Relative Contributions of Large and Small Airways to Flow Limitation in Normal Subjects before and after Atropine and Isoproterenol

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ABSTRACT Bronchodilatation was produced in normal subjects by the inhalation of atropine, a parasympatholytic agent, and isoproterenol, a beta adrenergic stimulator. Density dependence of maximal expiratory flow ($\dot{V}_{max}$), expressed as a ratio of $\dot{V}_{max}$ with an 80% helium-20% oxygen gas mixture to $\dot{V}_{max}$ with air at isolung volumes, indicated that the predominant flow regimes across upstream airways changed differently after each agent was given separately. After atropine $\dot{V}_{max}$ increased, elastic recoil pressure did not change, and density dependence decreased. Utilizing the equal pressure points analysis which defines upstream and downstream segments of the intrathoracic airways at flow limitation, these results suggest a greater relative dilatation of the larger upstream airways such that more of the driving pressure is dissipated across the smaller airways in which flow is less dependent upon gas density. After isoproterenol $\dot{V}_{max}$ increased, elastic recoil pressure did not change, and density dependence increased. This suggests a preferential dilatation of the smaller and more peripheral airways with less density-dependent flow regimes such that more of the driving pressure would be dissipated in the larger airways in which flow is more dependent upon gas density. Systematic decreases in critical alveolar pressures after atropine and increases after isoproterenol lead independently to the same conclusion. After both agents together, $\dot{V}_{max}$ increased and density dependence and critical alveolar pressures did not change from control, suggesting a relatively uniform dilatation of all the airways comprising the upstream segment.

INTRODUCTION

Both atropine and isoproterenol dilate the airways of normal subjects. Widdicombe and associates (1) reported a 42% increase in specific airway conductance after subcutaneous atropine, and Severinghaus and Stupfel (2) demonstrated a 29–47% increase in anatomic dead space after this agent. Aerosolized isoproterenol also increases specific airway conductance and maximal expiratory flow ($\dot{V}_{max}$)[1] (3, 4). Thus, there exists bronchial smooth muscle tone that can be lessened with therapeutic agents in normal subjects. To determine the influence of the autonomic nervous system on the distribution of airway resistance, Woolcock et al. (5), utilizing the retrograde catheter technique in dog lungs, demonstrated that bronchomotor tone is the result of a balance between parasympathetic and sympathetic influences. In this study, stimulation of the parasympathetic nervous system exerted a constricting influence at all levels of the tracheobronchial tree, but its effect on peripheral airways was inhibited by an intact sympathetic system. Since atropine blocks postganglionic cholinergic neural pathways and isoproterenol acts directly on bronchial smooth muscle by beta adrenergic stimulation, it is plausible that these different neuropharmacological agents might produce a relatively different distribution

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[1] *Abbreviations used in this paper:* EPP, equal pressure points; HeO_2, 80% helium–20% oxygen; IVPF, isovolume pressure flow; Palv', critical alveolar pressure; Pst(1), static elastic recoil pressure; Rus, resistance of upstream airways segment at maximal flow; $\dot{V}_{max}$, maximal expiratory flow.

of bronchodilatation. Thus, atropine might tend to have more influence on the larger, central airways and isoproterenol might tend to exert more influence in the smaller, more peripheral airways. This present study was designed to explore the site of bronchodilatation that was produced in normal subjects by these agents.

