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Reversibility of induced bronchoconstriction by deep inspiration in asthmatic and normal subjects

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Reversibility of induced bronchoconstriction by deep inspiration in asthmatic and normal subjects. J.R. Wheatley, P.D. Paré, L.A. Engel.

ABSTRACT: **Five normal and five asthmatic subjects underwent a progressive methacholine provocation study. At each concentration inspiratory pulmonary resistance (R_L) was measured, as well as isovolumic maximal flow and residual volume from both partial and complete forced expirations. Results were compared over the R_L range of 6–11 $cmH_2O \cdot l^{-1} \cdot s^{-1}$. The reversibility of bronchoconstriction by deep inspiration was quantified as the ratio of the flow increase to potential maximal increase; the reversibility of gas trapping was the ratio of decrease in residual volume to potential maximal decrease. The reversibility of bronchoconstriction did not differ between the groups. In contrast, the reversibility of gas trapping was smaller in asthmatic subjects (21±17%) than in normals (84±6%). As gas trapping reflects airway closure, our findings suggest that during induced bronchoconstriction airway closure is more resistant to the effects of deep inspiration in asthmatic than in normal subjects but the reversibility of bronchoconstriction by deep inspiration is not different.**

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In normal subjects with pharmacologically-induced bronchoconstriction a deep inspiration transiently reduces airway resistance [1]. However, in asthmatic subjects the effect of a deep inspiration is variable. With spontaneous asthma, deep inspiration usually results in bronchoconstriction [2–7] whereas during pharmacologically-induced airway narrowing transient bronchodilatation is the usual response [3, 6, 8, 9–12]. In fact, it has been suggested that the ability of a deep inspiration to reverse induced bronchoconstriction may be less in asthmatic than in normal subjects. Fish *et al.* [13] showed that when airway responsiveness to inhaled methacholine is used to distinguish normal and asthmatic subjects, a clear separation between the two groups can be demonstrated by using tests which involve a deep inspiration such as the forced expired volume in one second (FEV_1) or maximal expiratory flows. In contrast, tests such as airway resistance, or maximal flow from a partial flow-volume curve do not demonstrate a definitive separation. The authors suggested that a major difference between asthmatic and normal subjects might be this impaired bronchodilating capacity of a deep inspiration rather than enhanced end-organ responsiveness [4].

To further investigate these differences, we have quantitated the bronchodilating effect of a deep inspiration in a group of highly hyperresponsive asthmatics and a group of non-atopic normal subjects during a progressive inhaled methacholine provocation study. From increases in maximal expiratory flow at a fixed reference lung volume and decreases in residual volume, following a deep inspiration, we derived indices of reversibility that differed conceptually from those previously used and allowed quantitative comparisons between the two groups of subjects.

Methods

We studied five normal (4 men and 1 woman) laboratory personnel and five asthmatic (4 men and 1 woman) volunteers (table 1), none of whom had ever smoked cigarettes on a regular basis. The normal subjects gave no history to suggest that they were atopic and had no history of respiratory symptoms. Asthmatic subjects gave histories of regular episodic attacks of wheezing since childhood requiring bronchodilator treatment. All had refrained from use of inhaled bronchodilators for six hours prior to the study and none complained of dyspnoea or wheezing on the day. Theophylline was also withheld for 48 h. No subject gave a history of respiratory tract infection during the preceding month. Informed consent was obtained and the protocol was approved by the Medical Ethics Committee of the Institution.

Each subject was studied in the prechallenge baseline state and then inhaled doubling concentrations of nebulized methacholine (0.03–128 $mg \cdot ml^{-1}$) according to the protocol of Cockcroft *et al.* [14]. We used a Becton-Dickinson nebulizer which delivered 0.26–0.30 ml of

Table 1. – Baseline anthropometric data and lung function

	Age	Sex	FEV_1	FVC	TLC	FRC	RV	RL	$\dot{V}max_{30p}$	$\dot{V}max_{30c}$	$\frac{FEV_1}{FVC}$	PC_{20}	Treatment Regimens
	yrs		%pred	%pred	%pred	%pred	%pred	$cmH_2O \cdot l^{-1} \cdot s^{-1}$	$l \cdot s^{-1}$	$l \cdot s^{-1}$	%	$mg \cdot ml^{-1}$	
Normal													
1	35	M	108	102	96	108	78	1.4	3.8	3.3	87	>128	–
2	45	F	116	113	104	88	82	2.8	2.4	2.4	86	>64	–
3	26	M	107	106	112	102	114	2.7	2.7	3.0	83	>128	–
4	40	M	103	111	119	132	128	2.1	1.9	1.9	76	>64	–
5	31	M	100	102	112	142	143	2.6	2.5	2.5	82	>128	–
Mean ±SEM													
	35		107	107	109	114	109	2.3	2.7	2.6	83		
	±3		±3	±2	±4	±10	±13	±0.3	±0.3	±0.2	±2		
Asthmatic													
1	25	M	69	106	119	146	150	8.9	0.6	0.7	57	0.02	3
2	35	F	102	118	121	123	134	3.0	1.4	1.3	72	0.03	1
3	28	M	88	112	117	151	140	3.2	0.9	1.8	66	0.4	2
4	26	M	88	105	108	121	108	4.0	0.8	1.0	69	0.4	2
5	25	M	89	104	96	87	63	3.3	1.5	1.5	70	0.9	1
Mean ±SEM													
	28		87	109	112	126	119	4.5	1.0	1.2	67		
	±2		±5	±3	±5	±11	±16	±1.1	±0.2	±0.2	±3		

