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Bronchial vagal tone and responsiveness to histamine, exercise and bronchodilators in adult patients with cystic fibrosis

E.H.J. van Haren*, J-W.J. Lammers, J. Festen, C.L.A. van Herwaarden

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ABSTRACT: Atopy and bronchial responsiveness to histamine, exercise and bronchodilators were investigated in 18 adult patients with cystic fibrosis (CF). Reversibility of airflow limitation was measured after ipratropium bromide and terbutaline, and histamine and exercise provocation tests were performed.

Histamine hyperresponsiveness was observed in 10 out of 18 patients and was not confined to those with severe airway obstruction. The positive histamine responders showed significantly better bronchodilatation after terbutaline, when compared to negative histamine responders. Histamine responsiveness was not related to atopy or exercise responsiveness. Exercise challenge caused bronchodilatation without bronchoconstriction in all patients. The exercise-induced bronchodilatation correlated with bronchodilatation after ipratropium bromide.

It is proposed that an increased vagal tone may lead to an increased resting bronchomotor tone which can be reduced by ipratropium bromide and by exercise in adult patients with cystic fibrosis.

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Dept of Pulmonary Diseases, University Hospital, Nijmegen, The Netherlands.

Correspondence: *E.H.J. van Haren
Catharina Hospital
Dept. of Pulmonary Medicine
Michelangelolaan 2
5623 EJ Eindhoven
Netherlands

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The reported prevalence of bronchodilator responsiveness in children with cystic fibrosis (CF) varies from 0–43% in cross-sectional studies [1–4]. Bronchial hyperresponsiveness (BHR), as measured by bronchial inhalation provocation tests with histamine or methacholine, is present in 24–51% of children with CF [4–8]. A bronchoconstrictor or bronchodilator response to exercise challenge has been documented in 22–58% of children with CF [9–13]. Positive skin tests to inhalational allergens have been reported in 48–88% of children with CF [4, 9, 10].

For optimal treatment, it seems relevant to also determine the significance of these phenomena in adult patients with CF. The mean age of patients in previous studies on this subject was <18 yrs. The purpose of this study, therefore, was to investigate the presence of bronchial responsiveness to inhaled histamine, exercise and bronchodilators and atopy in adult patients with CF.

Methods

Subjects

All patients from our adult cystic fibrosis clinic were examined for entry to the study. Exclusion criteria were: age <18 yrs; a recent (<6 weeks) pulmonary exacerbation; forced expiratory volume in one second (FEV_1) <25% predicted [14]; respiratory insufficiency. Eighteen CF patients (12 M, 6 F; 18–43 yrs of age; mean age 25 yrs) (table 1) participated in the study.

Table 1. – Anthropometric data of 18 adult cystic fibrosis patients

Patient no.	Sex	Age yrs	Height cm	Weight kg
1	M	21	169	47
2	M	19	166	54
3	F	22	178	63
4	M	24	181	64
5	M	27	172	66
6	M	26	179	72
7	M	23	185	61
8	F	43	165	60
9	F	26	164	47
10	F	20	163	53
11	M	29	174	66
12	F	18	166	53
13	M	25	167	57
14	M	18	179	63
15	M	35	174	77
16	M	18	185	61
17	M	19	174	51
18	F	29	172	67
Mean		25	173	60
SEM		2	2	2

Table 2. – Ventilatory parameters before and after inhalation of 2 mg terbutaline and 80 μg ipratropium bromide, and before and immediately after exercise in 18 adult CF patients

