Evaluation of asymptomatic subjects with low forced expiratory ratios (FEV_1/VC)

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Abstract

Background - Heightened bronchial hyperreactivity is frequently associated with airflow limitation, atopy, or cigarette smoking. The purpose of this study was to evaluate healthy subjects with significantly low values of forced expiratory volume in one second/vital capacity % ($FEV_1/VC\%$) by measuring their airway response to exercise and methacholine challenge, compared with a control group with normal spirometric values.

Methods - Eighty four healthy subjects with significantly low flow rates (group A, $FEV_1/VC\% < 2$ SD% predicted) were evaluated and compared with 37 subjects with normal flow rates (group B). Static lung volumes, spirometric tests, exercise, and methacholine challenges were performed.

Results - Lung volumes were normal for both groups. Mean $FEV_1/VC\%$ was 69% for group A and 82% for the control group. Salbutamol improved baseline FEV_1 in eight subjects in group A (mean 15%), while methacholine induced a drop in FEV_1 in 12 subjects. The dose-response curve to methacholine reached a plateau in all the responders. None of the subjects in the control group improved their baseline $FEV_1/VC\%$ to salbutamol, but three showed bronchial hyperreactivity similar to those in group A.

Conclusions - Bronchial hyperreactivity does not occur more often in asymptomatic subjects with mildly low $FEV_1/VC\%$ so these subjects do not require special investigations for airway disease.

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Bronchial hyperreactivity to histamine and methacholine is a fundamental feature in both patients with bronchial asthma¹ and those with chronic obstructive pulmonary disease (COPD).² In patients with COPD the level of bronchial hyperreactivity is partially determined by the initial extent of airway obstruction. Ramsdale *et al*³ found a correlation between the initial forced expiratory volume in one second (FEV_1) and the degree of bronchial hyperreactivity in these patients.

Most studies performed on asthmatic subjects report no correlation between the extent of bronchial hyperreactivity and the baseline airway calibre.⁴⁻⁶ Ryan *et al*⁷ showed that asthmatic patients may have a moderate or severe increase in bronchial hyperreactivity ($PC_{20} < 2$ mg/ml to histamine) when their FEV_1 is

within 10% of maximum. In subjects with symptomatic airflow limitation bronchial hyperreactivity is a concomitant finding. We occasionally encounter young asymptomatic subjects with a low ratio of FEV_1 to vital capacity ($FEV_1/VC\%$), the significance of which is not entirely clear. We therefore measured the airway response to exercise and methacholine of healthy subjects with a low $FEV_1/VC\%$ and compared the results with a control group.

Methods

Eighty four subjects aged 17-39 (mean 24) years (group A) were included on the basis of two spirometric studies (including one in our laboratory) showing $FEV_1/VC\%$ of less than two standard deviations of their predicted mean.⁸ The subjects were examined at the Chest and Allergy Institute, Tel-Aviv Medical Center, based on previous routine spirometric measurements performed elsewhere.

Initial screening excluded subjects with obvious causes for bronchial hyperreactivity including smoking, atopy, or recent viral respiratory infection. The remaining 84 subjects underwent the following measurements: (1) physical examination; (2) spirometric testing and measurement of static lung volumes using a Jaeger Masterlab and slow vital capacity measured by an expiratory manoeuvre with the best of three reproducible measurements being recorded; (3) measurement of the effect of exercise challenge on the spirometric data as previously described.⁹ Each patient underwent spirometric tests followed by 10 minutes running on a treadmill (Quinton) reaching 90(5)% of maximal predicted heart rate. Spirometric testing was repeated 15 minutes later and a drop of $\geq 15\%$ in FEV_1 was considered significant; (4) methacholine challenge performed according to a modification of Chai's method, not using a dosimeter.¹⁰ A Devilbis (645) nebuliser delivering compressed air at a rate of 6 l/min was used for inhalation challenge. Each patient inhaled increasing concentrations of methacholine (0.07, 0.15, 0.3, 0.6, 1.5, 3, 6, 12, 25 mg/ml), each of which was inhaled by five inspirations from FRC to TLC. Spirometric parameters were measured at baseline and repeated 1.5 minutes after each dose of methacholine until at least two technically correct manoeuvres were obtained; the better value was recorded. The concentration inducing a 20% drop in FEV_1 was calculated from the semilogarithmic dose-response curve. The provocation was continued until the last dose in all subjects.