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; RL: pulmonary resistance; $\dot{V}max_{30p}$, $\dot{V}max_{30c}$: maximal expiratory flow at 30% of vital capacity on a partial and complete forced expiration, respectively; FEV_1/FVC: ratio of FEV_1 to FVC on a complete forced expiration; PC_{20}: provocation concentration of methacholine needed to produce a 20% fall in FEV_1; treatment regimens: 1: salbutamol *p.r.n.* 2: regular salbutamol daily; 3: regular salbutamol and theophylline SR daily.

methacholine solution over 2 min at an air flow rate of 6 $l \cdot min^{-1}$. After each dose of methacholine, subjects were instructed to avoid deep inspirations or sighing for 2 min, following which the measurements were made. Asthmatic subjects commenced with 0.03 $mg \cdot ml^{-1}$ methacholine and doubling concentrations were inhaled until FEV_1 decreased by at least 50%. In contrast, normal subjects started with 0.5 $mg \cdot ml^{-1}$ methacholine and were given doubling concentrations until 64–128 $mg \cdot ml^{-1}$ was reached.

After a stable end-expiratory lung volume had been established, pulmonary resistance (RL) was measured while subjects breathed at a spontaneous frequency. Tidal volume was fixed at 750 ml by having the subject breathe between predetermined limits displayed to them on an oscilloscope. A partial forced expiration from tidal end-inspiratory volume to residual volume (RV_p) was then performed, followed by a rapid inspiration to total lung capacity (TLC) and an immediate complete forced expiration to residual volume (RV_c) (fig. 1). This sequence of measurements was obtained under baseline conditions and after each dose of methacholine.

Transpulmonary pressure was measured by comparing mouth and oesophageal pressure using a Validyne MP 45 (±100 cmH_2O) differential pressure transducer. Oesophageal pressure was measured with a balloon using the technique of MILIC-EMILI *et al.* [15].

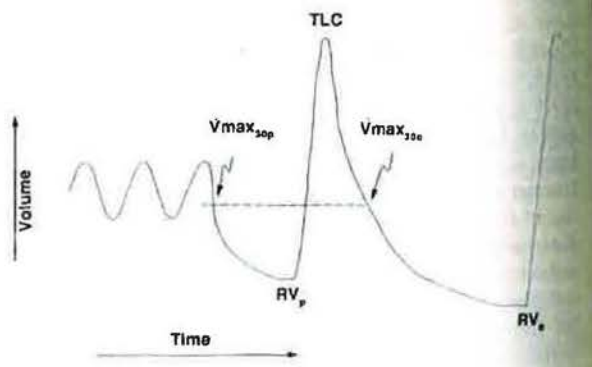

Fig. 1. – Schematic representation of the sequence of forced expirations for each set of measurements. RV_p and RV_c are the residual volumes after the partial and complete forced expirations, respectively. $\dot{V}max_{30p}$ and $\dot{V}max_{30c}$ are the maximal expiratory flows at 30% of baseline vital capacity on partial and complete manoeuvres, respectively. TLC is total lung capacity.

During measurements of RL, flow was recorded using a Fleisch No. 2 pneumotachograph coupled to a Validyne MP 45 (±5 cmH_2O) differential pressure transducer and the signal was electrically integrated to give volume. During forced expiratory manoeuvres, flow and volume were measured with an electronic autospirometer (Minato AS-800) and recorded with the pressure signals on a Hewlett-Packard 8-channel

stripchart recorder (7758B) and magnetic tape recorder (3968A). The transpulmonary pressure-flow relationship was subsequently measured by the method of MEAD and WHITTENBERGER [16] and RL was obtained from the inspiratory limb of the pressure-flow curve at a flow rate of 0.5 $l \cdot s^{-1}$. On a separate occasion, absolute lung volumes were measured in a volume displacement plethysmograph using the Boyle's Law method [17].

