display oscilloscope, became a line (19). The slope of this line as it passed through zero flow was read directly by a rotatable overlying grid and gave us inspiratory pulmonary resistance. The MEFV curves were obtained by displaying flow against volume on the x - y coordinates of a Tektronix 564 storage oscilloscope (Tektronix, Inc., Beaverton, Ore.) during forced expiration from TLC to RV. Each MEFV curve was repeated several times and curves that were not highly reproducible were rejected. After completing these measurements the subject breathed a 20% oxygen in helium mixture for 10 min, when R_L and MEFV curves were

measured again. Breathing helium oxygen does not influence the static pressure volume curves of the lung (13), so that the vital capacity was unchanged in any subject. Furthermore no changes in FRC were detected. The curves were stored and traced with an oscillotracer (R. A. Waters Co., Waltham, Mass.). Pressure, flow, and volume were also recorded on a four-channel direct writing Sanborn recorder.

The body plethysmograph was pressure compensated and had a frequency response adequate to 8 counts/sec. It was calibrated with a calibrating syringe of 500 ml capacity for large volume recordings and with a 50 ml syringe for small volume recordings. The pressure transducers were calibrated with water manometers. The pneumotachograph was calibrated for air and for the He-O₂ by passing the gases through the pneumotachograph which was coupled by 2 inch diameter smooth bore tubing to a 120 liter Tissot spirometer. The pneumotachograph resistance was linear for both gases up to flow rates of 6 liters/sec.

RESULTS

Results obtained in the lung function tests for the three groups of subjects are given in Table I. The asthmatics were further subdivided into responders and nonresponders according to their change in maximum expiratory flow when they breathed He-O₂ (see below). Mean values only are reported for the normal subjects and those with irreversible airway obstruction. Among asthmatics R_L was increased in all but one subject (Lew) either at the initial study or at a subsequent study. R_L was markedly increased in several subjects.

MEFV curves. There was a substantial increase in maximum expiratory flow rates in all normal subjects breathing He-O₂ compared with the curves obtained when they were breathing air. The increase was in good agreement with the data of Wood and Bryan (10). Only one patient with irreversible airway obstruction increased his maximum expiratory flow rates. The others demonstrated no change. The asthmatic subjects fell into two groups. In twelve there was an increase in maximum expiratory flow rates comparable to the increase observed in normal subjects. In 13 there was little or no increase in maximum expiratory flow, the response to He-O₂ being similar to that observed in irreversible airway obstruction. Representative MEFV curves from each group are shown in Fig. 1. Those asthmatics in whom maximum expiratory flow at 50% vital capacity (V_{max50}) increased less than 20% in He-O₂ were classified as nonresponders and those in whom V_{max50} increased by more than 20% were classified as responders. In normal subjects V_{max50} increased by a mean value of $48\% \pm 11.7$ (SEM); in patients with irreversible airway obstruction V_{max50} increased by a mean value of $13.0\% \pm 32.6$ (SEM). The large standard error in this group is due to one subject who increased V_{max50} by 85%. The others ranged between +12 and -13%. In responders V_{max50} increased by $53.5\% \pm 19.7$ (SEM), and in nonresponders V_{max50} increased by $1.5\% \pm 5.25$ (SEM). Among asthmatics there was no cor-

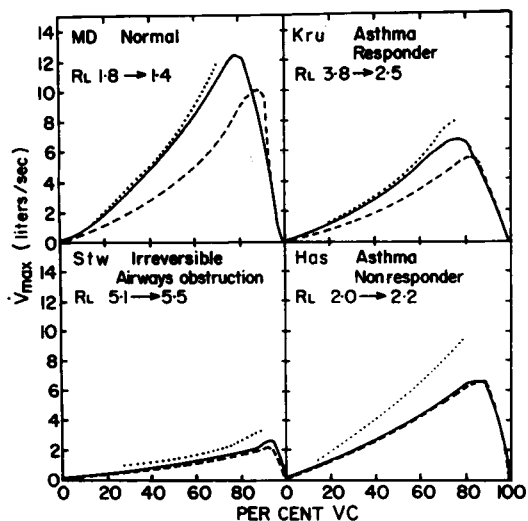


FIGURE 1 Representative maximum expiratory flow-volume curves for the four groups of subjects. ---- MEFV curves on air; — MEFV curves on He-O₂; ···· predicted MEFV curves on He-O₂ from the data of Wood and Bryan assuming that $V_{max} \propto (\text{density})^{-0.5}$ (10). Values for pulmonary resistance (R_L) in cm H₂O/liters per sec breathing air and breathing He-O₂ are given for each case.

relation between the change in V_{max50} and the severity of the obstruction as assessed either by the initial values for V_{max50} or for pulmonary resistance, R_L (Figs. 2 and 3).