METHODS

Seven normal subjects between the ages of 23 and 32 yr were studied after obtaining informed consent. All flow and volume measurements were made in an air-conditioned, integrated flow, pressure-corrected whole body plethysmograph (6). The volume signal was statically calibrated before each set of measurements, and the signal was pressure corrected by means of shaping a rapid step input of volume (6). Flow at the mouth was measured using a no. 4 Fleisch pneumotachograph (Dynamic Science Medical Products, Blue Ball, Pa.) with a Hewlett-Packard 270 differential pressure transducer (Hewlett-Packard Co., Palo Alto, Calif.). The pneumotachograph was linearized in the expiratory direction according to Finucane et al. (7), and calibrated by passing gas mixtures through it at a wide range of flows. Maximal expiratory flow volume curves were obtained breathing air and after the washin of an 80% helium-20% oxygen (HeO_2) gas mixture. The HeO_2 washin was judged complete when the end-tidal nitrogen concentration was less than 3% as measured by a Med-Science 300 AR Nitralyzer (Med-Science Electronics, Inc., St. Louis, Mo.). The maximal expiratory flow volume curves were displayed as the *x-y* coordinates of a storage oscilloscope and then photographed. The curves with the highest maximal flows whose vital capacities on air and HeO_2 matched exactly were chosen. The degree of density dependence of $\dot{V}_{max}$ was assessed as the ratio of $\dot{V}_{max}$ HeO_2 to $\dot{V}_{max}$ air at the same lung volume. Identical lung volumes were assured only if the vital capacities on the two gases matched within the reader error of 50 ml. Boyle's law technique was used to determine thoracic gas volume at the end of a normal tidal inspiration before the maximal expiratory flow volume maneuvers so that all lung volumes would be obtained. Intraesophageal pressure was used as an estimate of pleural pressure as measured by the technique of Milic-Emili et al. (8). Transpulmonary pressure was recorded as the difference between mouth pressure and pleural pressure by a Hewlett-Packard 268B differential pressure transducer. Static deflational pressure-volume curves were obtained on each subject in triplicate.

After control measurements, each subject inhaled either 0.6 mg of atropine sulfate or 2.5 mg of isoproterenol, or both agents given together. Only one study was performed per day. Larger doses were given to three subjects, and the results were not found to be significantly different from those seen with amounts stated above. All aerosols were generated using the same nebulizing unit, driven by a Bennett PR-2 pressure-cycled respirator (Bennett Respiration Products, Inc., Santa Monica, Calif.). This procedure was followed so that the particle size of the aerosol, although not precisely known, would be constant for each agent.

Another series of studies was performed on four of the seven subjects again on 3 separate days. Isovolume pressure flow (IVPF) curves were obtained before and after isoproterenol, atropine and isoproterenol plus atropine, by the methods of Hyatt and associates (9). Instantaneous values of transpulmonary pressure and expiratory flow were plotted as the *x-y* coordinates of a storage oscilloscope at the same lung volume using a modified gating circuit (10). Each vital capacity maneuver yielded one point at that lung volume. Pressure-flow points derived in this manner were obtained on air, and after a complete washin of HeO_2. The variables were recorded on a Hewlett-Packard four-channel FM tape recorder so the playback would allow display of the IVPF curves over a wide range of volumes. Lines of best fit as determined by inspection were drawn through the points. Assuming that tissue viscous resistance was negligible (i.e. dynamic transpulmonary pressure plus static recoil pressure (Pst[1]) equals alveolar pressure), the pressure at the beginning of the plateau when $\dot{V}_{max}$ was first achieved was referred to as the critical alveolar pressure (Palv'). Although it is difficult to define precise values for Palv' on any IVPF curve, specific values were obtained by using the mean of five observations from five individuals experienced in such measurements who selected the Palv' in a single blind fashion from unlabeled xerographic reproductions. The IVPF relationships at volumes approximately 40–50% of the vital capacity were analyzed using the equal pressure point concept of Mead et al. (11) and in a manner similar to that used by McFadden et al. (3). The total airway resistance was partitioned into two segments and arranged in series upstream and downstream from equal pressure points as follows: Rt = total airway resistance at the lowest alveolar pressure (Palv' at which maximum flow can be achieved ($Palv'/\dot{V}_{max}$); Rus = resistance of upstream segment at maximum flow ($Pst[1]/\dot{V}_{max}$); Rds = resistance of downstream segment ($Palv' - Pst[1]/\dot{V}_{max}$) or (transpulmonary pressure at plateau/$\dot{V}_{max}$):

$$Rt = Rus + Rds, \tag{1}$$

$$\frac{Palv'}{\dot{V}_{max}} = \frac{Pst(1)}{\dot{V}_{max}} + \frac{Palv' - Pst(1)}{\dot{V}_{max}}, \tag{2}$$

Substituting and rearranging,

$$Palv' = Pst(1)\,(1 + Rds/Rus), \tag{3}$$

(same as Eq. 5 in reference 3).

Thus, Palv' at a given Pst(1) depends only upon the ratio of upstream and downstream resistances and, therefore, is independent of Rt. From this relationship, Palv' at a given Pst(1) would be expected to decrease with increases in $\dot{V}_{max}$ if there were a greater decrease in resistance of downstream pressure and to increase if there were a disproportionate fall in Rus.

