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HELIUM/OXYGEN FLOW VOLUME CURVES IN NORMAL INDIAN MALES >50 YEAR, AND THE EFFECT OF BRONCHODILATOR AEROSOLS ON AIRFLOW VARIABLES IN THIS SUBJECT GROUP

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Abstract: Fourteen healthy males (mean age 54.7 yr) described maximal flow volume curves after Air breathing (AB) and after inspiring 10 deep breaths of a mixture of 80% Helium/20% Oxygen (He/O_2). Vmax 50% FVC as obtained from the AB curves was 3.11 ± 1.27 lps, and this increased by 38.1 ± 17%, with He/O_2. The Vmax 50% $He-O_2$/Air ratio was 1.32 ± 0.17, while the V iso V was 1.1 ± 0.35 litres (30.9% of the FVC). Inhalation of 80 micrograms (4 puffs) of Ipratropium bromide, a vagolytic aerosol, or salbutamol (200 micrograms; 2 puffs), a beta 2 adrenergic stimulant did not alter the He/O_2 curves significantly.

As another aspect of the study, airflow variables viz. Vmax 50% of the FVC, Vmax 25%-75%, and Vmax 25% were measured from the AB curves, and the effect of bronchodilator aerosols was investigated in order to evaluate the degree of control of the bronchomotor tone by either the adrenergic receptors, or the vagus. Only the Vmax 25%-75% increased significantly with Salbutamol administration. While the degree of increase brought about by salbutomol aerosol for all of the variables under investigation was more than that seen with ipratropium br., the difference in this increase between the two bronchodilators used was not significant. The result may indicate that almost an equivocal influence is exerted by the two arms of the autonomic nervous system on bronchomotor tone in middle aged normal males, and that a more sensitive test (viz $He-O_2$ breathing) does not elucidate this any further.

Key words: bronchomotor tone in elderly air low indices
Vmax 50% FVC V iso V Vmax 50% ratio

INTRODUCTION

Bronchomotor tone of the human airways is maintained by the combined influence of the sympathetic and the parasympathetic arms of the autonomic nervous system (ANS) (1). The non-adrenergic/non-cholinergic (NANC) mechanism is also thought to play a role (2), but iatrogenically, airway calibre may be altered only by using either sympathomimetic or vagolytic agents (1, 3).

The relative roles of adrenergic vs vagal influences in the control of airway calibre in normal humans has been investigated (1, 3). Whereas Ingram et al (1) used nebulised isoproterenol for vagolysis, MacNee et al (3) used salbutamol aerosol for specific beta 2 adrenergic excitation, and ipratropium bromide aerosol for vagolysis. This was done as it was suggested that adrenergic stimulation dilates mainly the small airways, while ipratropium bromide affects the large ones (1, 4). In order to confirm this, apart from measuring airflows obtained from the maximal expiratory flow volume curves (MEFVC) (1) and the MEFV and the partial expiratory flow volume curves (PEFV) (3), both the studies (1, 3) had utilised MEFV curves obtained while breathing 80% helium-20% oxygen mixture as this

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technique is thought to be a sensitive and specific index for evaluating subtle changes in airway calibre produced by alteration of the bronchomotor tone (5). Both the studies however, concluded that there is an overlap in the autonomic control of both types of airways - the large and the small.

It is also noticeable that almost all such studies have been done on *young* subjects (age range 20-40 yr) while information on the relative roles that the two main arms of the ANS play on the airway calibre of *normal* elderly people is universally lacking. The information is almost non-existent on the Indian respiratory physiology scenario except in a study by Sodhi and Dikshit (6). In this it was reported that the extent of airway dilatation produced by administering 100 micrograms of salbutamol aerosol as seen from changes produced in Vmax 40% and Vmax 25% of the FVC measured from PEFV curves in the elderly males (mean age 67.1 yr) was significantly less than the change in the same parameter as observed in young subjects (mean age 24.4 yr). The authors had hypothetised that this had occured perhaps because the response of the beta adrenergic receptors to stimulation wanes with age, or that the number of such receptors on the airways declines with age.

The role of vagal blockade on airway calibre in the two age groups was not evaluated in that study. Also, the study was done by *constructing* PEFV curves; and helium-oxygen breathing was not used to enhance its sensitivity. In the present work, an attempt has been made to address the hypothesis that brochodilatation produced by using ipratropium br. is more than that produced with salbutamol in healthy Indian males >50 yr.