Pulmonary resistance. In normal subjects breathing He-O₂, pulmonary resistance fell to $77\% \pm 17.9$ (SEM) of the value breathing air; in patients with irreversible airway obstruction these measurements were made in only five of the seven subjects. In these subjects when breathing He-O₂, the resistance was 100% of the value breathing air; in responders, pulmonary resistance fell to

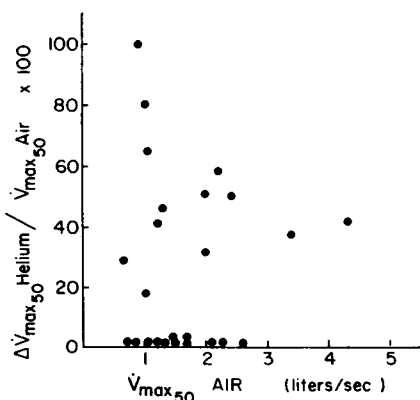


FIGURE 2 Per cent increase in maximum flow at 50% VC (V_{max50}) induced by breathing He-O₂ (ordinate) plotted against the initial V_{max50} breathing air (abscissa) in asthmatics.

$73\% \pm 25.5$ (SEM) of the air value; in nonresponders it was $90\% \pm 22$ (SEM).

Although the change in pulmonary resistance with gas density was similar to the change in V_{max50} when the groups were compared, there were several striking individual exceptions to this within each group accounting for the larger standard errors. There were three normal subjects in whom the R_L when breathing He-O₂ was greater than 90% of R_L when breathing air but in whom V_{max50} increased by 35–61%. By contrast, among the patients with irreversible airway obstruction there was one in whom R_L when breathing He-O₂ was only 68% of the R_L when breathing air, whereas V_{max50} increased only 7% in response to He-O₂. These two patterns were reflected among the responders and nonresponders. In the former group, there were three subjects in whom there was either no change or a slight increase in R_L when breathing He-O₂ but in whom V_{max50} increased 34–80%. In the latter group, there were three subjects in whom R_L on He-O₂ was 42, 67, and 73% of the value

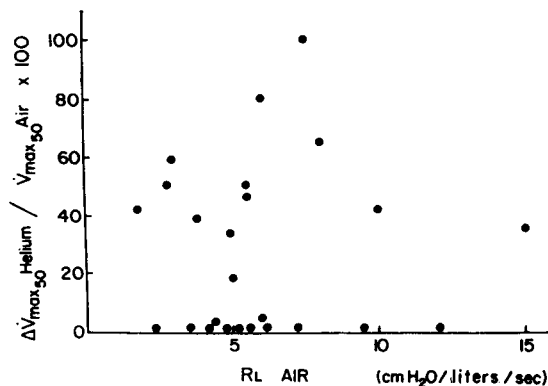


FIGURE 3 Per cent increase in V_{max50} induced by breathing He-O₂ (ordinate) plotted against the initial pulmonary resistance (R_L) breathing air (abscissa) in asthmatics.

on breathing air but in whom there was no change in V_{max50} . Among asthmatics there was no correlation between the severity of the obstruction as assessed either by the initial values of V_{max50} or R_L and the change in R_L between air and He-O₂ (Figs. 4 and 5).

Upstream resistance. By plotting maximum expiratory flow against the static deflation elastic recoil pressure at equal lung volumes, the pressure-flow curve for the airways upstream from EPP is obtained (8). From these curves the relationship between lung volume and R_{us} may be obtained. This is plotted in Fig. 6 for the responders and the nonresponders. It appears that the shape of the R_{us} vs. VC curve is different between responders and nonresponders. In nine of the 12 responders, R_{us} decreased as lung volume decreased over at least part of the vital capacity range. The mean value for R_{us} was essen-

tially unchanged between 50% VC and the highest lung volume at which R_{us} was recorded in each subject, as it changed only by $+0.008$ cm H₂O/liters per sec/per cent VC. In only four of 11 nonresponders, R_{us} decreased as volume decreased over a part of the vital capacity. In all others R_{us} increased as volume decreased. In contrast to the responders, the mean R_{us} increased by 5.5 cm H₂O/liters per sec/per cent VC between the highest lung volume at which R_{us} was recorded and 50% VC in each subject.

