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Bronchodilator response in adult patients with cystic fibrosis: effects on large and small airways

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Bronchodilator response in adult patients with cystic fibrosis: effects on large and small airways. E.H.J. van Haren, J-W.J. Lammers, J. Festen, C.L.A. van Herwaarden.

ABSTRACT: Spirometry, body plethysmography, maximal expiratory flow-volume curves (MEFV-curves) with air and with heliox (80% He + 20% O_2) before and after inhalation of bronchodilators were studied in a group of 20 adult cystic fibrosis (CF) patients. Most of them showed prominent bronchial obstruction and seven also had evidence of restrictive pulmonary disease. Large differences were observed between total lung capacity as measured with body plethysmography and with a helium dilution technique. A calculated air trapping index correlated well with parameters of peripheral airway obstruction. Both inhalation of terbutaline and ipratropium bromide caused dose-related bronchodilatation. Density dependence of expiratory flow increased significantly after terbutaline but not after ipratropium bromide.

We conclude that adult CF patients with varying degrees of obstructive and restrictive pulmonary function limitation show a dose-related improvement of lung function after terbutaline and ipratropium bromide with terbutaline being probably more effective on peripheral airways than ipratropium bromide.

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The reported prevalence of bronchodilator responsiveness in children with cystic fibrosis (CF) varies from 0–43% in cross-sectional studies with mean ages of studied patients below 18 yrs [1–3]. Some patients even demonstrated a reduction in airflow after inhaled isoproterenol [2]. End-expiratory flow rates appeared to be the most accurate parameters for reflecting the bronchodilator response in CF patients [4]. When breathing a low density gas mixture like heliox (80% helium and 20% oxygen) the density dependence expressed as delta maximal expiratory flow when 50% total lung capacity remains in the lung (MEF_{50}) can be assessed. A delta MEF_{50} of <20% is compatible with obstruction in peripheral airways [5–8]. When a bronchodilator predominantly dilates small airways, the central turbulent airflow pattern will contribute more to overall resistance and delta MEF_{50} increases. Effects of beta-adrenoreceptor agonists and muscarinic receptor antagonists on large and small airways have been determined in normal subjects and patients with asthma by assessing this density-dependence [6, 9–11].

The aim of the present study was to investigate the difference in bronchodilator effect between the beta-adrenoreceptor agonist terbutaline and the muscarinic receptor antagonist ipratropium bromide with regard to magnitude and preferential site of action in adult CF patients. The effects of two different doses of terbutaline and ipratropium bromide were measured on lung function and density dependence of expiratory flow in a group of 20 adult patients with CF.

Subjects and methods

Twenty patients (13 males, 7 females, 18–43 yrs of age, mean age 26 yrs) with CF participated in the study. They represented a wide variety in clinical severity (range of forced expiratory volume in one second (FEV_1) % predicted: 15.6–107.6%) and all were experienced in performing pulmonary function tests. None of the patients was treated with corticosteroids, theophylline or sodium cromoglycate. Bronchodilators were withheld for at least 12 h prior to each study. Baseline spirometric measurements, including total lung capacity measurement with a closed circuit helium dilution method (TLC-helium), were obtained with a wet spirometer (Pulmonet III, SensorMedics, Bilthoven, The Netherlands). A constant volume body plethysmograph (Jaeger Bodyscreen II, Wuerzburg, FRG) was used to measure the airway resistance (Raw), the residual volume (RV), the thoracic gas volume (TGV), total lung capacity (TLC-box) and the specific airway conductance (sGaw) [12]. For calculations a modified "air trapping" index (AT–index) was defined as follows:

Table 1. – Patient characterics and baseline results of spirometry and body plethysmography in 20 adult patients with CF