METHODS

Fourteen healthy male volunteers (age 54.9 ± 4.5 (SD) yr; 167.1 ± 5.7 cm), weight 62.0 ± 9.3 kg), all V.P. Chest Institute employees, were recruited for the study which was ethically approved locally. They were clinically examined to rule out the presence of any cardiorespiratory, or autonomic disorders, and trained to perform the maximal respiratory manouevres required for recording flow volume curves. Two were light smokers, while one was an ex-smoker. They were explained the nature of the study before the start of the experiments. None were taking any medication at that time.

The subject reported to the lung function laboratory at the VPCI at about 2.30 pm on the day of the test. He was then explained the procedure of the test, and asked to make at least 3 successful maximal respiratory efforts in to a computerised spirometer (PK Morgan). The output was passed into a Magna 88 computer which then analysed the efforts and displayed them as maximal flow volume curves. The "best" of the efforts (largest sum of FVC and FEV_1) was saved on the computer. After a brief, but adequate rest, the subject breathed the pre-prepared 80% Helium-20% Oxygen mixture (Indian Oxygen) (He-O_2) which was passed from the source cylinder into a 6 litre rubber breathing bag attached to the subject via a 3-way breathing valve. The subject breathed the mixture for atleast 10 deep breaths, and after inspiring the last breath of the mixture, made the maximal respiratory effort into the spirometer. Atleast 3 satisfactory efforts were recorded by repeating the whole process after brief rest periods, and the "best" effort was stored. Then, both the air and the He-O_2 curves were recalled on the computer, and superimposed at TLC (5), and a print out of the data was obtained. The subject was then administered 2 puffs of salbutamol aerosol (Asthalin; Cipla; 100 microgram/puff), of 4 puffs of ipratropium bromide (Ipravent; Cipla; 20 micrograms/puff) in a random manner. For this, the subject reached end expiratory level, at which point the aerosal cannister was inserted inside his mouth. A single puff was adminstered as the subject breathed in slowly to his TLC. After the aerosal was given, he held his breath for a few seconds, following which the next dose was given. The measurements of the respiratory variables were repeated as in the prebronchodilator manner after 20 min had

elapsed. Therefore, for each subject, there were two sets of data involving Air, and helium oxygen mixture breathing maximal flow volume curves. No attempt was made to disguise the aerosols administered. However, on the one day, only one aerosol was administered, while the experiment was repeated with the remaining aerosol, in most instances, on the following day. No attempt was made to study the bronchodilator effect of the aerosols given together. Only two subjects declined to carry out the ipratropium test, and hence data for this test is missing for these subjects. In this manner, all the 14 subjects completed the pre- and post salbutamol trials, while only 12 of them completed the ipratropium trials. Hence, pre-drug data was available for analysis from 26 efforts in the 14 subjects, and has been pooled for obtaining data for the density dependent flow volume curves, while for the post treatment phase, 14 efforts from the salbutamol trials, and 12 from the ipratropium tests were available for analysis. A typical record is shown in Fig. 1.

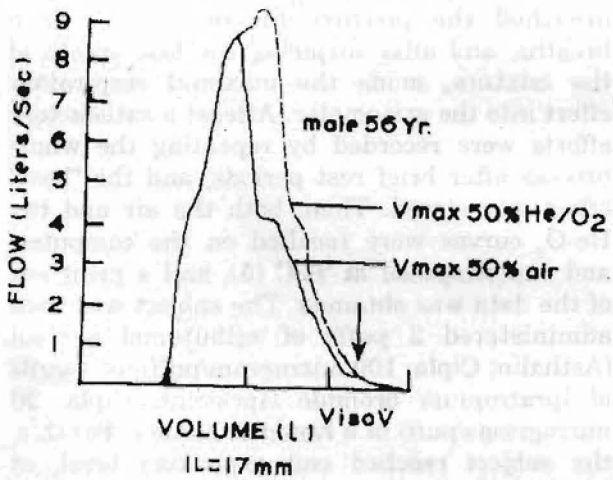

Fig. 1 : Shows typical flow volume curves while breathing air (continuous line) and while breathing Helium-oxygen mixture (....). The point at which the two curves coincide is the V iso V.