Three nonresponders and five responders were studied on more than one occasion. Although the severity of their asthma was substantially different during the different studies, the pattern of response was always the same in that the responders remained responders and nonresponders remained nonresponders (Fig. 7). As the asthmatics as a group were selected on the basis of demonstrable improvement in their obstruction resulting from bronchodilator therapy, the responders and nonresponders

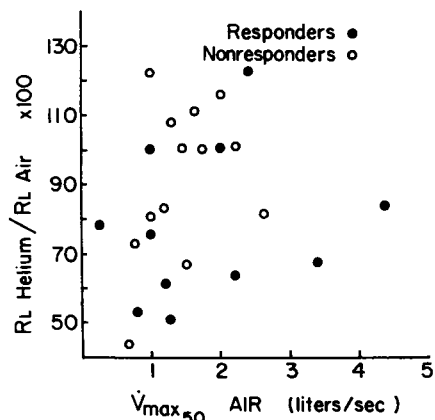


FIGURE 4 Pulmonary resistance breathing He-O₂ as a percentage of that breathing air (ordinate) plotted against the initial value for \dot{V}_{max50} breathing air (abscissa) in asthmatics.

could not be distinguished on this basis. Similarly, there did not appear to be any difference in the degree of wheezing between the two groups although this was specifically looked for.

DISCUSSION

It is apparent that the responders behaved in a qualitatively similar way to normal subjects when gas density was altered. Maximum expiratory flow rates increased and pulmonary resistance decreased. Furthermore, in both normals and responders there were the same paradoxical responses in which increased maximal expiratory flow rates were observed with little or no change in R_L . Finally, in both groups R_{us} tends to increase at lung volumes above 50% VC (8).

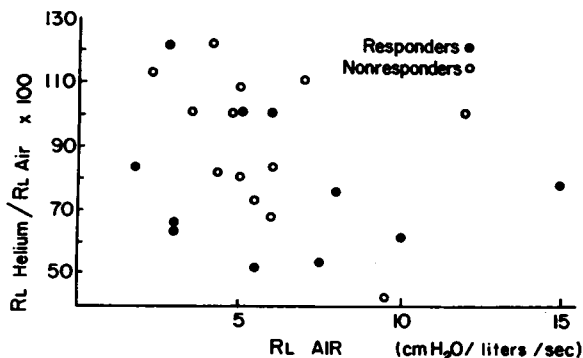


FIGURE 5 Pulmonary resistance breathing He-O₂ as a percentage of that breathing air (ordinate) plotted against the initial value of R_L breathing air (abscissa) in asthmatics.

The nonresponders behaved similarly to patients with irreversible airway obstruction when gas density was altered. Neither maximum expiratory flow nor R_L was much changed. In both nonresponders and patients with irreversible obstruction paradoxical responses occurred in which there was no increase in maximum expiratory flow, but there was a substantial reduction in R_L . R_{us} tended to decrease at lung volumes above 50% VC in the nonresponders.

The similarity between responders and normal subjects on one hand and between nonresponders and patients with irreversible airway obstruction on the other is circumstantial evidence that the mechanisms limiting maximum expiratory flow were also similar between normal subjects and responders and between patients with irreversible airways obstruction and nonresponders.

Maximum expiratory flow at any lung volume is equal to the ratio of lung elastic recoil at that volume, to the resistance of airways upstream from equal pressure points (8). This is expressed in the following relationship:

$$\dot{V}_{max} = \frac{P_{st}(l)}{R_{us}}$$

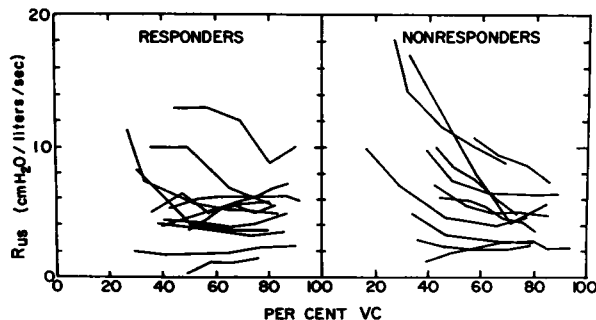


FIGURE 6 Relationship between resistance upstream from equal pressure points (R_{us}) and lung volume expressed as per cent VC in responders and nonresponders.