Pt no.	FEV_1 % pred before T	FEV_1 % pred after T	FEV_1 % ↑ after T	FEV_1 % pred before IB	FEV_1 % pred after IB	FEV_1 % ↑ after IB	FEV_1 % pred before EXE	FEV_1 % pred after EXE	FEV_1 % ↑ after EXE	PC_{20} histamine $mg \cdot ml^{-1}$
1	29	34	18	32	35	10	32	34	7	>16
2	43	51	16	47	49	4	50	53	7	1.38
3	41	49	19	40	59	47	37	53	43	>16
4	67	73	10	67	79	17	69	74	8	>16
5	96	109	14	96	101	6	101	104	3	1.82
6	55	67	23	50	72	43	67	82	23	5.35
7	46	51	12	45	52	16	43	48	10	0.49
8	67	78	16	67	82	23	71	74	5	3.23
9	31	38	22	36	41	16	36	38	7	0.27
10	75	78	3	74	80	9	76	82	7	>16
11	95	97	2	93	107	15	94	106	13	3.68
12	45	59	33	45	58	29	45	53	19	0.99
13	40	48	18	42	49	17	45	53	17	1.72
14	108	110	2	109	128	18	116	126	8	>16
15	61	68	12	63	70	11	71	83	16	>16
16	70	76	9	71	78	10	74	84	13	>16
17	42	49	17	43	47	10	44	50	13	>16
18	70	74	5	72	83	17	72	82	14	3.80
Mean	60	67	15	61	71	18	63	71	13	
SEM	5	5	2	5	6	3	6	6	2	

T: terbutaline; IB: ipratropium bromide; EXE: exercise; CF: cystic fibrosis; ↑: increase; hist: histamine.

They represented a wide variety in clinical severity. None of the patients was treated with corticosteroids, theophylline or sodium cromoglycate. All patients were questioned about wheezing, bronchodilator use and family history of atopy and/or asthma. Bronchodilators were omitted for at least 12 h before each study. The study protocol was approved by the institutional Ethic's Committee and informed consent was obtained from each patient.

Bronchodilator responsiveness

Reversibility of airflow limitation was measured by obtaining ventilatory parameters before and 40 min after inhalation of 80 μg ipratropium bromide (IB) and, on a separate day, before and 20 min after inhalation of 2 mg terbutaline (T) through a spacer device (table 2). All ventilatory parameters were measured with flow-volume equipment (Pneumoscreen, Jaeger, FRG). Several components of airflow rate and exhaled lung volumes were assessed with the so-called "envelope method": the indices were read on the composite curve, obtained by taking the envelope of three individual curves superimposed at total lung capacity (TLC) level [15]. Results were compared with predicted values for height and age [14].

Bronchial provocation tests

In random order, on two different days, with seven days between the two tests, we performed histamine inhalation challenges and exercise tests. Histamine provocation was performed according to the method of COCKCROFT *et al.* [16], with twofold increasing concentrations of histamine from 0.03 to 16 $mg \cdot ml^{-1}$. After reaching a >20% fall in FEV_1, a computerized calculation of the provocative concentration of histamine producing a 20% fall in FEV_1 (PC_{20} histamine) was made.

Standardized exercise provocation tests were performed by running on a treadmill in a room with constant temperature (20°C) and relative humidity (60%) [17]. After adaptation to the treadmill for 2 min at a speed of 4–6 $km \cdot hr^{-1}$, the slope and speed were raised until the heart rate reached 90% or more of the age-related predicted maximum [18]. At this level the exercise continued for 6 min. All patients reached 90% of their age-related predicted maximum heart rates. A noseclip ensured mouth breathing during the exercise performance. Pulmonary function tests were performed before, immediately after, and 1, 3, 6, 9, 12 and 15 min after completion of the exercise tests. The largest rises and falls in FEV_1, expressed as % rise or % fall of baseline FEV_1, were calculated. A >15% fall or >15% rise in FEV_1 was considered as a positive response to exercise [19].

Atopy

Blood was collected to detect specific immunoglobulin E (IgE) antibodies to 10 common inhalational allergens (house dust, *Aspergillus fumigatus*, dog hair, cat fur, *Dermatophagoides pteronyssinus*, tree pollen

and four mixes of grass pollen) using a standard radio allergosorbent test (RAST) method [20]. Atopy was defined as at least one positive test result by the RAST method [21].

Statistics

For statistical analysis, t-tests for paired and unpaired data and Pearson correlation coefficients were used. Five percent was taken as the level of significance. All data are presented as means±SEM.