Pt no.	Age yr	FEV_1 % pred	MEF_{50} % pred	MEF_{25} % pred	TLC-He % pred	VC % pred	AT-index %	RV/TLC %	sGaw % pred	FEV_1/VC %
1	21	29	10	7	77	66	30	50	27	36
2	19	32	16	7	79	73	15	33	96	50
3	22	41	21	14	78	68	28	53	18	53
4	24	67	39	19	90	82	13	37	81	66
5	27	96	73	51	107	108	0	8	204	72
6	43	24	9	10	61	46	47	73	17	44
7	24	16	7	7	54	42	57	75	53	31
8	26	55	28	20	94	81	22	44	53	54
9	23	46	18	13	74	67	21	47	60	54
10	43	67	43	40	90	90	17	42	46	62
11	26	31	11	8	82	66	29	53	31	40
12	20	75	60	30	89	87	10	29	106	75
13	29	995	74	31	105	107	3	25	179	72
14	18	45	18	14	91	80	23	42	38	48
15	25	40	17	15	86	65	10	49	72	51
16	18	108	82	53	115	119	7	15.	128	74
17	35	61	30	22	86	91	10	33	85	53
18	18	70	57	456	88	78	7	27	145	73
19	19	42	21	13	76	65	15	34	58	53
20	29	70	57	31	103	110	7	289	86	55
Mean	26	55	35	22	86	80	19	40	79	56
±SEM	2	6	5	3	3	45	3	4	12	3

Pt: patient; CF: cystic fibrosis; FEV_1: forced expiratory volume in one second; MEF_{50} and MEF_{25}: maximal expiratory flow when 50% and 25% TLC remains in the lung, respectively; TLC: total lung capacity; AT: air trapping; RV/TLC: residual volume as percentage of TLC; sGaw: specific airways conductance; FEV_1/VC: FEV_1 as percentage of vital capacity.

Table 2. – Correlation of ventilatory parameters in 20 adults patients with CF, expressed in Spearman's rank correlation coefficients

	FEV_1 % pred	MEF_{50} % pred	MEF_{25} % pred	AT-index %	RV/TLC %	sGaw % pred
MEF_{50} % pred	0.97 ***					
MEF_{25} % pred	0.89 ***	0.93 ***				
AT-index %	-0.85 ***	-0.84 ***	-0.79 ***			
RV/TLC %	-0.91 ***	-0.88 ***	-0.79 **	0.91 ***		
sGaw % pred	0.83 ***	0.77 **	0.68 **	-0.92 ***	-0.90 ***	
Increase FEV_1(T)	-0.61 **	-0.58 *	0.50 *	0.60 **	-0.59 *	-0.70 **

Increase FEV_1(T) % increase in FEV_1 after inhalation of 2 mg terbutaline.*: $p<0.05$; **: $p<0.01$; ***: $p<0.001$. For abbreviations see legend to table 1.

"AT-index" = {(TLC-box) - (TLC-helium)} + (TLC-helium)×100% [13, 14]. Five technically satisfactory plethysmographic determinations were obtained and averaged. Measurements were expressed in percentage of predicted values [15]. A restrictive pattern of pulmonary disease was defined by the following criteria: 1) vital capacity (VC) ≤75% of predicted; and 2) TLC ≤80% of predicted [16]. Maximal expiratory flow-volume curves (MEFV curves) were obtained with a Jaeger Pneumoscreen (Jaeger, Wuerzburg, FRG). All the subjects performed two series of MEFV curves with air and two with He-O_2. Before each set of measurements, the flow-volume equipment was calibrated separately with room air and with the He-O_2 mixture. Ventilatory parameters were taken from the composite curve with the highest sum of forced vital capacity (FVC) and FEV_1. The composite curve was obtained by taking the "envelope" of a series of three individual curves superimposed at TLC level [17]. The He-O_2 MEFV curves with the best fitting FVCs compared to the air MEFV curves were used for calculation. The He-O_2 mixture was washed in during 1 min tidal breathing in which the patient was asked to inhale three slow vital capacities [9, 11]. Density dependence was expressed as delta-MEF_{50} = {MEF_{50} (He-O_2) - MEF_{50} (AIR)} / MEF_{50} (AIR) × 100% [6].

Bronchodilator effects were investigated on two different days in randomized order with 7 days between the two days of investigation. The difference in baseline FEV_1 (MEFV-curves) on the two days was <5%. MEFV curves with air and He-O_2 were obtained before, and 20 min after inhalation of 1 and 2 mg terbutaline cumulatively on the first day, and before and 40 min after inhalation of 40 and 80 μg ipratropium bromide cumulatively on the second study day. The doses of the two drugs were selected on account of previous dose-response studies in asthmatic patients. Both bronchodilators were inhaled as pressurized aerosol through a 750 ml spacer (Nebuhaler®) to ensure proper deposition in the airways.