The variables obtained for analysis from the computer printout were forced vital capacity (FVC; L); Vmax 50% FVC, Vmax 25-75% FVC; and Vmax 25% FVC (when 25% of the volume has been breathed out). For a comparison, courtsey Medical Director, Clinical Research Centre, VPCI, data for FV curves of 13 established cases of COPD (45-66 yr) was obtained from the old records. He-O_2 data was not available in these patients. For studying the He-O_2 curve data, variables used were FVC, Vmax 50%; and increase in Vmax 50% calculated as Vmax 50% He/O_2-Vmax 50% Air Breathing/Vmax 50% AB; Vmax 50% ratio (Vmax 50% He-O_2/Vmax 50% AB) (5). The volume for iso flow (Visov) was the volume at which the AB and the He/O_2 curves first crossed, or coincided (5, 7) (Fig. 1). Thus all the variables derived were the standard ones. We also obtained various variables from He-O_2/Air Breathing MEFV curves of 12 normal young men (all non-smokers) age range 21-39 yr). Only the relevant data of He-O_2 curves was statistically compared with values obtained in normal men > 50 yr, while for reporting on the characteristics of He-O_2 curves for this groups men, pooled data (26 efforts) has been utilised.

Statistics

The values were expressed as mean ± SD. Paired "t" test was used for comparing the effects of brochodilator on the variables obtained from the flow-volume curves of the older men (>50 yr).

For comparison of He-O_2 data between the older men and the young men, 13 best values (highest for % increase in Vmax 50% and for Vmax 50% ratio He/Air; and *lowest* for V iso V, and V iso V as % FVC) were used for the older men. Thus for this part of data treatment, it was n=13 men > 50 yr; and n=12 men < 40 yr. Each variable under consideration viz. the % increase in Vmax 50%; Vmax 50% ratio; V iso V; V iso v % FVC, was analysed separately. Normality was tested by Kolmogorov-Smirnov d statistic (8). In view of a positive co-relation between some variables and the height, all study variables in this comparison were standardised to a height of 165 cm (9). "t" test

was used to find the significance of each of the physical characteristics, and the study variables between the two groups after ascertaining homogeneity of the variances. It was assumed that the two groups were homogeneous with respect to other extraneous variables. Level of significance was fixed at $P < 0.05$.

RESULTS

Bronchodilator aerosols and MEFV curves : The main airflow variables (lps) measured from the MEFV curves were Vmax 50%, Vmax 25%-75%, and Vmax 25% FVC. When data for all the pre-aerosol efforts was pooled (n=26 efforts), the values for these variables were 3.11 ± 1.27 lps, 2.14 ± 0.89, and 0.699 ± 0.296 lps.

When the comparison of the bronchodilator aerosols effect on these variables was to be made, it was ensured that the FVCs for the pre and post aerosol efforts (3.65 1 pre- and 3.62 1 post for salbutamol; 3.52 1 and 3.51 1 pre- and post for ipratropium respectively) were well within 5% of each other as required. The pre- and post salbutamol (n=14), and the pre- and post ipratropium (n=12) values for the airflow variables are given in Fig. 2.

In these variables, only the mean change produced by salbutamol for Vmax 25-75% was significant ($P < 0.01$; Table I). In order to determine as to which of the two aerosols used was a more effective bronchodilator, the post aerosol values were converted to percentage of the baseline value, and compared. It was seen that though each one of the variables showed a higher % baseline with salbutamol, the mean difference in the parameter between this, and that produced by ipratropium was not significant (Table II).

Helium/oxygen MEFV curves, and the effect of bronchodilator aerosols : Vmax 50% FVC for all 26 best efforts as given earlier was 3.11 ± 1.27 lps, and this increased by 38.1 ± 17% with He/O_2. The effect that the aerosols produced on this variable (n=14 for salbutamol, and n=12 for ipra.) is given in Table III. There was no significant change brought about in this variable by the use of the bronchodilators.