Results

The individual data for FEV_1 before and after terbutaline, ipratropium bromide and exercise are given in table 2, together with the PC_{20}-histamine. Data with respect to the histamine responders and nonresponders are given in table 3. The family histories did not reveal atopy or asthma in this group. One patient reported wheezing and five patients regularly used bronchodilators. Bronchodilator responses were measured on two separate days and baseline lung function did not differ between the two days. Inhalation of both terbutaline and ipratropium bromide significantly improved expiratory airflow. When expressed as percentage change from baseline, mean FEV_1 increased 15±2% after terbutaline and 18±3% after ipratropium bromide.

Table 3. – Baseline lung function, bronchodilator response and response to exercise in 18 adult CF patients, comparison of histamine responders and histamine nonresponders

	Histamine responders	Histamine nonresponders	p
Patients n	10	8	
Male/female	7/3	5/3	
Age yrs	26±2	23±2	NS
FEV_1 % pred	56±7	65±8	NS
VC % pred	80±5	79±8	NS
% rise in FEV_1 after terbutaline	17±3	10±2	<0.05
ipratropium bromide	18±4	17±5	NS
% rise in FEV_1 immediately after exercise	12±2	15±4	NS
% fall in FEV_1 after exercise	1±0.4	1±1	NS
Atopic subjects n	6	3	NS

Results are expressed as mean±SEM. NS: not significant; FEV_1: forced expiratory volume in one second; VC: vital capacity; CF: cystic fibrosis.

Ten patients showed a positive response to histamine inhalation (*i.e.* PC_{20} <8 mg·ml^{-1}). In these 10 patients there was no correlation between the log PC_{20}-histamine and baseline FEV_1 expressed as percentage predicted (r=0.5; p>0.1). The eight patients with a negative response to histamine were not included in this correlation analysis, since a numerical value of PC_{20}-histamine was not determined above a histamine concentration of 16 mg·ml^{-1}. Among the patients with histamine hyperresponsiveness, several patients had severe airflow limitation (*e.g.* no. 9: FEV_1 31% pred) whereas others had a relatively normal lung function (*e.g.* no. 5: FEV_1 96% pred). Baseline lung function did not differ between histamine responders and non-responders. The bronchodilator response to terbutaline was significantly larger in histamine responders (17.4±2.5%) than in non-responders (9.8±2.3%) (p<0.05; table 2). Seven out of 10 histamine responders showed significant reversibility of airflow limitation (>15% rise in FEV_1) after terbutaline compared to 2 out of 8 nonresponders. The response to ipratropium bromide was similar in both groups.

The response to exercise challenge was as follows. The percentage rise in maximal expiratory flow at 50% forced vital capacity (MEF_{50}) immediately after exercise was 46.1±8.7%, whilst FEV_1 increased 12.9±2.1% compared to pre-exercise values. The percentage fall in MEF_{50} after exercise was 1.1±0.8% and FEV_1 decreased 0.7±0.5% after exercise. Five patients showed relevant bronchodilatation (*i.e.* a >15% rise in baseline FEV_1) immediately after exercise.

No significant fall in any expiratory airflow parameter was observed after exercise. Histamine responders and nonresponders did not differ in their responses to exercise (table 3). A significant correlation was found between the increase in FEV_1 immediately post-exercise and the improvement in FEV_1 after inhalation of ipratropium bromide (r=0.80; p<0.001) (fig. 1). No such correlation existed between the responses to exercise and terbutaline (r=0.32; p=0.2). There was also no relationship between baseline FEV_1 and the increase in FEV_1 immediately post-exercise (r=-0.29; p=0.24).