Data analysis

Total lung capacity was assumed not to change throughout the study, including the period of induced bronchoconstriction [18]. The functional residual capacity was derived from the difference between the end expiratory lung volume during quiet breathing and TLC. Other subdivisions of lung volume were derived from the forced expiratory manoeuvres by reference to TLC. Baseline residual volume (RV) was calculated as the mean of three reproducible manoeuvres. The FEV_1 and forced vital capacity (FVC) were obtained from the complete manoeuvre, and the FEV_1/FVC ratio was calculated. The methacholine concentration at which FEV_1 reached a value 20% below baseline (PC_{20}) was determined by interpolation.

The volume from TLC to 30% of baseline vital capacity (VC_b) was used to define a fixed reference volume point at which flows were compared between the partial and complete flow-volume curves. Isovolumic points for each dose of methacholine were obtained by subtracting this reference volume (equal to 70% VC_b) from TLC. The volume at 30% VC_b was chosen as it allowed maximal volume overlap between the asthmatic and normal subjects when measuring effort-independent flows from the partial ($\dot{V}max_{30p}$) and complete ($\dot{V}max_{30c}$) manoeuvres (fig. 1). The isovolumic points are more accurately determined by subtracting a fixed volume from TLC (which does not change) than by adding a fixed volume to RV (which increases with bronchoconstriction).

To compare the effectiveness of a deep inspiration in reversing bronchoconstriction and gas trapping in normal and asthmatic subjects, we measured the responses to a deep inspiration at similar levels of RL (as a measure of induced bronchoconstriction). Mean values of $\dot{V}max_{30p}$, $\dot{V}max_{30c}$, RV_p and RV_c were compared in the range 6–11 $cmH_2O \cdot l^{-1} \cdot s^{-1}$. This resistance range was chosen as there was a reasonable overlap of values between the two groups (fig. 2). One normal subject did not reach an RL of 6 $cmH_2O \cdot l^{-1} \cdot s^{-1}$, so values obtained at his maximum level of RL were used for analysis.

The mean values during bronchoconstriction (BC) were compared with the mean baseline (BL) values within each group as well as between the two groups. The reversibility of bronchoconstriction by a deep inspiration was defined as the ratio of the actual increase in flow to the potential increase back to the baseline value [4] (fig. 3):

$$\frac{\dot{V}\ max_{30c}\ (BC) - \dot{V}\ max_{30p}\ (BC)}{\dot{V}\ max_{30c}\ (BL) - \dot{V}\ max_{30p}\ (BC)} \times 100 \text{ (reversibility index)}$$

Gas trapping was quantitated by calculating the post-methacholine RV_p and RV_c values as a percent of baseline RV_c. The reversibility of induced gas trapping was calculated as the ratio of actual decrease in residual volume to the potential maximal decrease (fig. 4):

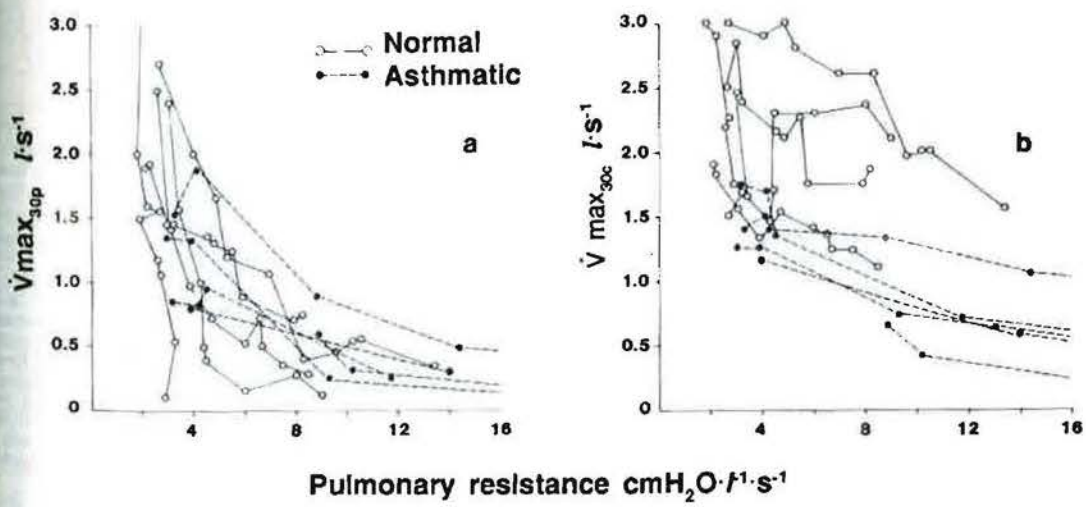

Fig. 2. – Maximal expiratory flow at 30% baseline vital capacity (a) before deep inspiration ($\dot{V}max_{30p}$) and (b) after deep inspiration ($\dot{V}max_{30c}$) plotted against pulmonary resistance (RL) during progressive bronchoconstriction induced by methacholine aerosol in asthmatic and normal subjects. Curves represent results for individual subjects, and in the absence of data points indicate further results at a higher resistance or maximal flow. a: Note the similarity of flows for normal and asthmatic subjects with progressive bronchoconstriction over the same RL range. b: Note the greater flows for the normal relative to the asthmatic subjects, and also the higher values in both groups than during a partial forced expiration (a).