The study protocol was approved by the local Ethics Committee and informed consent was obtained from all patients before entry into the study. For statistical calculations, analysis of variance (ANOVA), Mann-Whitney U tests and Spearman's rank correlation coefficients were used as appropriate. Five percent was taken as the level of significance.

Results

Baseline lung function showed bronchial obstruction in 13 patients, whereas seven patients (Nos 1, 2, 3, 6, 7, 9, 19) had a combined obstructive and restrictive lung function pattern (table 1). Three patients (Nos 5, 13, 16) had only a lowered MEF_{25} (% pred) or no functional abnormalities. In several patients a marked difference was found between TLC-box and TLC-helium. When expressed as a ratio, the mean "air trapping index" was 18.5±3.2% (range 0–56%). This AT-index was significantly correlated with other parameters of airway obstruction (table 2). The AT-index appeared to be greater with decreasing values of sGaw, FEV_1 MEF_{50} and MEF_{25} and with increasing values of RV/TLC (fig. 1 and table 2). Inhalation of both terbutaline (T) and ipratropium bromide (IB) induced significant, dose-related bronchodilatation (figs 2 and 3). The FEV_1 increased from 55.9±5.6% predicted (mean±SEM) to 62.5±5.7% after 2 mg T and to 66.0±6.1% after 80 μg IB. The MEF_{25} increased from 22.4±3.4% to 27.7±4.5% after 2 mg T and to 31.2±5.2% after 80 μg IB. There was no significant difference (p=0.672; analysis of variance) between the magnitude of bronchodilatation induced by T or IB. The increase in FEV_1 after T was significantly correlated with baseline lung function (table 2). The response to IB was not determined on the same day as baseline lung function, so a correlation was not investigated here.

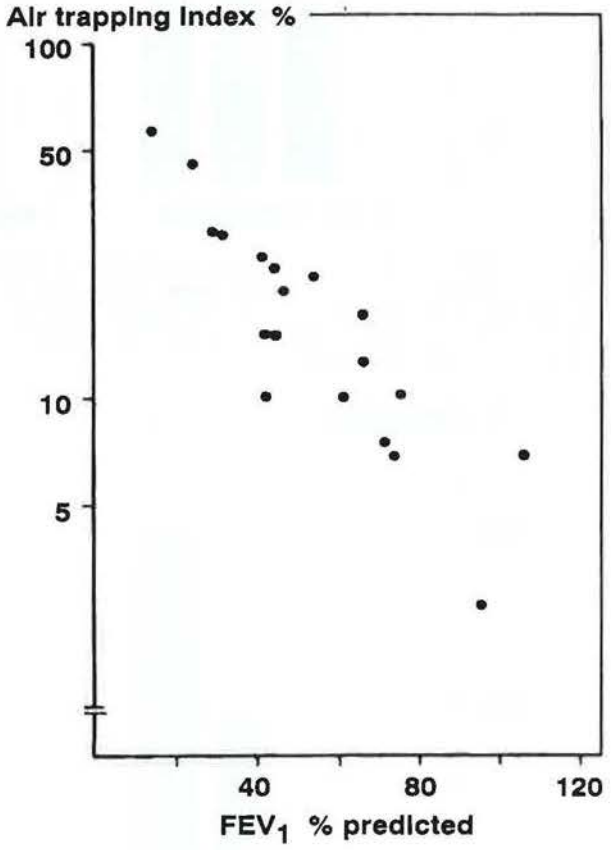

Fig. 1. – Correlation between air trapping (AT) index and baseline FEV_1 (% predicted) in 20 adult CF patients. Log expression of AT-index is used. Ryx =-0.83; p=0.0008. CF: cystic fibrosis; FEV_1: forced expiratory volume in one second.