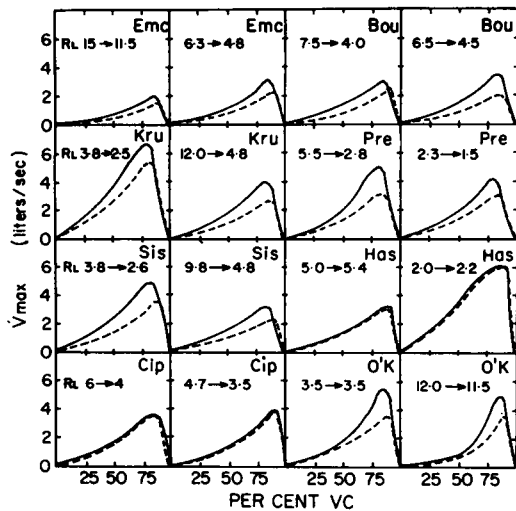


FIGURE 7 MEFV curves on separate occasions in eight asthmatics. ---- Breathing air; — breathing He-O₂. Values for R_L breathing air and breathing He-O₂ are given in each case.

where $P_{st}(1)$ is the elastic recoil pressure of the lung at the particular lung volume. Because change in gas density does not influence the static pressure-volume relationships of the lung, any change in V_{max} must be due to a change in R_{us} . When V_{max} did not change with gas density, R_{us} must have been independent of density.

R_{us} is the sum of two components, the frictional resistance to airflow (R_{fr}) and the resistance due to convective acceleration (R_{ca}) between alveoli and EPP. R_{ca} is given by the following relationship:

$$R_{ca} = \frac{P_{ca}}{\dot{V}_{max}} = \frac{K \cdot \rho \dot{V}_{max}}{2g \cdot A_{EPP}^2}, \quad (1)$$

where P_{ca} is the pressure drop due to convective acceleration, K is a constant relating to the velocity profile, ρ is gas density, g is the acceleration due to gravity, and A_{EPP} is the cross-sectional area at EPP.

Rearranging,

$$\dot{V}_{max} = \left(\frac{2g \cdot P_{ca}}{K \cdot \rho} \right)^{0.5} \cdot A_{EPP} \quad (2)$$

Thus if all other variables remain constant and $R_{ca} \gg R_{fr}$, V_{max} is proportional to $\rho^{-0.5}$. R_{fr} is the sum of a laminar and turbulent component. If the turbulent component were much greater than the laminar component and $R_{fr} \gg R_{ca}$, then V_{max} would be proportional to $\rho^{-0.48}$ (8). If both the turbulent component of R_{fr} and R_{ca} contributed substantially to R_{us} , V_{max} would be proportional to gas density to a power ranging between -0.5 and -0.43 . This would result in an increase of 56–70% in V_{max} on switching from air to He-O₂. The responders in-

creased V_{max50} by 53.5%, indicating that the laminar component of R_{us} was relatively small and that most of the resistance upstream from EPP was either due to convective acceleration or turbulence or both.

The lack of response to He-O₂ among the nonresponders indicates that R_{us} is not density dependent in this group. Thus, neither turbulence nor convective acceleration, nor even the density-dependent formation of parabolic velocity profile (20) contributes substantially to R_{us} . Flow upstream from EPP must have been almost entirely fully developed laminar flow, in which for a given pressure drop, flow is inversely proportional to viscosity and independent of density. If the total R_{us} was composed of fully developed laminar flow we would have expected to see a 12% fall in maximum expiratory flow rates because of the higher viscosity of the He-O₂ mixture. This was not observed. Schilder, Roberts, and Fry (11) observed a decrease in flow at very low lung volumes in normal subjects breathing He-O₂ as compared with air. This may have been present in our normal subjects as well, but because we were particularly interested in the effects at higher lung volumes we did not look for it and thus lacked sensitivity to detect small changes at low flow rates. On the other hand reference to Figs. 4 and 5 reveals that four nonresponders and one responder increased R_L by 10–20% breathing He-O₂, which is consistent with pulmonary resistance being directly proportional to viscosity in these subjects.