The data were analyzed by *t* test for paired observations and by factorial analysis.

RESULTS

The static lung volumes did not change from control values after the bronchodilators were administered. Control residual volume (mean±SD), 1.62±0.33; atropine, 1.71±0.48; isoproterenol, 1.59±0.30, both agents, 1.72±0.35; $F = 0.20$; P NS. Control total lung capacity, 7.15±0.51; atropine, 7.25±0.57; isoproterenol, 7.15±0.56; both agents, 7.10±0.47; $F = 0.04$; P, NS.

The effects of atropine and isoproterenol on $\dot{V}_{max}$ at 40% of vital capacity ($\dot{V}_{max40}$), the degree of density dependence of $\dot{V}_{max40}$, and calculated upstream resistances are shown for all subjects in Table I. There were significant increases in air flow rates for each agent alone and in combination when compared with control observations. The response to atropine was not

TABLE I

Maximal Expiratory Flow on Air and Helium Oxygen

	$\dot{V}_{max40}$ Air				$\dot{V}_{max40}$ HeO_2				DD				Rus air				Rus HeO_2			
Subject	C	A	I	A + I	C	A	I	A + I	C	A	I	A + I	C	A	I	A + I	C	A	I	A + I
1	5.0	5.8	5.7	5.7	7.8	8.3	9.4	8.8	1.56	1.43	1.65	1.54	0.94	0.81	0.82	0.82	0.60	0.57	0.50	0.53
2	3.1	3.7	3.4	3.8	4.9	5.1	5.5	5.9	1.58	1.38	1.62	1.55	1.42	1.19	1.29	1.16	0.89	0.86	0.80	0.75
3	4.1	4.6	4.5	4.6	5.9	6.4	7.1	6.9	1.44	1.39	1.58	1.50	1.46	1.30	1.33	1.30	1.02	0.94	0.84	0.87
4	4.6	5.6	4.8	5.2	7.1	8.0	7.9	8.0	1.54	1.42	1.64	1.54	1.11	0.91	1.06	0.98	0.72	0.64	0.64	0.64
5	2.2	2.8	2.6	2.7	3.1	3.7	4.1	3.8	1.41	1.32	1.58	1.41	2.41	1.89	2.04	1.96	1.71	1.43	1.29	1.39
6	3.3	3.7	3.9	4.1	5.4	5.6	6.9	6.5	1.64	1.51	1.77	1.58	1.45	1.29	1.23	1.17	0.89	0.86	0.69	0.74
7	4.7	4.8	5.0	5.2	7.8	7.2	8.6	8.9	1.66	1.50	1.73	1.67	1.55	1.52	1.46	1.40	0.94	1.01	0.85	0.82
Mean	3.86	4.43	4.27	4.47	6.00	6.33	7.07	6.97	1.55	1.42	1.65	1.54	1.48	1.27	1.32	1.26	0.97	0.90	0.80	0.82
SD	1.02	1.09	1.05	1.03	1.72	1.65	1.82	1.81	0.09	0.07	0.07	0.08	0.47	0.36	0.38	0.37	0.36	0.28	0.25	0.28

Comparisons	*P* values				
C vs. A	<0.005	NS	<0.001	<0.02	NS
C vs. I	<0.001	<0.001	<0.001	<0.02	<0.02
C vs. A + I	<0.001	<0.001	NS	<0.005	<0.005
A vs. I	NS	<0.02	<0.001	NS	<0.01
A vs. A + I	NS	<0.025	<0.001	NS	<0.02
I vs. A + I	<0.02	NS	<0.005	<0.01	NS

$\dot{V}_{max}$, maximum flow at 40% of the vital capacity in liters/second; DD, density dependence; C, control observations; A, postatropine; I, postisoproterenol; A + I, postatropine plus isoproterenol; Rus, upstream resistance in centimeters H_2O/liters per second.

significantly different from that to isoproterenol, nor was the atropine response different from that observed when the drugs were given in combination. However, the response to both agents in combination was significantly greater than that of isoproterenol alone. With respect to $\dot{V}_{max}$ HeO_2, there were significant increases after isoproterenol and after both drugs in combination, but there was a smaller and less consistent change after atropine. When the atropine response was further compared to that of isoproterenol and the combined regimen, the atropine response was found to be significantly smaller. The resulting density-dependence ratios fell significantly after atropine, increased after isoproterenol, and were unchanged from control when both drugs were combined. Upstream resistances on air were consistently smaller after all three bronchodilator regimens. However, the decrease in HeO_2 Rus was not significant after atropine and was significantly less than the decreases after the other two regimens.