Baseline values of density dependence, expressed as delta MEF_{50} showed that 16 of the 20 CF patients were "nonresponders" for heliox (delta MEF_{50} <20%). The FEV_1 and MEF_{25} of the "responders" (79.5±14.0% and 37.3±18.3% predicted; mean±SEM) were significantly higher (p<0.05; Mann-Whitney U test) than the FEV_1 and MEF_{25} of the "nonresponders" (50.1±5.3% and 18.7±3.0%, respectively). Terbutaline caused a

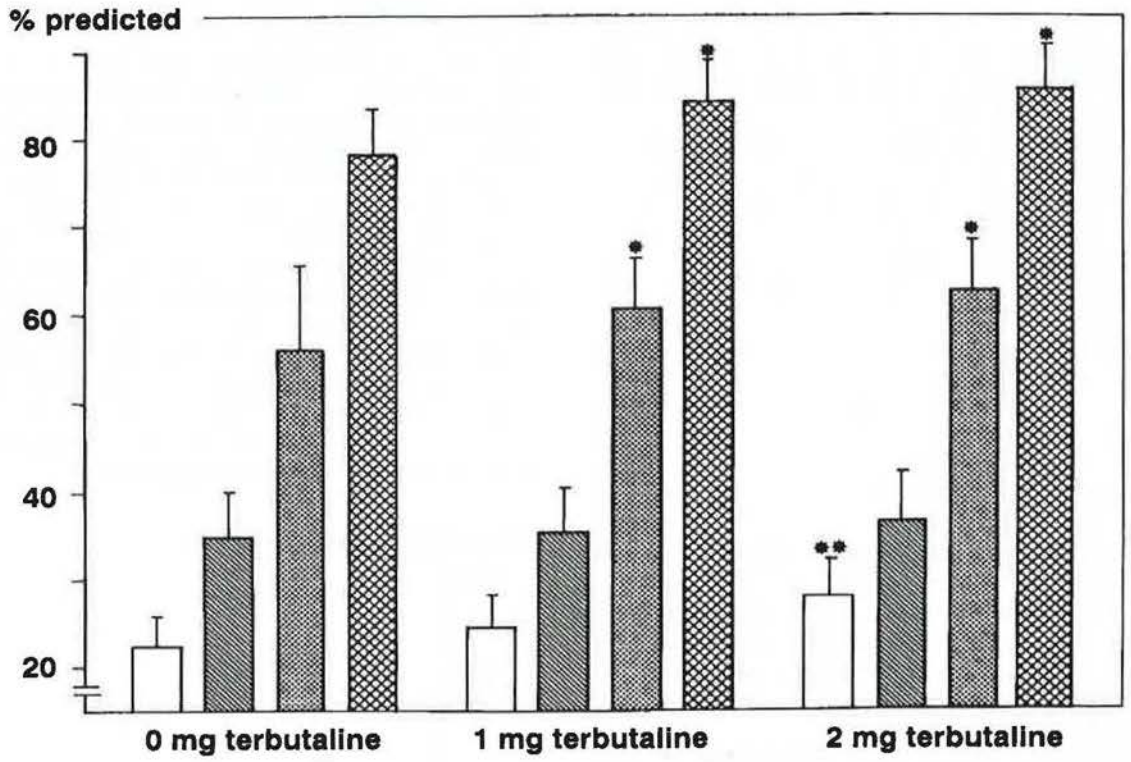

Fig. 2. – Changes (mean±SEM) in ventilatory parameters as a percentage of baseline values after inhalation of cumulative doses of terbutaline in 20 adult patients with CF. ▭ : MEF_{25}; ▨ : MEF_{50}; ▩ : FEV_1; ▩ : FVC. Asterisks indicate a significant difference when compared with baseline values (analysis of variance for repeated measures). *: $p<0.001$; **: $p<0.05$; CF: cystic fibrosis; MEF_{50} and MEF_{25}: maximal expiratory flow when 50% and 25% TLC, respectively, remains in the lung; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity.