Table 2. – Maximal expiratory flows

	Normal n=5		Asthmatic n=5		Between group comparisons, p
$\dot{V}max_{30p}$ $l \cdot s^{-1}$					
Baseline	2.66±0.31		1.04±0.17		<0.005
Bronchoconstricted	0.46±0.09		0.57±0.09		NS
p	<0.005		<0.04		
$\dot{V}max_{30c}$ $l \cdot s^{-1}$					
Baseline	2.62±0.24		1.26±0.19		<0.005
Bronchoconstricted	1.84±0.17		0.92±0.13		<0.005
p	<0.03		NS		
$\dot{V}max_{30c}$-$\dot{V}max_{30p}$ $l \cdot s^{-1}$					
Baseline	-0.04±0.13		0.22±0.18		NS
Bronchoconstricted	1.38±0.21	(<0.005)	0.34±0.07	(<0.01)	<0.005
$\frac{\dot{V}max_{30c}\ (BC) - \dot{V}max_{30p}\ (BC)}{\dot{V}max_{30c}\ (BL) - \dot{V}max_{30p}\ (BC)}$ %	64±8		53±9		NS
$\frac{\dot{V}max_{30p}\ (BC)}{\dot{V}max_{30c}\ (BC)}$ %	28±7		63±6		<0.01
$\frac{\dot{V}max_{30c}\ (BC)}{\dot{V}max_{30p}\ (BC)}$ %	516±448		162±33		NS

Data expressed as mean±SEM. Statistical comparisons between baseline (BL) and bronchoconstricted (BC) data used paired t-tests (p). Between-group comparisons used non-paired t-tests. Numbers in brackets refer to p value (paired t-test). NS: not significantly different; $\dot{V}max_{30p}$, $\dot{V}max_{30c}$: maximal expiratory flows at 30% of baseline vital capacity on partial and complete forced expirations, respectively; $\dot{V}max_{30c}$ (BC) - $\dot{V}max_{30p}$ (BC)/ $\dot{V}max_{30c}$ (BL) - $\dot{V}max_{30p}$ (BC): reversibility index.

$$\frac{RV_p\ (BC) - RV_c\ (BC)}{RV_p\ (BC) - RV_c\ (BL)} \times 100 \text{ (reversibility index)}$$

Statistical analysis was made using Student's t-test for paired and unpaired samples.

Results

Table 1 shows the baseline values for subdivisions of lung volume, FEV_1/FVC, RL, partial and complete maximal expiratory flows and the calculated PC_{20} for each subject. The starting FEV_1 of the asthmatic group (87±5% predicted) was significantly less than that of the normals (107±3% predicted, p<0.05). The FEV_1/FVC ratio was also significantly lower for the asthmatic group. The individual values for maximal flow at 30% VC_b showed a wide degree of variability between subjects. Nevertheless, the mean values of both $\dot{V}max_{30p}$ and $\dot{V}max_{30c}$ were significantly reduced in the asthmatic subjects (p<0.005). Following a deep inspiration there was no change in the mean flow at 30% VC_b for either group (p>0.4). However, one of the asthmatic subjects did show a substantial increase in $\dot{V}max_{30}$, whereas none showed a bronchoconstriction response.

In the RL range 6–11 $cmH_2O \cdot l^{-1} \cdot s^{-1}$, there was no significant difference in $\dot{V}max_{30p}$ between the asthmatic (0.57±0.09 $l \cdot s^{-1}$) and normal groups (0.46±0.09 $l \cdot s^{-1}$) (fig. 2, table 2). Following a deep inspiration, the maximal flows (corresponding to the same RL range) increased in both the normal and asthmatic subjects, with a significantly greater increase in the normal

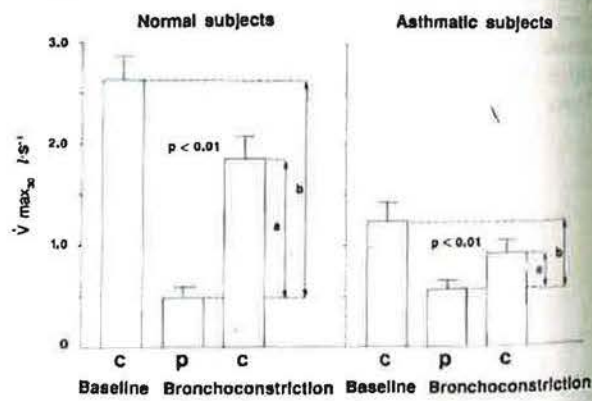

Fig. 3. – Isovolumic maximal expiratory flows ($\dot{V}max_{30}$) for normal and asthmatic subjects under baseline conditions (c) and during bronchoconstriction (pulmonary resistance 6–11 $cmH_2O \cdot l^{-1} \cdot s^{-1}$) before (p) and after (c) a deep inspiration. Bars represent ±1 SEM. Reversibility of the induced bronchoconstriction by a deep inspiration is defined as the ratio of the actual increase in flow (a) to the potential maximal increase (b). Note i) the significant increase in flows after deep inspiration in both asthmatic and normal subjects and ii) the similar reversibility index (a/bx100) in both groups (see table 2).