Each subject participated in three study

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days at the same time of the day within a two week period. On day 1 baseline pulmonary function tests and response to salbutamol were measured, on day 2 exercise challenge was performed, and on day 3 a methacholine challenge was performed. Subjects who demonstrated bronchial hyperreactivity underwent skin tests (prick) with environmental allergens (dust, mite, cockroach, mixed moulds, mixed grasses, mixed trees, dog, cat, with histamine and saline as control). These subjects also had an additional bronchial hyperreactivity evaluation by measuring peak expiratory flow rates (mini Wright) twice a day for a week.

As a control group 37 young healthy men were included in the study (group B). All were employed by the hospital and had volunteered for the study. None were smokers, and none had atopy nor recent viral respiratory infections. They all underwent the same evaluations as those in group A.

The study was approved by our local Helsinki Ethical Committee.

STATISTICAL ANALYSIS

The data obtained from both groups (static lung volumes, flow rates, and the rates of bronchial hyperreactivity) were analysed using the Student's paired *t* test.

Results

The subjects in group A fulfilled the criteria of having FEV₁/VC% < 2 SD% predicted, while those in group B had normal spirometric values (FEV₁/VC% > 2SD). The difference between the two groups was significant for FEV₁/VC% (*p* < 0.05). All were healthy men with no history of airways disease and most participated in strenuous physical activity. Simple anthropometric data of the groups are summarised in table 1.

A summary of their baseline pulmonary function is given in table 2. Although the mean values for lung volumes (VC, FVC, TGV, and TLC) were high in group A, all were within the normal range and no significant differences were found. Salbutamol inhalation (1 ml of 5 mg/2 ml normal saline) significantly improved the baseline FEV₁ (by more than 10%) in eight of the subjects in group A (table 3) and in none of the control group. Treadmill running did not have any effect on spirometric parameters in either group. Methacholine induced a significant drop in FEV₁ in 12 subjects from group A and in three from group B. An interesting feature of the airway responses in both groups was the fact that at certain points all the subjects reached a plateau, after which no further drop in FEV₁ was observed (figure). The rates of bronchial hyperreactivity in both groups and the shape of the dose-response curve were not significantly different. Two of the subjects in group A and one in group B had positive skin tests (> 5 mm weal diameter), two to mite, and one to grass mix; they denied atopic symptoms.

Table 1 Subject characteristics

	Group A		Group B	
	Mean	Range	Mean	Range
Age (years)	24	17-44	27	22-48
Height (cm)	178	170-185	174	169-182
Weight (kg)	75	60-100	76	62-92

Table 2 Baseline pulmonary function parameters expressed as percentage predicted

	Group A		Group B	
	Mean	Range	Mean	Range
VC	108	82-125	102	83-110
FVC	109	86-130	103	84-108
TGV	121	80-145	109	80-110
TLC	107	81-126	103	83-109
RV/TLC	115	91-155	106	92-112
TGV/TLC	111	93-164	105	90-110
FEV ₁	86	66-118	91	77-110
FEV ₁ /VC	69*	64-73	82*	76-92
MEF ₂₅	62	25-84%	74	64-89
MEF ₅₀	64	28-83%	73	62-91

VC=vital capacity (slow); FVC=forced vital capacity; TGV=thoracic gas volume; TLC=total lung capacity; RV=residual volume; FEV₁=forced expiration volume in one second; MEF₂₅, MEF₅₀=maximal expiratory flow at 25% and 50% of VC.
* *p* < 0.05.