Fig. 1 depicts the density dependence ratios as a percent of vital capacity for all seven subjects studied. These data demonstrate that the pattern of ratios shown in Table I held true for all lung volumes below 50% vital capacity.

Figure 2 displays the static deflational pressure-volume curves for all subjects before and after each regimen. It is apparent that no significant changes in the mean elastic properties of our subjects' lungs were induced by any of the bronchodilators given singly or in combination. Comparisons of individual curves also failed to show any effects.

Table II contains the data from IVPF curves in the four subjects in whom such measurements were made. A representative example of the curves from which data were taken is shown in Fig. 3. The Palv' was consistently lower after atropine, higher after isoproterenol, and unchanged after both drugs in combination. In addition, Palv' while breathing HeO_2 was often lower than air both before and after the bronchodilators but the differences were not statistically significant. The $\dot{V}_{max}$ values, density dependence ratios, and upstream resistances measured in this series of experiments are similar to those in the previous studies outlined above. Downstream resistance values derived from the data in Table II showed a significant fall after atropine (air, 2.93–2.29, paired $t = 3.97, P < 0.05$; HeO_2, 1.66–1.34, paired $t = 0.94$, P, NS). There was a small yet consistent decrease in air and HeO_2 Rus after all three bronchodilator regimens.

DISCUSSION

Through the use of maximal expiratory flow volume curves with both air and Helium-oxygen, we have shown differences in the response of normal subjects to beta agonist vs. anticholinergic bronchodilatation,