The essential difference between the responders and the nonresponders then is a difference in the components of R_{us} . R_{us} in responders is similar to that in normal subjects and at high lung volumes is principally made up of convective and turbulent components. In nonresponders R_{us} is similar to that in subjects with irreversible airway obstruction and is principally due to fully developed laminar flow.

Do known differences in airway dynamics between normal subjects and patients with irreversible airway obstruction shed light on the cause of the differences between responders and nonresponders? Because EPP are at the level of segmental or lobar bronchi, in normal lungs where the cross-sectional area at equal pressure points approximates to the trachea, R_{ca} is the major component of R_{us} at high lung volumes (9, 21). The density-dependent component of R_{fr} is presumably larger than it would be if EPP were further upstream, because R_{us} contains airways with higher Reynold's numbers in which fully developed laminar flow would be the exception rather than the rule. This accounts for the density dependence of maximum expiratory flow in normal subjects (10, 12).

In patients with chronic bronchitis and emphysema, there is obstruction in peripheral airways smaller than 2 mm diameter (1). This results in an upstream move-

ment of EPP into airways where the total cross-sectional area at equal pressure points is presumably substantially increased. Because R_{ca} is inversely proportional to the square of this cross-sectional area and because V_{max} is greatly reduced, one would predict that R_{ca} would become small (see equation 1). In order for the density-dependent component of R_{tr} to become small as well it would seem likely that the upstream motion of EPP would have to be quite considerable indeed, but one cannot state exactly how far. Thus, in order to account for density independence of maximum flow it is necessary to postulate peripheral airway obstruction with EPP situated where the total cross-sectional area at EPP is large and the flow upstream is laminar and fully developed. The upstream displacement of EPP is consistent with what is known about airway dynamics in irreversible airway obstruction (22).

We suggest that the nonresponders were similar to the patients with irreversible airway obstruction and that EPP were in airways where the total cross-sectional area was large and the flow upstream laminar. We suggest that this was due to obstruction in small airways.

The responders had a similar degree of airway obstruction as assessed by R_L and V_{max50} . In spite of this, we suggest that the site of obstruction was different and was located in larger airways so that EPP did not move so far upstream, with the result that the cross-section at EPP was sufficiently small so that R_{ca} was a large component of R_{us} or the flow upstream was turbulent or both. Our data do not permit us to determine the exact location of EPP, but if R_{ca} were substantial there may well have been bronchoconstriction at the site of EPP. We return to this point later.

If these considerations are correct, the site of obstruction in asthma is different in different individuals, being located in small airways in some and in larger airways in others. Because responders do not appear to become nonresponders and vice versa, it appears likely that the site remains fixed in any given asthmatic although a more prolonged longitudinal study would be necessary to make this statement unequivocally.

Our conclusions are consistent with the experimental evidence published by Barnett (17). He found that the resistance produced by obstruction in a large airway (the trachea) was decreased when He-O₂ was breathed compared with air, whereas when the obstruction was more peripheral, induced by histamine, the resistance was essentially independent of gas density. Vagal stimulation produced an intermediate response.

How can our conclusions and Barnett's observations be reconciled with the paradoxical responses that we observed? Among the responders and the normal subjects there were individuals in whom R_L did not change, but in whom there were substantial increases in maximal

expiratory flow. During the measurements of R_L the subjects were breathing quietly. Resistance due to convective acceleration is not a component of R_L . Thus any response to He-O₂ must have been due to density dependence of the frictional resistance of the airways. If the frictional resistance was principally due to laminar flow, very little density dependence would be apparent. During forced expirations, however, R_{ca} does contribute to R_{us} and is directly proportional to density (equation 1). The paradoxical finding that V_{max50} increased while R_L remained unchanged may be explained if R_{ca} was a major component of R_{us} but in the absence of dynamic compression during the measurement of R_L (to which R_{ca} does not contribute) flow was essentially laminar through those airways with the highest resistance. If this were the case it seems likely that the cross-sectional area at the site of EPP, where the transmural pressure across these airways is presumably close to zero, would have to be substantially less than it is during quiet breathing when these airways are distended. This might well be consistent with an increase in bronchomotor tone at this site.