Table 3. – Residual volumes

		Baseline		Bronchoconstriction	
		RV_p l	RV_c l	RV_p l	RV_c l
Normal	1	1.50	1.38	2.52	1.42
	2	1.33	1.34	2.01	1.41
	3	1.74	1.87	2.51	1.92
	4	2.45	2.28	2.96	2.50
	5	2.45	2.41	2.66	2.49
	Mean	1.89	1.86	2.53†	1.95*‡
	±SEM	0.24	0.22	0.15	0.24
Asthmatic	1	1.91	1.77	1.96	2.02
	2	2.09	2.17	2.64	2.47
	3	2.88	2.32	3.27	2.92
	4	2.18	1.61	2.29	1.83
	5	0.93	1.00	1.12	1.13
	Mean	2.00	1.77	2.26†	2.07‡
	±SEM	0.31	0.23	0.36	0.30

RV_p, RV_c: the residual volumes at the end of the partial and complete forced expirations, respectively; *: $p<0.02$ with respect to RV_p (bronchoconstriction); †: $p<0.05$ with respect to RV_p (baseline); ‡: $p<0.05$ with respect to RV_c (baseline); statistical comparisons used paired t-tests (p).

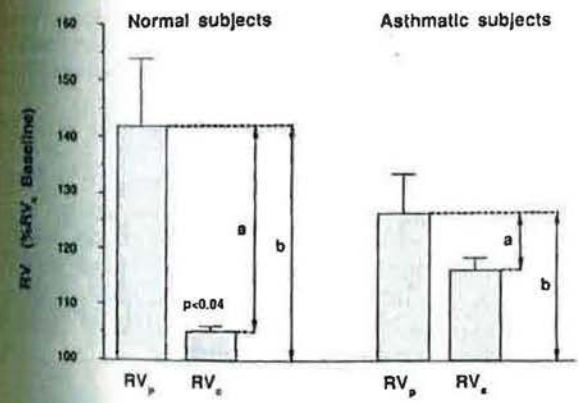

Fig. 4. – Residual volumes (RV) as a percentage of RV after complete forced expiration to residual volume before methacholine challenge (%RV_c baseline) for normal and asthmatic subjects during bronchoconstriction before deep inspiration (RV_p) and after deep inspiration (RV_c). Bars represent ±1 SE. Reversibility of the induced gas trapping (increase in RV) is defined as the ratio of the actual decrease in RV (a) to the potential maximal decrease (b). Note i) the significant decrease in gas trapping after deep inspiration in normal subjects ii) the smaller reversibility index (a/bx100) in asthmatic subjects (see text).

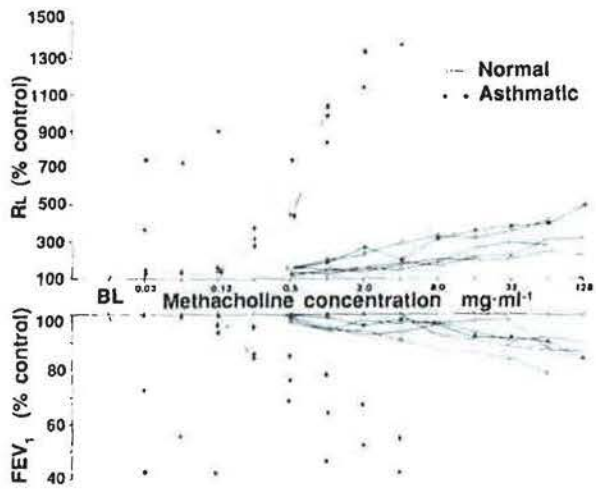

Fig. 5. – Methacholine dose-response curves for individual asthmatic and normal subjects, showing the increase in pulmonary resistance (R_L) and decrease in forced expiratory volume in one second (FEV_1) with progressive increase in aerosol concentration. Note the lower threshold concentrations as well as the steeper rises and absence of plateaus in both the R_L and FEV_1 curves of asthmatic subjects. BL: baseline.

subjects (fig. 2, table 2). The increase in maximal flow following deep inspiration was used to calculate the reversibility of bronchoconstriction (fig. 3), by taking the ratio of the actual increase in flow (shown as 'a') to the potential maximal increase (shown as 'b'). The reversibility index was calculated as a/b×100 and indicated substantial reversibility of bronchoconstriction for both the normal (64±8%) and asthmatic (53±9%) subjects with no significant difference between the two groups (table 2). For both groups, reversibility decreased with increasing R_L, resulting in small degrees of reversibility for asthmatics at high R_L, but similar degrees for the two groups over the range of 6–11 $cmH_2O \cdot l^{-1} \cdot s^{-1}$.