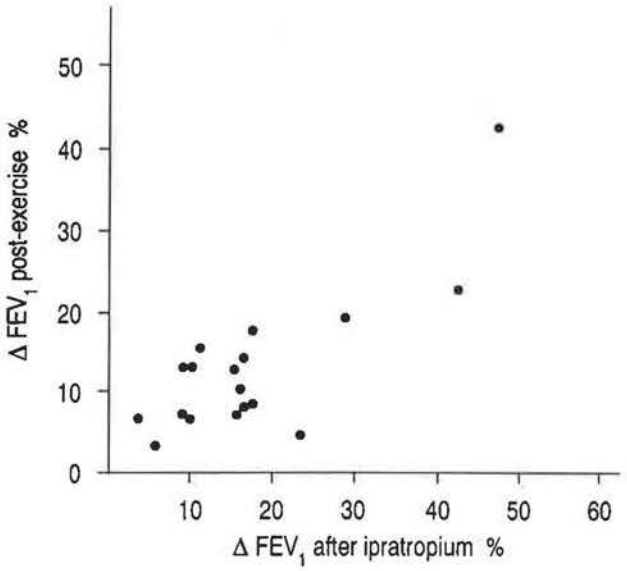

Fig. 1. – Correlation between increase in FEV_1 immediately post-exercise and increase in FEV_1 after inhalation of ipratropium bromide in 18 adult CF patients. (Regression analysis r=0.80; p<0.001). FEV_1: forced expiratory volume in one second; CF: cystic fibrosis.

Nine of the 18 adult CF patients (50%) were atopic as defined by RAST criteria. The incidence of reactions to specific allergens was: tree pollen 3 patients, timothy grass 5 patients, *Secale cereale* 5 patients, *Dermatophagoides pteronyssinus* 5 patients, *Aspergillus fumigatus* 5 patients, house dust 2 patients, dog hair 3 patients, cat fur 3 patients. There were no patients with only one positive test result; nine patients had two or more positive tests and were considered atopic. Four of these 9 patients regularly used bronchodilators. Lung function and bronchodilator responses did not differ between atopic and nonatopic patients. Atopy seemed to be more prevalent in the CF patients responding to histamine than in the nonresponders, but the difference did not reach significance (table 3).

Discussion

Bronchial hyperresponsiveness (BHR) to inhaled histamine was observed in 56% of this group of adult CF patients with a wide variety of clinical severity. Others found BHR to inhaled histamine in 21–40% of children with CF with mean ages 10–14 yrs [5–7]. It is possible that hyperresponsiveness to histamine increases with age in CF patients. A conventional histamine challenge test with adherence to a 20% reduction of baseline FEV_1 (% pred) may theoretically not be as relevant in patients with severe airflow limitation as in other groups because further narrowing of airways in response to histamine may not occur. DARGA *et al.* [22] found that a true hyperreactive response to cold air provocation occurs more in CF patients with mild to moderate disease than in patients with severe CF lung disease. However, the present study shows that histamine can also provoke further airflow limitation in patients with severe airway obstruction. Moreover, hyperresponsiveness to histamine, as demonstrated in this study, is not only confined to CF patients with airflow limitation [4, 5, 11].

The underlying mechanism of BHR in CF is unknown. It has been suggested that BHR in CF is genetically determined, associated with abnormalities of the autonomic nervous system and with atopy [8, 23, 24]. The CF patients with BHR in the present study showed a significantly better bronchodilator response to inhalation of terbutaline than patients without histamine hyperresponsiveness, whereas the response to ipratropium bromide was not different between both groups. Histamine responsiveness did not correlate with atopy. In one study, all histamine responsive CF patients were also atopic on skin testing, but a selection bias was introduced since only CF patients with minor pulmonary disease were enrolled [5]. We and others could not find a correlation between atopy and histamine responsiveness [4, 6, 25].

BHR in CF is possibly secondary to the chronic pulmonary disease, since inflammation and epithelial damage alter mucosal permeability and histamine penetration [26]. Moreover, in the presence of airway narrowing and thickening, a small further change in airway calibre produces a larger change in airflow resistance on a geometrical basis alone [27, 28]. It has been shown in CF patients that hyperresponsiveness to methacholine is an unfavourable prognostic finding [8], worsening the prognosis of the pulmonary disease in CF.

The presence of nonspecific BHR warrants future prospective investigation with drugs that control BHR, *e.g.* inhaled corticosteroids.