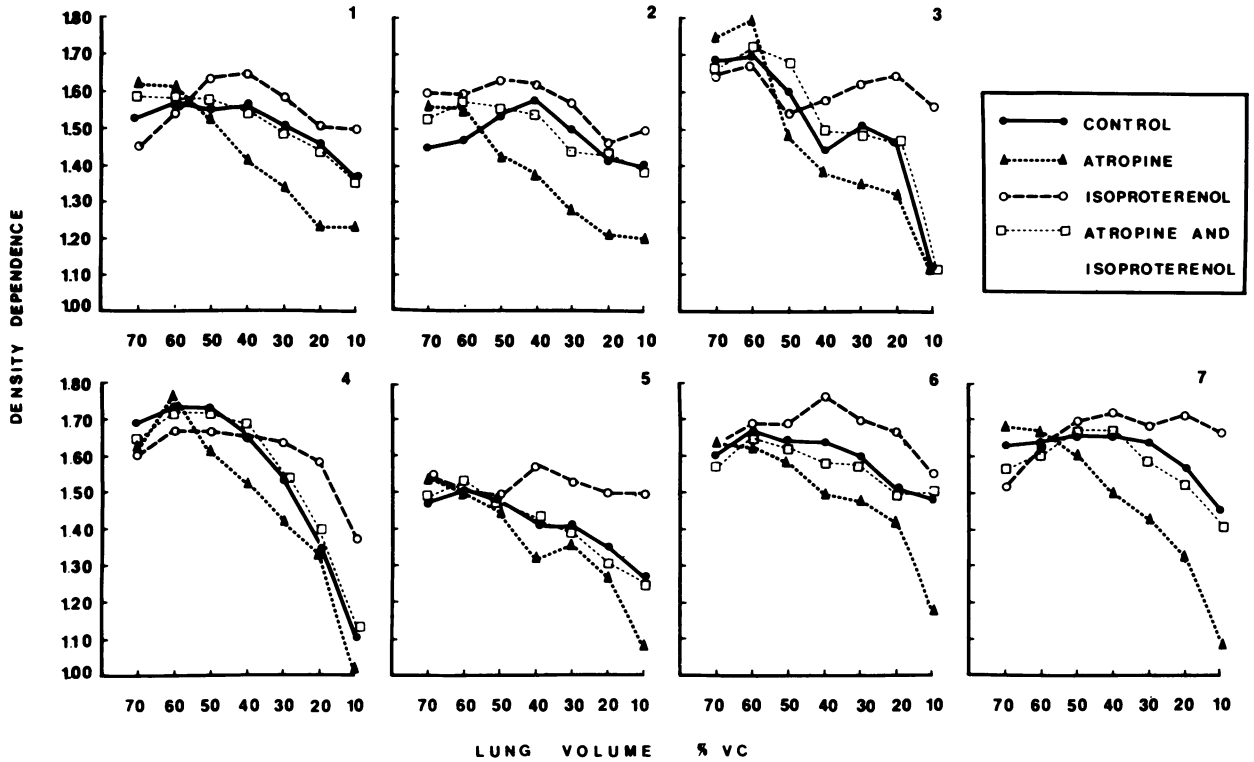

FIGURE 1 Density dependence of $\dot{V}_{max}$ at indicated percentages of vital capacity before and after each agent given separately and both in combination. Density dependence is expressed as the ratio of $\dot{V}_{max}$ with HeO_2 to $\dot{V}_{max}$ with air.

differences that would not have been apparent if only air had been used. Through the analysis of density dependence of $\dot{V}_{max}$ and changes in IVPF curves, inferences are drawn concerning differences between these two agents in terms of site of action. The ensuing discussion will briefly review previous studies of bronchodilator response in normal subjects before considering the demonstrated differences in response to the two agents.

Bouhuys and van de Woestijne (4) and others (3, 12) have shown that isoproterenol causes greater inceases in airways conductance than in $\dot{V}_{max}$. One report (3) demonstrated that isoproterenol given in large doses reduced Pst(1). These authors suggested that this was the basis for the greater increases in airways conductance rather than in maximal flows. Bouhuys and van de Woestijne (4) could find no changes in Pst(1) and concluded that isoproterenol made large airways more compliant and therefore increased their dynamic compressibility. Green and Mead (13), studying the volume and time-dependent behavior of airway smooth muscle tone, concluded that a deep inspiration produced bronchodilation and suggested that, since isoproterenol abolished this time-dependence of $\dot{V}_{max}$, the reappearance of airway tone

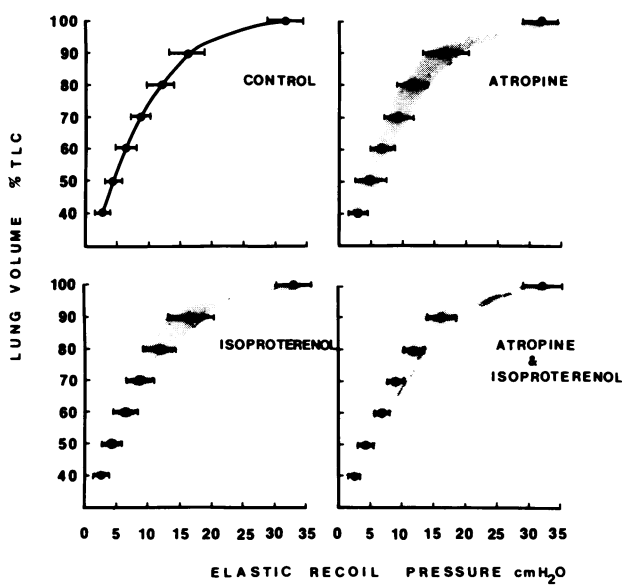

FIGURE 2 Mean static deflational transpulmonary pressure vs. percent total lung capacity (TLC) curves±SD before and after each agent given separately and both in combination. Shaded areas on the upper right and on both lower curves represent the control data shown on the upper left graph.