The other paradoxical response (a decrease in R_L without substantial change in V_{max50}) also requires explanation. An increase in the tone of large airways makes them less compressible but increases their resistance to airflow (23). During quiet breathing at a given flow rate, this would increase the Reynold's numbers, and the degree of turbulence within them, which would render the frictional resistance more density dependent. Because they are less compressible, however, EPP would move further upstream so that R_{us} would not contain the frictional resistance of these airways. Thus, the paradoxical change in R_L without much change in V_{max50} would be explained if EPP were located upstream from narrowed airways whose frictional resistance was density dependent and contributed substantially to R_L but not at all to R_{us} .

A curious finding among most responders, similar to that in normal subjects was, that R_{us} increased as lung volume increased above 50% VC (Fig. 6). In normal subjects this has been attributed to changes in R_{ca} with lung volume. As volume decreases, EPP move upstream so that the cross-sectional area at EPP increases. Furthermore, as volume decreases V_{max} decreases. Both of these will result in a decrease in R_{ca} as volume decreases (equation 1). If a similar mechanism were operating in the responders to account for the change in R_{us} with volume, the contribution of R_{ca} to R_{us} would have to be large. Because V_{max} was markedly reduced, the cross-section at EPP would also have to be reduced in order for R_{ca} to be large. Mead, Turner, Macklem, and Little plotted V_{max} against $P_{s(1)}$ at the same lung volumes to obtain pressure-flow curve of the airways upstream from EPP. They also plotted isopleths of R_{ca} using different

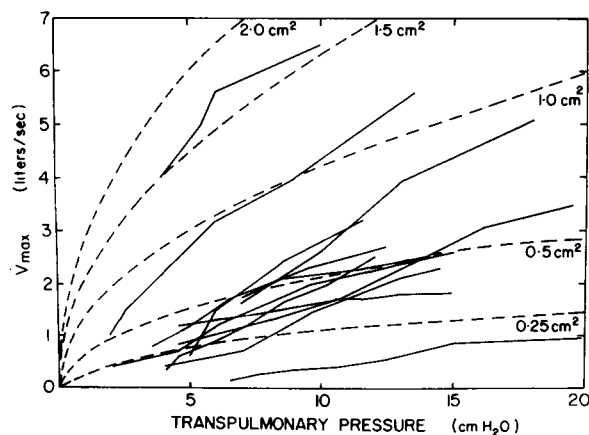


FIGURE 8 Relationship between \dot{V}_{\max} and static elastic recoil pressure breathing air in responders. Dashed lines are the graphical solution of the equation

$$\dot{V}_{\max} = \left(\frac{2g \cdot P_{ca}}{K\rho} \right)^{0.5} \cdot A_{EPP}$$

for different values of A_{EPP} (given at the end of each isopleth) constructed assuming that P_{ca} equals the static recoil pressure.

assumed values for the cross-section at EPP. They found that the curve relating maximal flow to static recoil became asymptotic to the one or other of the R_{ca} isopleths. They suggested that if $R_{ca} \gg R_{tr}$, the isopleth to which the curve became asymptotic would give the cross-sectional area at EPP in each subject. Cross-sectional areas so determined correlated well with the cross-sectional area of the trachea in their subjects (8).

Similar curves in the responders are shown in Fig. 8. If the decrease in R_{us} with an increase in volume is due to the same mechanism as in normals, the cross-sectional area at EPP would in most cases fall between 1.0 and 0.25 cm^2 . In normal subjects the cross-section at EPP ranged between 1.1 and 2.7 cm^2 (8). Thus in responders the cross-section at EPP would have to be substantially smaller than the diameter of the trachea, but this is feasible given an increase in bronchomotor tone.

The alternative explanation for the change in R_{us} with volume is a fall in R_{tr} as volume decreases. This could in part be due to the decrease in flow if R_{tr} was turbulent but it does not seem likely that this could account for all of the change. It has recently been shown that airway resistance increases in humans and dogs at high lung volumes, although the mechanism for this is obscure (24). If this were present in asthma to a greater degree than normal then this could account for the change in R_{us} . If so one might expect to see similar curves in nonresponders, but this was not the case (Fig. 6). For this

reason we favor the explanation that the cross-sectional area at EPP in asthmatics who respond to He-O_2 , is substantially smaller than the trachea, that this reduction is due to bronchospasm and that it results in a resistance to convective acceleration that is a major component of the upstream resistance even though flow rates are markedly reduced.

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