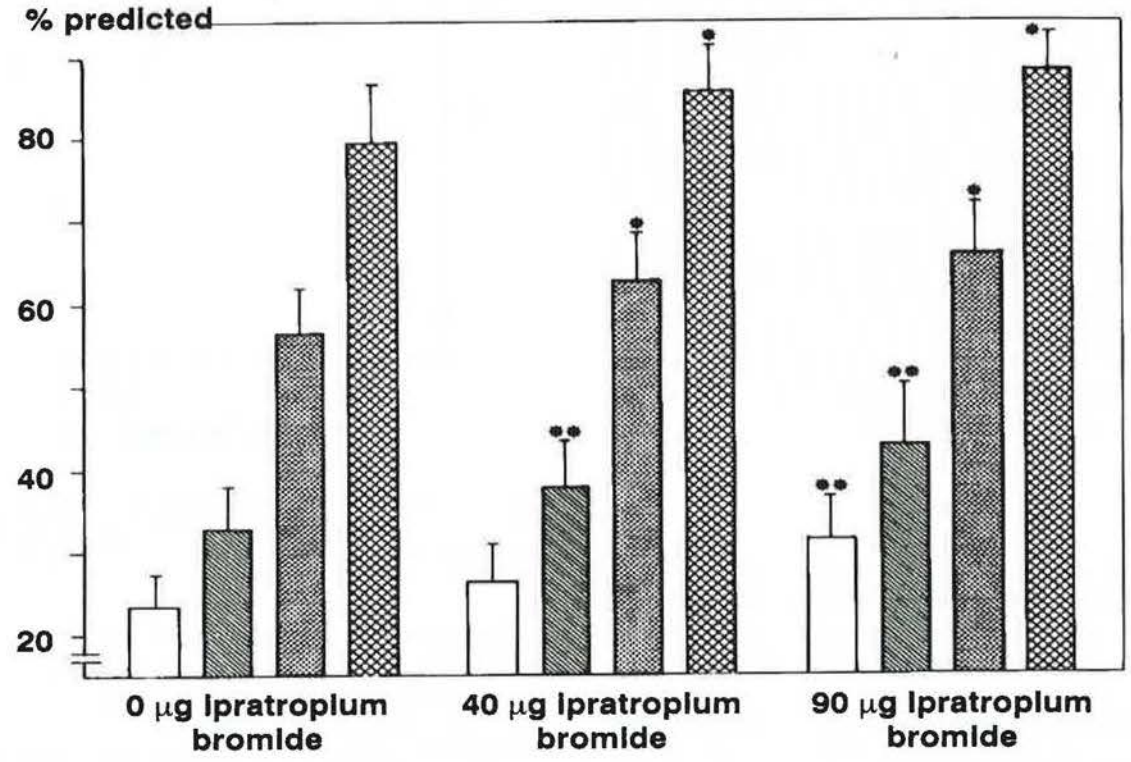

Fig. 3. – Changes (mean±SEM) in ventilatory parameters as a percentage of baseline values after inhalation of cumulative doses of ipratropium bromide in 20 adult patients with CF. ▭ : MEF_{25}; ▨ : MEF_{50}; ▩ : FEV_1; ▩ : FVC. Asterisks indicate a significant difference when compared with baseline values (analysis of variance for repeated measures). *: $p<0.01$; **: $p<0.01$. For abbreviations see legend to figure 2.