Table 3 Effect of salbutamol inhalation on pulmonary function in responders (percentage)

Patient no.	VC%	FEV ₁ %	FEV ₁ /VC%	MEF ₅₀
4	-1	14	14	50
6	-2	13	14	43
20	0	12	12	28
25	-2	17	20	53
40	-2	15	17	35
51	2	17	15	25
60	3	18	14	40
72	-2	13	15	33
Mean		15	15	38
SD		2	2	10

Individual methacholine dose-response curves in 12 asymptomatic subjects with low flow rates (FEV₁/VC%) (group A) and in three subjects with normal flow rates (group B).

The mean change in peak expiratory flow rate (Δ PEF%) was expressed by:

$$\frac{\text{PEF morning} - \text{PEF evening}}{\text{PEF morning}}$$

For the nine subjects in group A who completed the test for the whole week Δ PEF was 12 (3)%; for the six subjects who had $PC_{20} < 8 \text{ mg\%}$ (asthmatic range) the mean Δ PEF was 17 (2)%, and for the three who had $PC_{20} > 8 \text{ mg\%}$ it was 9 (3)%. There was a good correlation between the PC_{20} of the six hyper-reactive subjects to the Δ PEF ($p < 0.05$). The mean Δ PEF for the control group was 11%.

Discussion

Asymptomatic subjects found on routine screening to have significantly low $FEV_1/VC\%$ ($< 2 \text{ SD\%}$ predicted) were evaluated for airway disease. None of the subjects had any common risk factors for developing airway disease^{11,12} or viral respiratory tract infection,¹³ and none had a first degree relative with bronchial asthma.¹⁴ Two who had bronchial hyperreactivity were also atopic upon skin testing.

In spite of the significantly low $FEV_1/VC\%$ in group A the other pulmonary function tests were found to be in the normal range. Following heavy exercise there was no change in FEV_1 and the rate of bronchial hyperreactivity was not significantly different between the two groups. It also appears that high lung volume, as seen in a few of the subjects, did not affect the rate or the degree of bronchial hyperreactivity. As expected, the subjects with bronchial hyperreactivity also had significant fluctuation in their PEF during the day.

There are relatively few reports on the relation between non-specific bronchial hyperreactivity and pulmonary function. In these reports increased responsiveness was associated with a decreased level of pulmonary function.¹⁻³⁷ However, little insight was provided of this relation in healthy subjects as most studies have concentrated on selected populations such as smokers, asthmatics, bronchitics or other groups of subjects with disease. Possible selection bias and the occurrence of disease itself on other factors may therefore have affected the association between non-specific bronchial hyperreactivity and pulmonary function.

Malo *et al*¹⁵ examined 100 non-smoking volunteers who were completely free of respiratory symptoms in a cross sectional study and found that PC_{20} methacholine was related to the baseline FEV_1 . Welty *et al*¹⁶ studied a random population of 171 adults and found no statistically significant association between bronchial hyperreactivity (assessed by cold air

challenge test) and pulmonary function after adjusting for smoking habits.

The small decrease of $FEV_1/VC\%$ in our symptomatic subjects had no effect on bronchial hyperreactivity. Interestingly, our subjects showed a particular dose-response pattern following methacholine, with a relatively small drop in FEV_1 , previously shown by Woolcock *et al* to occur in healthy subjects.¹⁷

We conclude that the low $FEV_1/VC\%$ ratios of our group of otherwise normal subjects was not associated with any evidence of disease. Bronchial hyperreactivity does not occur more frequently in this group of subjects than in healthy controls, but when it is found a plateau of FEV_1 is seen that is similar to the normal bronchoconstrictor response to methacholine and unlike that of asthmatics. Low $FEV_1/VC\%$ with normal values of VC in asymptomatic subjects does not merit special investigation for airway disorders.

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