The data for RV_p and RV_c (in litres) is presented in table 3. Following induced bronchoconstriction, RV_p increased significantly in both the normal and asthmatic

groups. A deep inspiration then decreased RV significantly in the normal but not in the asthmatic group. RV_p (as % RV_c baseline) increased significantly in both normal (142±12%) and asthmatic subjects (126±7%) during bronchoconstriction. RV (as % RV_c baseline) during bronchoconstriction decreased significantly after a deep inspiration in the normal subjects (38±13%, $p<0.04$), but not in the asthmatic group (9±6%) (fig. 4). The decrease in RV following deep inspiration was used to calculate the reversibility of gas trapping (fig. 4), by taking the ratio of the actual decrease in RV (shown as 'a') to the potential maximal decrease (shown as 'b'). The reversibility index was calculated as a/b × 100 and showed almost complete reversal of gas trapping in the normal group (84±6%) but significantly less in the asthmatic group (21±17%, $p<0.01$).

Asthmatic subjects were clearly more sensitive to methacholine, showing significant changes in RL and FEV_1 at very much lower concentrations (fig. 5). In addition, the shape of the dose-response curves using both RL and FEV_1 differed between the two groups. The asthmatic subjects had a steeper rise in RL and fall in FEV_1, with no plateau despite increases in RL to 40–60 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ and decreases in FEV_1 to values less than 50% of baseline. In normals, much higher concentrations of methacholine were used and the degree of bronchoconstriction produced was much less whether measured as RL (before deep inspiration) or FEV_1.

Discussion

The findings in this study demonstrate that during induced bronchoconstriction the increase in maximal flow following a deep inspiration represents similar reversibility of bronchoconstriction for both asthmatic and normal subjects. In contrast, the reversibility of gas trapping is systematically smaller in subjects with asthma.

In previous studies the bronchodilatation after deep inspiration has been quantified by the absolute change in maximal flow ($\dot{V}max_c$-$\dot{V}max_p$) or the ratios of measurements, *e.g.* $\dot{V}max_{30p}/\dot{V}max_{30c}$ and $\dot{V}max_{30}/\dot{V}max_{30p}$ [2, 7, 9]. However, we feel that it is necessary to relate the absolute change in maximal flow to the largest potential change from control values. This is the basis of the reversibility index which was chosen for two reasons. Firstly, it takes into account the inter-individual differences due to variations in baseline maximal flows. This is important in our study, as the differences in baseline flow between asthmatic and normal subjects were large (table 1). Secondly, the reversibility of acute bronchoconstriction by a deep inspiration involves mechanisms that differ from those responsible for more chronic airway narrowing. The latter may be caused by relatively permanent changes in the mucosa and bronchial wall thickness in addition to the acute effects of smooth muscle shortening. Thus, the absolute changes (or ratios) of maximal flow will not only measure the effect of a deep inspiration on acute bronchoconstriction, but also be determined by other factors which contribute to permanent changes in the airway wall. Therefore, the reversibility index is more appropriate to quantitate the reversal of acute induced bronchoconstriction by a deep inspiration.

In our study, the reversibility of induced bronchoconstriction by a deep inspiration was not significantly different between normal and asthmatic subjects (fig. 3). This result differs from that obtained by FISH *et al.* [4] who showed only a 17% reversibility in their asthmatic group compared to a 60% reversibility in the non-asthmatics. The other ratios, *e.g.* $\dot{V}max_{30p}/\dot{V}max_{30c}$ and $\dot{V}max_{30}/\dot{V}max_{30p}$, have been calculated for our subjects (table 2). Although the ratios are useful to detect the presence of bronchodilatation, for reasons given above, a quantitative comparison is more appropriately achieved by the reversibility index.

Thus it appears that both asthmatic and normal subjects bronchodilate following deep inspiration. Bronchodilatation is larger in the normal subjects in terms of absolute flow but reversibility of the induced bronchoconstriction by deep inspiration is no different between the two groups.

Our results, from the only study to directly compare a normal and asthmatic group, are consistent with the majority of published data. There certainly is a smaller response to deep inspiration in the asthmatic group if only the absolute flow increase is considered. However, for reasons previously discussed, it is more appropriate to use a reversibility index to compare the two groups. Due to the lower baseline flows in the asthmatic group, the degree of reversibility in response to deep inspiration is in fact similar to the normal. Therefore it is the superiority of our data analysis, and the ability to directly compare asthmatic and normal groups that leads to conclusions different from those in previous published work. We believe that our analysis more accurately reflects the magnitude of reversibility of acute bronchoconstriction by a deep inspiration.