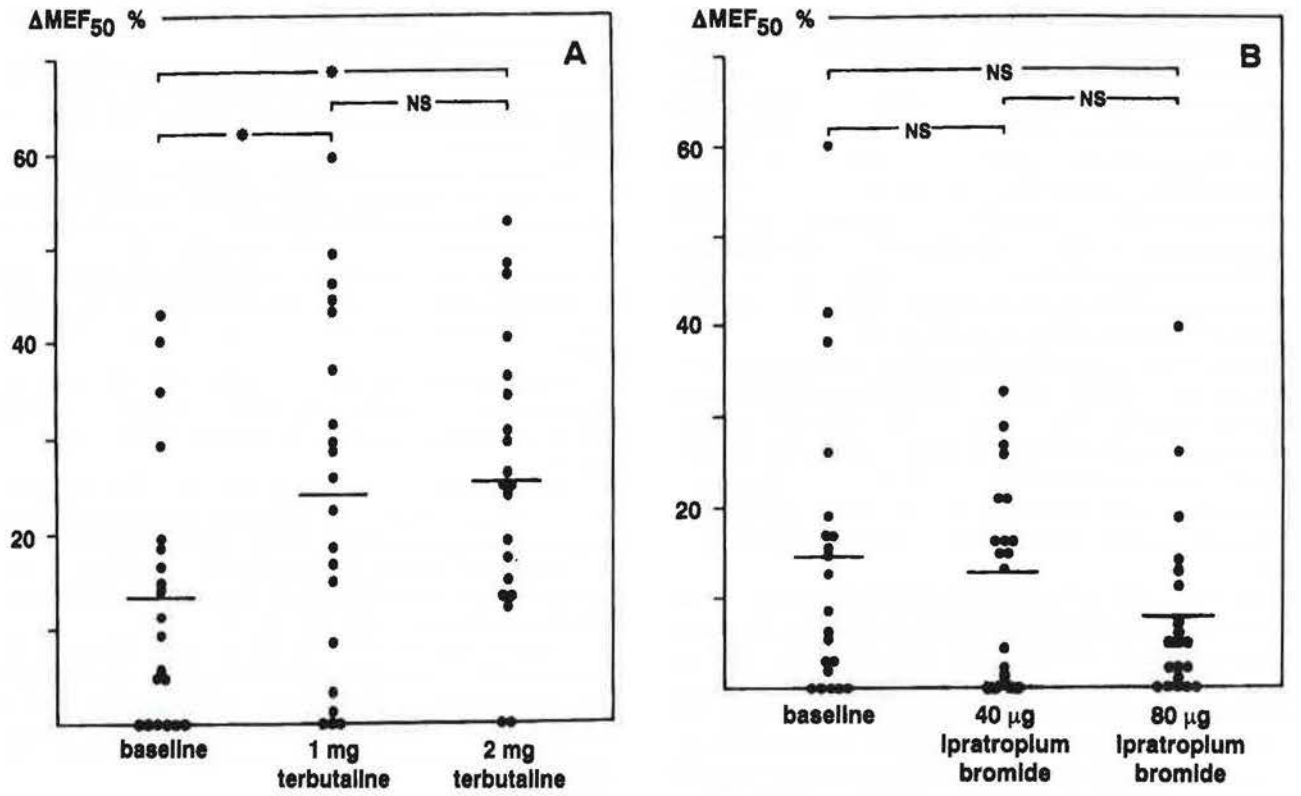

Fig. 4. – Effects of different doses of terbutaline (fig. 4a) and ipratropium bromide (fig. 4b) on density dependence expressed as delta MEF_{50} (mean±SEM) in 20 adult patients with CF. Asterisks indicate a significant difference when compared with baseline values (analysis of variance for repeated measures). *: $p<0.001$. For abbreviations see legend to figure 2.

significant increase in delta MEF_{50} and eight of the 16 "nonresponders" became "responders" after 2 mg terbutaline. Ipratropium bromide had no significant effect on delta MEF_{50} (Figs 4 A+B).

Discussion

Obstructive pulmonary function limitations are common in patients with CF [18] and many patients also have evidence of restricted pulmonary function. In the present study 7 of 20 adult CF patients showed restricted pulmonary function but it is uncertain whether restriction indicates more severe disease in CF patients [16].

Specific airway conductance (sGaw) and airway resistance (Raw) are usually normal in children with CF and mild pulmonary involvement, presumably because small airways are responsible for only 10–20% of total airway resistance [19, 20]. In the present study, markedly decreased values of sGaw were found in adult CF patients with severe obstructive lung disease. sGaw values correlated well with other ventilatory parameters (table 2) and reflected either extensive small airway obstruction or large airway involvement or both.

Obstruction of small airways leads to poor ventilation of certain areas of the lung. The resulting air trapping and hyperinflation is reflected by a large RV/TLC ratio and a large trapped-gas volume: *i.e.* the difference between TLC-box and TLC-helium [13]. In children with CF an increased ratio of RV/TLC was mainly due to air trapping and to a lesser extent to decreased elastic lung recoil [21]. It seems to be an early and consistent abnormality, correlated to clinical severity of the disease [22]. In asthmatic patients with significant airflow obstruction, TLC-box seems to overestimate the true total lung capacity [22, 23]. The magnitude of overestimation probably depends on the distensibility of extrathoracic airways and the degree of small airway obstruction, especially in severe cases. Even if this does explain the changes in measurement of TLC-box, this artefact still remains a function of the degree of airway obstruction and the determination of the air trapping index has relevance in the assessment of these patients [13, 14]. In this study the air trapping index correlated significantly with RV/TLC, MEF_{50} and MEF_{25} and probably represents air trapping due to peripheral airway obstruction.