TABLE II
Isovolume Pressure Flow Data

		Air				HeO_2					
		Palv'		$\dot{V}_{max}$		Palv'		$\dot{V}_{max}$			
	Subject	B	A	B	A	B	A	B	A	Pst(1)	VC
											%
Atropine	2	16.9	15.6	3.3	3.6	15.6	15.1	4.9	5.0	7.3	44
	3	18.2	15.6	4.4	5.0	17.0	15.6	6.5	7.1	8.2	47
	6	18.2	16.3	3.5	4.0	16.6	14.3	5.7	6.1	5.3	45
	7	23.0	22.3	5.0	5.1	22.7	19.2	8.3	8.1	8.8	48
		$t = 3.99$		$t = 3.38$		$t = 3.00$		$t = 1.29$		—	—
		$P < 0.025$		$P < 0.025$		$P > 0.05$, < 0.10		P = NS		—	—
Isoproterenol	2	17.0	18.1	3.3	3.7	13.3	16.6	4.6	5.7	5.6	44
	3	19.2	19.7	4.3	5.4	18.3	21.2	7.0	9.0	8.8	44
	6	17.7	18.9	3.5	3.8	15.1	16.9	5.5	6.3	5.0	43
	7	17.6	19.2	4.2	4.6	18.7	21.7	6.7	7.6	6.7	38
		$t = 4.84$		$t = 2.98$		$t = 4.89$		$t = 4.38$		—	—
		$P < 0.025$		$P > 0.05$, < 0.10		$P < 0.02$		$P < 0.025$		—	—
Atropine + isoproterenol	2	19.5	19.6	3.7	4.1	18.7	19.4	6.1	6.7	6.5	48
	3	13.3	14.7	4.2	4.9	16.5	13.6	6.1	7.2	6.5	46
	6	15.5	16.4	3.4	3.7	14.7	15.9	5.8	6.4	4.4	45
	7	20.5	20.7	5.2	5.4	19.2	20.4	8.4	8.8	7.6	49
		$t = 0.52$		$t = 3.34$		$t = 0.05$		$t = 4.52$		—	—
		P = NS		$P < 0.05$		P = NS		$P < 0.025$		—	—

Palv', critical alveolar pressure in centimeters H_2O; $\dot{V}_{max}$, maximum flow in liters/second; t values are from paired t tests; B, before; A, after.

would explain the airways conductance maximal flow dichotomy. Vincent et al. (14) demonstrated that a deep breath reduced normal bronchomotor tone and concluded that efferent vagal impulses mediated this tone because the resistance changes were abolished by atropine administration. Thus the results of these various studies with atropine and isoproterenol establish the presence of airway smooth muscle tone in normal human subjects. The present study extends these findings by demonstrating that although similar degrees of bronchodilatation result from the inhalation of atropine and isoproterenol, the predominant flow regimes across the upstream airways are different after these two agents.

Assuming homogeneous behavior of the lungs, the present findings are conveniently discussed within the framework of the equal pressure points (EPP) analysis of $\dot{V}_{max}$ determinants. According to Mead et al. (11), the $\dot{V}_{max}$ at a particular lung volume is defined by the Pst(1) at that volume and the Rus between alveoli and the point where intrabronchial pressure equals pleural pressure. These authors reasoned that flow regimes across upstream airways would vary with the position of EPP. If EPP are located in major airways, where cross-sectional area is small and Reynolds numbers are large, there will be considerable density dependence of $\dot{V}_{max}$ due to turbulence and convective acceleration. In normal subjects, EPP become fixed at lobar or segmental bronchi between 70 and 25% of vital capacity during forced expiration (15). Therefore upstream segments contain both small peripheral and larger, more central airways, and $\dot{V}_{max}$ is highly density dependent in such subjects (16). On the other hand, if EPP were located in peripheral airways where cross-sectional area is large and Reynolds numbers are small, $\dot{V}_{max}$ would be less density dependent. Indeed such a peripheral location has been proposed to explain diminished density dependence due to peripheral airway obstruction in patients with obstructive lung disease (17) and in cigarette smokers without established disease (18).

With bronchodilatation after isoproterenol, increasing density dependence could be explained, at least in part, by a more mouthward EPP location. On the other hand, the atropine results, if attributed to shifts in EPP, would indicate a more peripheral location. Although there are no data on EPP location after bronchodilatation of human lungs, qualitative predictions of