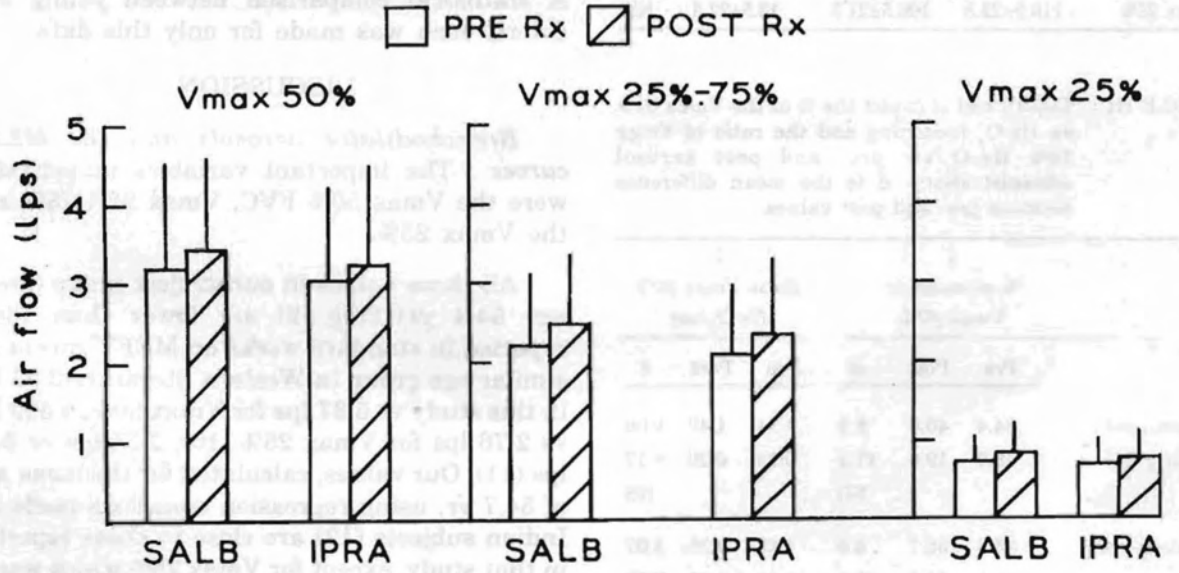

Fig. 2 : Mean values for pre- and post bronchodilator airflows are given. The vertical bars are the SDs. SALB is Salbutamol; IPRA is Ipratropium bromide.

TABLE I : The mean ± SD (lps) change from control in airflows produced by salbutamol (Salb) and impratropium bromide (IPRA) inhalations as measured from Vmax 50% of FVC, Vmax 25-75%, and Vmax 25%. The significance was calculated from control values.

	With SALB	*Sig.*	*With IPRA*	*Sig.*
	n=14		n=12	
Vmax 50%	0.289 ±0.442	NS	0.181 ±0.522	NS
Vmax 25-75%	0.274 ±0.317	**	0.231 ±0.380	NS
Vmax 25%	0.117 ±0.217	NS	0.037 ±0.189	NS

**P<0.01

TABLE II: The difference between the % of base line for salbutamol and for ipratropium, Values are mean ± SD.

	Salbutamol	*Ipratropium*	*d*	*Sig.*
Vmax 50%	117.8±18.0	109.6±20.4	8.2±25.6	NS
Vmax 25-75%	121.4±19.1	110.9±13.7	10.5±20.9	NS
Vmax 25%	119.9±22.8	106.5±21.3	13.5±22.6	NS

TABLE III : Table I and II depict the % in the Vmax 50% on He-O_2 breathing and the ratio of Vmax 50% He-O_2/air pre- and post aerosol administrations. d is the mean difference between pre- and post values.

	1 *% increase in Vmax 50%*			*2* *Ratio Vmax 50% He-O_2/air*		
	Pre	Post	d	Pre	Post	d
Salbutamol :	34.4	40.5	6.1	1.34	1.40	0.06
mean ± SD	18.9	19.6	17.2	0.19	0.20	0.17
			NS			NS
Ipratropium	33.8	36.7	2.9	1.28	1.35	1.07
	11.1	19.6	18.0	0.14	0.21	0.19
			NS			NS

Vmax 50 ratio for He-O_2/Air breathing : The mean ± SD value for this variable for the pooled data (26 efforts) was 1.32 ± 0.17 (CV 12.1%). For the salbutamol trial this increased from 1.34 ± 0.19 (n=14) to 1.40 ± 0.20, the mean difference of 0.06 ± 0.21 being statistically insignification (P>0.05). Similarly, the values of this variable for ipra. trials increased from 1.28 ± 0.14 to 1.35 ± 0.21, the mean difference of 0.07 ± 0.17 being insignificant (P>0.05). The overall effect of salbutamol (108.2 ± 10.2% of baseline) was slightly more than the effect of ipra. (106.1±18.55), but the mean difference between these values (2.12=16.4%) was insignificant. This indicated that neither aerosol affected the ratio significantly.

Volume iso flow (V iso V) : The mean ± SD value for pooled data for 26 best efforts in the 14 subjects was 1.1 ± 0.35 1 (30.9 ± 7.6% of the FVC recorded). Bronchodilators did not affect this value significantly.