Bronchodilatation was the predominant response to exercise challenge in this group of adult CF patients. Using exercise as a test of bronchial responsiveness in CF raises some problems. In CF, cardiac function does not limit exercise performance, but a reduced ventilatory capacity plays the major role in limiting exercise [29]. The CF patients tend to maintain a high minute ventilation ($\dot{V}E$) during exercise to compensate for an enlarged dead space ventilation [30–32]. Particularly in more disabled patients, the $\dot{V}E$ at maximal exercise approaches or exceeds the estimated maximum voluntary ventilation, indicating that a ventilatory limit has been reached [29]. BRAGGION *et al.* [33] performed exercise tests in a group of CF patients, with only mild airway obstruction (mean FEV_1 77% pred), and these patients reached a similar $\dot{V}E$ ($l \cdot kg^{-1} \cdot min^{-1}$) during exercise, when compared to a control group. In our study, two patients (nos 5 and 11) without significant airway obstruction (FEV_1 95% pred in both patients) were hyperresponsive to histamine but showed no exercise-induced bronchoconstriction. However, patients with a very low FEV_1 will probably not generate high enough ventilation rates to "dry" or "cool" the airways and to get exercise-induced bronchoconstriction. This may explain why five patients in our study (nos 2, 7, 9, 12, 13) with a PC_{20}-histamine <2 $mg \cdot ml^{-1}$ and a FEV_1 <50% predicted failed to have exercise-induced bronchoconstriction.

There are several possible explanations for the bronchodilatation observed during exercise in CF patients. Improvement of mucus clearance relieves partially obstructed airways, however, this does not usually occur immediately following exercise. LOUGHLIN *et al.* [34] showed that dynamic compression of conducting airways early during a forced expiratory manoeuvre can produce supramaximal flow transients, thus contributing to peak flow. Following exercise, changes in peak flow and correlated changes in the volume of the flow transients occurred and an increase as well as a decrease of both flows could be observed in their studied group. However, these flow transients would not be expected to contribute to maximal mid-expiratory flow (MMEF) and maximal expiratory flow when 25% forced vital capacity remains to be exhaled (MEF_{25}). Since MMEF and MEF_{25} also increased during exercise, bronchodilatation of peripheral airways may have occurred as well, diminishing the value of this theory of flow transients.

The observation that the exercise-induced bronchodilatation significantly correlated with the bronchodilatation after ipratropium bromide is interesting. It has

been found that CF patients show increased activity and responsiveness of the cholinergic nervous system [23, 24]. Moreover, there is indirect evidence that vagal pathways are involved in exercise-induced asthma [35]. An increased vagal tone may lead to an increased resting bronchomotor tone which is reduced by anticholinergic agents, as demonstrated in this study by the bronchodilator effect of ipratropium bromide, and possibly also by exercise.

Fifty percent of the CF patients studied were atopic as defined by RAST criteria. Lung function and response to histamine and bronchodilators did not differ between atopic and nonatopic subjects. An impaired clearance of trapped antigens in the viscid bronchial mucus and the abnormal permeability of the damaged bronchial mucosa might cause an increased antigen exposure of IgE-producing submucosal cells, which may explain this high incidence of atopy [25]. This is in accordance with the observation that the frequency of positive skin tests in CF increases with age [4]. By contrast, with the hyperresponsiveness to methacholine, which has clear prognostic implications, the presence of atopy has not been shown to be related to severity and prognosis of CF. This was also confirmed by this study. Atopy does not predict the patients' response to bronchodilators, to histamine or to exercise.

In conclusion, this study demonstrates that bronchial responsiveness to histamine is prevalent in a high proportion of adult CF patients with a wide variety of clinical severity and is not confined to patients with severe airflow limitation. Bronchial responsiveness to histamine is related to bronchodilator responsiveness to the $beta_2$-agonist terbutaline, but not to atopy. The presence of atopy in CF patients seems of minor importance and does not provide information on bronchial responsiveness to bronchodilators, exercise or histamine. Exercise improves expiratory airflow without necessarily causing bronchoconstriction and the bronchodilator response after ipratropium bromide correlates well with exercise-induced bronchodilatation. An increased vagal tone in CF patients may lead to an increased resting bronchomotor tone, which can be reduced by ipratropium bromide and exercise.

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