EPP movement in association with bronchodilatation can be made. At a given Pst(1), the length of the upstream segment (i.e. position of EPP) would vary with the frictional resistance per unit length, the magnitude of the cross-sectional area decrease (i.e. degree of tapering mouthward from alveoli), and on the magnitude of $\dot{V}_{max}$. The length of the upstream segment would decrease (i.e. peripheral movement of EPP) with increases in frictional resistance per unit length, the degree of tapering, and $\dot{V}_{max}$. With bronchodilatation, the effects on frictional resistance per unit length and on the degree of tapering would tend to lengthen the upstream segment, and increases in $\dot{V}_{max}$ would tend to shorten it. The net effect would be difficult to predict because the direction of movement of EPP would also depend on the distribution of the bronchodilatation as may be seen from the following extreme examples. If bronchodilatation occurred mainly in small upstream airways that have relatively little influence on $\dot{V}_{max}$, upstream resistance would then have to move toward the alveoli. Thus creases in frictional resistance per unit length and degree of tapering would, in this example, result in lengthening of the upstream segment. At the other extreme, if bronchodilatation occurred predominantly in large airways, mainly in those downstream from the previous EPP, $\dot{V}_{max}$ might increase with relatively little change in frictional resistance per unit length or in the degree of taper in the former (i.e., before bronchodilatation) upstream segment. To bring about the required reduction in upstream resistance, EPP would then have to move toward the alveoli. Thus it is possible to explain the atropine results in terms of a more peripheral EPP movement. However, the data of Gardiner and colleagues (19) indicate that, in dog lungs, a more mouthward EPP location is found after bronchodilatation produced by vagotomy, which is presumably similar to atropine administration. We do not know if the distribution of innervation in human airways is similar to that seen in dogs. Nonetheless we must deal with the possibility that a mouthward shift of EPP might have occurred after atropine and such a shift would be expected, if anything, to increase density dependence. Hence the paradox that we must explain is a decrease in density dependence in association with a more mouthward location of EPP. For the sake of illustration, we will consider the upstream segment as having two subsegments, one of which consists of density-independent, small airways and the other density-dependent, large airways. With a constant Pst(1), if there were greater dilatation of large airways after atropine there would be a relatively greater proportion of the Pst(1) dissipated across small airways of this segment. The result would be a relatively greater increase in $\dot{V}_{max}$ with air than with HeO_2 (i.e., decrease in density dependence). In con-

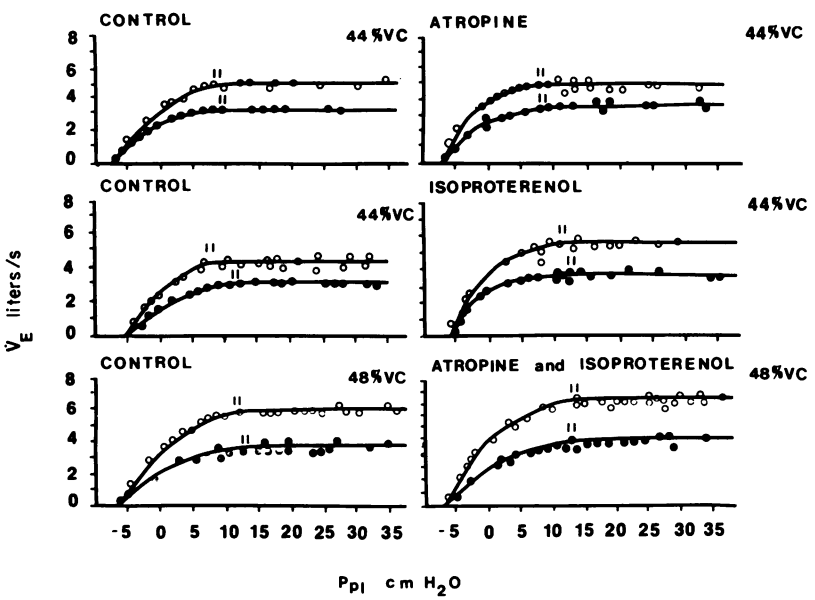

FIGURE 3 Representative IVPF curves with air (●) and HeO_2 (○) shown for one subject before (as control curves on the left) and after the agents (curves on the right) at percentages of vital capacity (VC) indicated on the figure. The vertical parallel lines (‖) indicate the range of critical pressures as selected in the single blind fashion outlined under Methods. The actual values shown here represent dynamic transpulmonary pressure to which Pst(1) was added to give Palv'. Tabulated values represent the mean of the five observations made by five individuals. P_{Pl}, pleural pressure.

trast, greater dilatation of small airways would result in a proportionally greater pressure drop across larger airways of the upstream segment. The result in this instance would be a relatively greater increase in $\dot{V}_{max}$ HeO_2 than air (i.e., increase in density dependence). Thus we propose that atropine predominantly dilates large upstream airways with the result that there is an increase in the relative contribution of small airways to flow limitation, and isoproterenol would seem to produce predominant dilatation of small upstream airways which would increase the relative contribution of large upstream airways to flow limitation.