The overall response of our normal subjects both young and > 50 yr to He/O_2 is given in Table IV, alongwith MEFV curve data of patients. Table V gives the He-O_2 13 best values from men > 50 yr and for young men (< 40 yr). A statistical comparison between young and elderly men was made for only this data.

DISCUSSION

Bronchodilator aerosols and the MEFV curves : The important variables investigated were the Vmax 50% FVC, Vmax 25%-75% and the Vmax 25%.

All these values in our subject group (mean age 54.4 yr) (Fig. 2) are lower than those reported in standard works on MEFV curves for similar age group in Western literature-3.11 lps in this study vs 5.87 lps for Vmax 50%; 0.699 lps vs 2.76 lps for Vmax 25% (10); 2.14 lps vs 3.45 lps (11). Our values, calculated for the mean age of 54.7 yr, using regression equations made for Indian subjects (12) are close to those reported in that study, except for Vmax 25% which works out to about 0.9 lps vide Udwadia et al (12) as against 0.7 lps in our study. Sodhi and Dikshit

(6) have reported a Vmax 25% of about 0.7 lps in their elderly subjects (all ex-military personnel) in Pune, who albeit, were older than the subjects of this study. Nevertheless, even that value is much lower than the 2.57 lps for the same variable in a comparable age group in the West (10). The MEFV data for similar age group in (10, 11), though it is close to that reported in (12) for Indian males. It is difficult to attribute the findings to socio-economic status of the subjects as most were *not* from a low socio economic status; or to lower respiratory tract infections in childhood which have been linked to poor lung functions in adulthood though epidemiologically proof for this has been lacking (13). Influence of local environmental pollution is also difficult to assess. The possibility that the diameter of the airways in Indians is anatomically smaller than that in Westerners can not be ruled out. Our measurements were made on a well tried spirometer system (PK Morgan), which is regularly calibrated. Also, the FVC values obtained were reproducible to within 5% of each other as required for making valid comparisons of airflows from different expiratory efforts. The extent to which these "normal" values differ from those in patients of COPD of a similar age group, is highlighted in Table IV (no statistical comparison is attempted) to establish the bonafides of our normal data, which is also comparable to the well recognised Indian study (12).

It has been suggested that cholinergic blockade is likely to produce pronchodilatation in airways which are more centrally located while beta adrenergic stimulation bronchodilates more peripheral ones represented by Vmax 25% (1, 3, 4). However, in the young subjects (<40 yr) who formed the spectrum in these referred studies, it was concluded that there is an overlap in the dual autonomic control of the larger and the small airways. Information on this issue in the senior age groups is generally lacking. As per an earlier study (6), we expected that the bronchodilatation of cholinergic blockade in this age group will be greater than that produced with beta adrenergic stimulation. However, it was salbutamol inhalation that produced the only significant increase in airflow (Table I; Vmax 25%-75%). Also, the overall bronchodilatation with salbutamol was greater than that achieved with ipratropium though the difference in the changes produced by the two agents was not significant (Table II). The doses of the aerosols (200 micrograms for salbutamol; 80 micrograms for ipratropium) used are known to produce the desired degree of broncho-dilatation (14, 15). It must be conceded though that on most occasions, these doses are used in patients of obstructive airways disease (14). Also there is a possibility that the maximum effect of bronchodilatation with ipratropium may not have been achieved as in some instances, it may take more than 30 min for this to occur (16). This part of the study thus failed to indicate any difference in the bronchodilator effects of the two aerosols used.

Helium-oxygen flow volume curves and bronchodilator effect : He-O_2 flow volume curves may detect subtle variations in bronchomotor tone (17), while volume of iso flow (V iso V) derived form these curves may be used for early detection of abnormalities in lung mechanics. The method was therefore, used in this study to delineate further as to the role of the two autonomic nervous system arms in control of bronchomotor tone in men > 50 yr. In the process, we report for the first time normal values for the standard variables derived from the He-O_2 flow volume curves-viz % increase in Vmax 50%; ratio Vmax 50% He-O_2/Vmax 50% Air; V iso V; and V iso V as % FVC (5, 17) for Indian men > 50 yr of age (Table IV).

The percentage increase in Vmax 50% He-O_2 breathing in our subjects (38.1%) is lower than the $\geq$ 45% reported (17). In the same context, the ratio Vmax 50% (He-O_2/Air mean of 1.32) in this study, though "normal" ie > 1.2, was lower than the average value of 1.42 for adults > 25 yr (18). When statistical comparison is made between He data of young and elderly individuals in this study, the only difference of significance is seen in the V iso V and the V iso V as % FVC (Table V).