It is noteworthy that we deliberately chose a group of asthmatic subjects with a high degree of sensitivity to methacholine, and a group of normal subjects who were unresponsive. Given the wide range of variability in responsiveness of asthmatic subjects, we reasoned that by choosing a very reactive group, we would be more likely to see a significant difference from a normal group if such a difference existed. Hence, the fact that we could not find a difference in reversibility of bronchoconstriction between these two groups at the opposite end of the sensitivity spectrum strengthens our conclusions.

Assuming that the major cause of gas trapping is airway closure, the similar amount of gas trapping induced in the asthmatic and normal subjects implies a similar degree of closure in both groups for a comparable amount of induced bronchoconstriction. However, the response to a deep inspiration consisted of an almost full reversal of the gas trapping in normals, whereas no significant decrease was observed in asthmatic subjects (fig. 4). The difference in reversibility

of the induced gas trapping between the two groups emphasizes the importance of measuring maximal flow at a fixed volume decrement below TLC rather than up from RV.

The different response of airway closure to deep inspiration in the two groups could theoretically be due to a prolonged time constant of expiration in the asthmatic subjects. If the expiratory time were inadequate, the subjects would not be able to reach true RV. However, in our study the expiratory times during bronchoconstriction for normal and asthmatic subjects were similar for both partial and complete manoeuvres and visual inspection of the volume-time records showed an adequate plateau in the volume signal for all subjects.

The smaller reversibility of airway closure may not conflict with the larger reversibility of bronchoconstriction. The luminal narrowing in normal airways may be entirely due to smooth muscle contraction, but in asthmatic airways, some of the narrowing may also be due to airway secretions and/or mucosal oedema. The bronchodilatation response to deep inspiration is less likely to be due to a neurological reflex [19] than to stress relaxation of contracted bronchial smooth muscle. If this were the case, a deep inspiration could cause relaxation of contracted airway smooth muscle, but would not decrease airway secretions or mucosal oedema. This would result in a similar relaxation of contracted muscle in larger airways where the contribution of any mucus lining is relatively small. In contrast, reversibility of airway closure in asthmatic subjects could appear to be less due to secretions and/or mucosal oedema encroaching onto the lumen of the smaller airways. This explanation does not exclude the possibility that peripheral airways of asthmatic subjects respond differently to inhaled methacholine.

The published studies present a somewhat confusing picture of the bronchodilating effect of a deep inspiration. In normal subjects, with induced bronchoconstriction, NADEL and TIERNEY [1], measuring airway resistance, demonstrated bronchodilatation following a deep inspiration. Without bronchoconstriction, this effect was minimal. In asthmatic subjects, there seems to be a difference in response to deep inspiration between spontaneous asthma and pharmacologically-induced bronchoconstriction. OREHEK *et al.* [6] have clearly shown that the majority of subjects with spontaneous asthma respond to a deep inspiration with bronchoconstriction, although some show little change and others even bronchodilate [2, 5, 7, 8]. The situation is much less clear with pharmacologically-induced bronchoconstriction in asthmatic subjects, [4, 6, 8, 20] where the response again varies from bronchodilatation to bronchoconstriction [3, 4, 6, 8, 20]. However, in only two of the studies was maximal flow measured before and immediately after deep inspiration [4, 9].

In contrast to the findings in previous studies, all our asthmatic subjects showed an increase in maximal flow after deep inspiration (fig. 2). FISH *et al.* [3] measured specific airway conductance at the earliest 7 s after the deep inspiration. Assuming that maximal bronchodilatation occurs at the time of maximal inflation, a 7 s delay in measuring airway conductance could lead to significant underestimation of the degree of bronchodilatation. There may be a shorter time-course of the bronchodilatation response in asthmatic subjects, leading to an apparent difference between asthmatic and normal responses to deep inspiration when measured by airway resistance. To avoid methodological errors, it is preferable to make a measurement as close as possible to the time of maximal inflation. Thus maximal flow manoeuvres should measure the magnitude of bronchodilatation after deep inspiration more accurately than airway resistance. In one study in which maximal flow after a deep inspiration was measured, FISH *et al.* [4] found no significant increase of maximal flow in the group, although some subjects increased flow substantially. Another study of maximal flow after deep inspiration [9] showed marked bronchodilatation in eight asthmatic subjects. These two studies provide some support for the concept of similar reversibility of induced bronchoconstriction in asthmatic subjects.

Previous studies have used specific airway conductance as a measure of bronchoconstriction. Pulmonary resistance is influenced by the same range of variables and therefore provides the same basis for assessment of the amount of airway narrowing. Inspiratory pulmonary resistance is also volume dependent, but as functional residual capacity (FRC) did not change significantly in either group over the relatively low R_L range in which maximal flows were compared, we used the R_L measurements without volume corrections to assess the degree of bronchoconstriction prior to a deep inspiration. Thus the use of pulmonary resistance in our study is neither a source of error nor a source of difference from other studies.