If our hypothesis is valid that atropine dilates the larger airways within the upstream segment and isoproterenol preferentially dilates the smaller airways upstream from EPP, then both agents given simultaneously should result in increased $\dot{V}_{max}$ and intermediate effects on density dependence. The data in Table I and Fig. 1 clearly demonstrate that this was the case. That the increase in flow did not approximate the sum of the increases in $\dot{V}_{max}$ for each agent given separately can probably be explained by considering the relative distribution of parasympathetic and sympathetic influences on airway caliber. In dog lungs the parasympathetic nervous system appears to exert a constricting influence at all levels of the tracheobronchial tree but the dilatation after vagotomy occurs predominantly in larger airways (3–8 mm in diameter) (20). Beta adreneregic agents might preferentially exert their dilator effect on the peripheral airways since propranolol administration results in increased peripheral airway resistance (5). Therefore it is not surprising that the anticholinergic agent resulted in greater increases in $\dot{V}_{max}$ than beta adrenergic stimulation alone. Moreover, since there is no doubt that there is some overlap in the sites of action of each agent, the administration of both together would not be expected to result in an algebraic sum of the increases in $\dot{V}_{max}$ when given separately.

From the IVPF curves, the demonstrated decreases in Palv′ after atropine indicate that downstream airways were affected more than upstream airways. Since it is unlikely that large upstream airways could be dilated without a measureable change in downstream airways, the fall in Palv′ is consistent with our interpretation of the atropine results (Table II). After the administration of isoproterenol, the findings of a fall in Rus with both gases and an increase in Palv′ taken together indicate greater dilatation of upstream than downstream airways. It might be argued that isoproterenol had an effect on larger airways equivalent to that of atropine, but with a greater effect on small airways. However, since resistance of downstream segment decreased significantly (from a mean of 2.92–2.28, $P < 0.05$) after atropine and did not change after isoproterenol (from a mean of 3.02–2.94, P, NS), we think the latter argument unlikely to be true, although, undoubtedly, isoproterenol has some effect on larger airways.

It is of interest to compare in some detail our findings with those of McFadden et al. (3). They were the first to point out that changes in Palv′ could be used to interpret the distribution of airway resistance changes and, indeed, that such changes, according to EPP concepts, would be related to this distribution and to Pst(1), but unrelated to total airway resistance. In their experiments with aerosolized isoproterenol, small but consistent reductions in Pst(1) had a dominant effect on Palv′ such that they found a slight reduction in contrast to the increase we have found. We are unable to explain the different findings with regard to Pst(1) in the two studies except to note that their dose was approximately twice that used in this study. Yet is is interesting that our failure to find changes in Pst(1) rendered Palv′ solely dependent upon resistance distribution. Using their method of analysis, we have concluded that the changes with isoproterenol are not uniformly distributed, as they suggested. On closer examination, several of their findings are consistent with our conclusions. First they observed that the greatest percentage change in flow rates occurred at volumes below 50% of vital capacity and they pointed out that "at small lung volumes the increase in flow is, if anything, more pronounced than the changes in conductance." Since as lung volume decreases, peripheral airways contribute progressively more to upstream resistance, this volume dependence is consistent with predominant peripheral dilatation. Second they applied their measurements of Pst(1) to their eq. 5 and, in solving for the ratio of downstream to upstream resistance, they found slight increases. They emphasized the variability of their estimates of Palv′ and concluded that the increase in airway dimensions was relatively evenly distributed within the tracheobronchial tree. However, it is worth noting that the direction of change in the ratio is what would be expected for predominantly peripheral airway dilatation.

How much would our interpretation of differing predominant sites of bronchodilatation be altered if there were different EPP locations with the two gases? Should EPP systematically have a more peripheral location with HeO_2 than with air, the HeO_2 peripheral airway (i.e. airways with internal diameters ≤ 2 mm) resistance would approach the HeO_2 upstream resistance as has been shown in dog lungs (21). Failure of HeO_2 Rus to change consistently and appreciably after atropine and the consistent fall in this value after isoproterenol (Table I) are observations that are most compatible with minimal change in these airways after atropine, and predominant dilatation of these air-

ways after isoproterenol. Thus our conclusions would not be altered if there were a more peripheral EPP location with HeO_2.

In summary, this study demonstrates that atropine and isoproterenol differ not only in neuropharmacological terms but also in their predominant site of bronchodilatation within the lungs. It is possible that this difference may have clinical usefulness in designing a regimen for the treatment of reversible airways obstruction.

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