TABLE IV : Depicts mean ± SD of variables for MEFV curves, in normal men (>50 yr and <40 yr); and in patients of COPD. He-O_2 curve data is not available for COPD patients, FVC was standardised to a height of 165 cm as per method given in ref. 9. The corrected FVC for men >50 yr is close to the FVC value reported using regression in ref. 20, and is also close to FVC for same age group vide regression in ref. 12.

		Normal *>50 yr* *14* *(26 efforts)*	*Normal* *<40 yr* *12*	*COPD Pts.* *>50 yr* *13*
	n			
1.	Mean age (yr)	54.9	26.8	55.1
2.	Mean ht. (cm)	167.1	166.8	162.8
3.	FVC ± SD (1)	3.59 0.67	4.32 0.77	2.61 0.83
4.	FVC standardised to a ht. of 165 cm	3.50	4.20	2.68
MEFV variables				
5.	Vmax 50% (lps)	3.11 ± 1.27	4.95 ± 1.29	0.59 ± 0.22
6.	Vmax 25-75% (lps)	2.14% ± 0.89	4.95 ± 0.74	0.36 ± 0.09
7.	Vmax 25% (lps)	0.699 ± 0.296	1.73 ± 0.42	0.19 ± 0.08
	He-O_2 : Curves			
8.	% increase in Vmax 50% with He-O_2	38.1 ± 17.0	-	-
9.	Ratio Vmax 50% He/Air	1.32 ± 0.17	-	-
10.	V iso V (1)	1.10 ± 0.35	-	-
11.	V iso V as % FVC	30.9 ± 7.6	-	-

The mechanism for increase in airflow from the lungs while breathing a low density mixture (He-O_2) has been given elsewhere (5). With advancing age, when the choke points tend to get relocated towards the periphery because of age related changes in the lungs, the Vmax 50% decreases as per the findings of this study though the absolute values for the Vmax variables were much lower than those reported in Western literature. In the same context, it is expected that the % increase in Vmax 50% with He-O_2 must also decrease in the older age group. Dosman et al (17) have opined that the parameter in question does not alter with advancing age. We too have reached a similar conclusion (Table V refers). It is of course possible that what we are reporting here as a less increase, may in fact be a normal tendency because the range of % increase in the variable can be from 20-80% (5, 14). However, Dosman et al (17) again differ from us and others (19) in that their subjects of about 55 yrs had a value of 15% for the V iso V as a % of the FVC. Also we have found that V iso V, and V iso V % FVC are significantly greater in older subjects, reflecting the age associated changes. Thus it may be unfruitful to use the V iso V, which, though a sensitive index of reducing elasticity, is not as specific as the % increase in Vmax 50% in investigating airway calibre response (15). No further comment is therefore offered on the effects of the bronchodilators on V iso V.

While using the He-O_2 data for investigating the relative roles of beta-adrenergic stimulation and vagolysis on airway calibre, it was observed that both the aerosols improved the % increase

TABLE V : Depicts a comparison between He-O_2 curve data for men > 50 yrs (A) and young men < 40 yrs (B). For men > 50 yr, out of 26 efforts from which data was available only 13 best values (highest for % increase in Vmax 50%, and Vmax 50% ratio; and lowest for V iso V and V as % FVC) have been taken. Values are means±SD. All variables standardised to a ht. of 165 cm.

	n	*(A)* *13*	*(B)* *12*	*P value* *(A vs B)*
1.	Age (yr)	54.9 4.5	26.8 4.6	
2.	Height (cm)	167.1 5.7	166.8 6.9	NS
3.	Weight	62.0 9.3	65.7 8.8	NS
4.	% increase in Vmax 50% with He	37.10 11.78	42.68 9.87	NS
5.	Ratio Vmax 50% He/Air	1.36 0.12	1.43 0.10	NS
6.	V iso V (1)	0.866 0.256	0.657 0.167	P<0.05
7.	V iso V as % of FVC	25.3 5.2	15.4 3.3	P<0.05

in Vmax 50%, and the ratio Vmax 50% He-O_2/ Air (Table II), but the mean differences (post-pre aerosol values) were not significant, the conclusion drawn being that equal dilatation has been produced in the central and the peripheral regions (5). Also, eventhough the salbutamol effect appears to be greater than that produced by ipratropium, it was not significantly so. Thus this method was not helpful in delineating the relative roles of the sympathetic and parasympathetic influences in controlling airway calibre.

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