A significant, dose-related, bronchodilatation after both terbutaline and ipratropium bromide was found in the adult CF patients. The bronchodilator effects were reflected by increases in FEV_1, MEF_{50} and MEF_{25} values. Six of the 20 patients did not respond to either bronchodilator. A clinically relevant bronchodilator response, defined as a more than 15% increase in FEV_1, was found in 70% of the adult CF patients. In contrast to ZACH *et al.* [4] who observed impairment of lung function in some children with CF, we did not observe any negative responses to bronchodilator

therapy. In adults, bronchodilator responsiveness therefore appears to be more common than in children with CF where a 0–43% prevalence in cross-sectional studies was observed [1–4]. In contrast to most earlier studies we used two different doses of two bronchodilator drugs and performed flow-volume curves instead of spirometry, which has been reported to be less sensitive to assess bronchodilator responsiveness in CF patients [4]. Another explanation for the observed difference might be that bronchodilator responsiveness is more prevalent in adults when compared to children with CF but this remains to be proved.

Most of the adult CF patients were nonresponders for heliox (delta MEF_{50} <20%) compatible with predominant peripheral airway obstruction. The CF patients who were responders (delta MEF_{50} >20%) had significantly better pulmonary function tests than nonresponders, also indicating the important contribution of small airways obstruction to airflow limitation in CF.

Several authors found different localizations of the effects of bronchodilators on normal subjects and patients with asthma [6, 9–11]. The most consistent finding was that beta-sympathicomimetics predominantly cause dilatation of small airways, especially when these contribute to a large extent to total airway resistance [6, 10, 11]. In the present study terbutaline induced a significant and consistent increase in density dependence in adult CF patients. Therefore, it seems that terbutaline mainly caused dilatation of the peripheral airways, whereas ipratropium bromide presumably dilates large and small airways equally, leaving density dependence relatively unchanged [6].

In conclusion, adult CF patients usually have mild to severe bronchial obstruction, especially of small airways. Moreover, many of these patients also have a restricted lung function pattern. Terbutaline and ipratropium bromide caused a dose-related bronchodilatation, terbutaline being probably more effective on small airways than ipratropium bromide. Longitudinal studies are needed for further evaluation of the potential beneficial effects of bronchodilator drugs on lung function and life expectation of CF patients.

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Réponse bronchodilatatrice chez les adultes atteints de fibrose cystique: effets sur les voies aériennes de grand et de petit calibre. E.H.J. van Haren, J-W.J. Lammers, J. Festen, C.L.A. van Herwaarden.

RÉSUMÉ: Nous avons étudié dans un groupe de 20 adultes atteints de fibrose cystique, les valeurs spirométriques, la plethysmographie corporelle et les courbes de débit expiratoire moyen forcé à l'air et au moyen d'un mélange à 80% de He et de 20% d'O_2 (heliox).

La plupart d'entre eux avaient une obstruction bronchique marquée et 7, en outre, des signes de maladies pulmonaires restrictives. D'importantes différences ont été observées entre la capacité pulmonaire totale, mesurée par la plethysmographie corporelle, et celle obtenue par la technique de dilution de l'hélium. Un index calculé d'air trapping, est en bonne corrélation avec les paramètres d'obstruction des voies aériennes périphériques. Tant l'inhalation de terbutaline que celle de bromure d'ipratropium, ont provoqué une bronchodilatation en relation avec la dose. La dépendance du débit expiratoire à l'égard de la densité augmente de façon significative après terbutaline mais non après bromure d'ipratropium.

Nous concluons que les patients adultes atteints de fibrose cystique avec divers degrés de limitation fonctionnelle pulmonaire obstructive ou restrictive, démontrent une amélioration de la fonction pulmonaire en rapport avec la dose après terbutaline et bromure d'ipratropium, la terbutaline étant probalement plus efficace sur les voies aériennes périphériques que le bromure d'ipratropium.

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