Many previous studies suggest that there is a fundamental difference in the response of asthmatic airways to a deep inspiration [4, 6, 13]. FISH *et al* . [13] showed that during induced bronchoconstriction the responses are similar for specific airway conductance but differ for FEV_1 between non-asthmatic subjects with hay fever and those with asthma. This has been interpreted as an impaired ability of asthmatic subjects to reduce bronchomotor tone by a deep inspiration. It was even postulated that this impaired ability may be the major factor in the bronchial hyperreactivity of asthmatic subjects [4]. However, our results indicate that the difference in responsiveness between asthmatic and normal airways cannot be adequately explained by an impaired response to a deep inspiration (fig. 5). Airways of asthmatic subjects are more sensitive in terms of the threshold dose for methacholine and more responsive as shown by the increased slope of the dose-response curves [21]. Although we deliberately chose an asthmatic group with low threshold values, it is clear that our asthmatic subjects had much steeper slopes of their dose-response curves. This was true for both the increase in R_L (before deep inspiration) or the decrease in FEV_1 (after deep inspiration). If bronchial reactivity were determined by the response to a deep inspiration, then the slope of the R_L dose-response curve would

increase at a similar rate for both normal and asthmatic subjects whereas the slope of the FEV_1 dose-response curve would be less steep in normal subjects. The difference in the slopes of the R_L dose-response curves between the two groups (before deep inspiration) supports a true difference in bronchial responsiveness to methacholine.

Surprisingly, the curves of $\dot{V}max_{30}$ plotted against R_L (fig. 2), were similar in both shape and position for all subjects. This shows that for a given degree of bronchoconstriction, both asthmatic and normal subjects have similar maximal flows at the same lung volume. The factors which influence maximal flow and R_L are similar, but tests of forced expiration have an additional sensitivity to the critical alveolar-to-mouth pressure difference which is sufficient to achieve maximal flow. This is determined by the magnitude of lung elastic recoil and the properties of the airways. However, there appears to be no change in the elastic properties of asthmatic lungs in pharmacologically-induced bronchoconstriction [22], and since the flows are measured at isovolume, elastic recoil pressure in each subject is similar at baseline and during bronchoconstriction. If the elastic recoil pressure does not change, and the maximal flows are similar, the pressure-area characteristics of the airways should also not differ. Thus, our results suggest that for a given degree of induced bronchoconstriction, asthmatic and normal subjects show similar dynamic collapsibility of their airways.

In summary, asthmatic and normal subjects show a difference in bronchial responsiveness that is not explained by lung volume history. For a given degree of induced bronchoconstriction, both groups show similar dynamic collapsibility of their airways. Following a deep inspiration normal subjects show greater bronchodilatation than asthmatic subjects. However, the degree of reversibility of induced bronchoconstriction by deep inspiration does not differ between the two groups. In so far as gas trapping is related to airway closure, our results suggest that in asthmatic subjects airway closure is more resistant to the effects of a deep inspiration than it is in normal subject

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Réversibilité de la bronchoconstriction induite par l'inspiration profonde chez des sujets asthmatiques et normaux. J.R. Wheatley, P.D. Paré, L.A. Engel.

RÉSUMÉ: Cinq sujets normaux et cinq sujets asthmatiques ont été comparés au cours d'une étude de provocation progressive à la métacholine. L'on a mesuré à chaque concentration la résistance pulmonaire inspiratoire (R_L), ainsi que le débit maximal isovolume et le volume résiduel, au cours d'expirations forcées partielles et complètes. Les résultats ont été comparés dans toute la zone de R_L de 6 à 11 $cmH_2O \cdot l^{-1} \cdot s$. L'effet de l'inspiration profonde sur la bronchoconstriction a été quantifié par un index de réversibilité défini comme la relation de l'augmentation effective de débit à l'augmentation potentielle maximale; la réversibilité du trappage des gaz est la relation de la diminution effective du volume résiduel à sa diminution maximale potentielle. Après une inspiration profonde, les sujets normaux augmentent le débit maximal davantage (bronchodilatation plus marquée) que les sujets asthmatiques. Toutefois, la réversibilité de la bronchoconstriction par l'inspiration profonde n'est pas différente entre les sujets normaux (64±8%) et les sujets asthmatiques (53±9%). Par contre, la réversibilité du trappage des gaz est plus faible chez les sujets asthmatiques (21±17%) que chez les normaux (84±6%; $p<0.01$). Comme le trappage des gaz est le reflet de l'occlusion des voies aériennes, nos observations suggèrent que pendant la bronchoconstriction induite, l'occlusion des voies aériennes est plus résistante à l'effet de l'inspiration profonde chez les asthmatiques que chez les sujets normaux, mais que la réversibilité de la bronchoconstriction par une inspiration profonde ne diffère pas sensiblement entre les deux groupes.

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