



Original Article

Reversible airway obstruction in cystic fibrosis: Common, but not associated with characteristics of asthma

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Abstract

Background: As asthma-like symptoms are common in CF, we evaluated reversible airway obstruction and associated characteristics.

Methods: Retrospective analysis of charts including spirometry and bronchodilator response.

Results: Of 190 CF patients (103 at Schneider's, 87 at Hadassah), aged 14.4 (4–76) years, median (range), 39% had reversible obstruction ($\Delta FEV_1\%$ predicted $\geq 12\%$), associated with younger age ($p = 0.01$) and severe genotype ($p = 0.02$). There was no association with family history of asthma, serum IgE, blood eosinophils, pancreatic status, $FEV_1 < 40\%$ predicted, Aspergillus or pseudomonas infection. Of patients with reversible obstruction, 74% were on bronchodilator and 68% on inhaled corticosteroid therapy but 54% and 57% respectively receiving these therapies did not have reversible obstruction.

Conclusions: Reversible airway obstruction is common in CF, more frequent in younger patients and with severe genotype, with no correlation to markers of atopy or CF clinical severity. Bronchodilator and inhaled corticosteroid therapies are commonly prescribed even without reversible obstruction.

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Introduction

Cystic fibrosis (CF) is an obstructive airways disease [1]. Nevertheless the association between CF and bronchial asthma is unclear. The term 'CF asthma' refers to asthma-like symptoms and bronchial hyper-responsiveness in CF patients [2]. Both CF and

asthma are characterized by airway inflammation and smooth muscle contraction due to inflammatory mediators, although the nature of the inflammation may differ. Severe neutrophilic inflammation is the hallmark of CF lung disease whereas eosinophilic inflammation is more characteristic of asthma [1,3].

Airway obstruction in atopic asthma is characterized by smooth muscle contraction, mucosal edema and increased mucus secretion resulting from a Th2 lymphocytic immune response associated with IgE-mediated inflammation. While reversible bronchospasm is central, structural airway remodeling occurs [3]. In CF lung disease, absent *CFTR* within airway smooth muscle may cause a persistent contracted state. With

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time, a dysregulated vicious cycle of inflammation and infection results in development of severe cystic bronchiectasis over time. Chronic *Pseudomonas aeruginosa* infection is associated with a predominant Th2 immune response [4].

There is no consensus on how to define 'CF asthma'. As asthma is a common disease in the general population, with a prevalence of 5–17% worldwide [5], it is difficult to determine which CF patients have asthma as well as CF, and which have asthma-like symptoms due to changes in bronchomotor tone or CF lung inflammation. The diagnosis of asthma in CF patients is mainly clinical, based on suggestive features such as a strong family and personal history of atopy, and a family history of asthma, in addition to CF [2].

Our study aims to describe the prevalence of reversible airway obstruction and bronchodilator use in patients with CF and to assess its possible association with different characteristics of this disease thus leading to a better understanding and rationale for therapy of CF lung disease.

Methods

Patients with CF followed at the Graub CF Center, Schneider Children's Medical Center and the CF Center at Hadassah-Hebrew University Medical Center were studied by retrospective chart review between 1991 and 2014. Inclusion criteria were a diagnosis of CF according to accepted criteria [6], the ability to perform spirometry according to ATS/ERS guidelines [7] and at least one recorded response to bronchodilator in the patient's chart.

Pulmonary function tests

Both CF centers used the Polgar prediction equations for children up to the age of 18 years, and the ECSC/ERS or Knudson prediction equations for patients aged 18 years and above. Laboratory protocol for evaluating the response to bronchodilator required at least 6 h since the last dose of short acting beta agonist (SABA) and at least 12 h since the last dose of long acting beta agonist (LABA) or combined LABA-inhaled corticosteroid (ICS) inhalation. We evaluated spirometry pre- and post-bronchodilator routinely during annual review but also when increased reversibility was suspected at times of increased wheezing or bronchial obstruction. The spirometry result demonstrating maximal improvement in FEV₁ following bronchodilator was recorded from the patients' charts.

Definitions

We defined reversible airway obstruction according to ATS/ERS guidelines [8] as an improvement in %predicted FEV₁ (Δ FEV₁) of $\geq 12\%$. An improvement in MEF_{25–75%} (Δ MEF_{25–75%}) of $\geq 30\%$ following bronchodilators reflected reversibility of small airway obstruction [9]. Allergic bronchopulmonary Aspergillosis (ABPA) was defined according to the CF foundation consensus criteria [10]. A stool elastase of <200 mcg/g was required for the definition of pancreatic insufficiency [11]. We

classified patients as having a severe *CFTR* genotype if they had 2 mutations from class I, II or III, known to be associated with minimal *CFTR* function and a mild *CFTR* genotype if they had at least one mutation from class IV or V, known to be associated with residual *CFTR* function [12]. If patients had 1 unknown and 1 severe mutation or 2 unknown mutations we classified them as of unknown genotype severity and did not include them in the analysis of the association of genotype with bronchodilator reversibility. Chronic infection with *P. aeruginosa* was defined as at least 3 positive sputum cultures over a period of at least 6 months [13].

Patient data

Data collected from each patient included demographics at the time of selected spirometry result: weight, height and BMI; CF disease characteristics including *CFTR* mutations, sweat chloride, fecal elastase, chronic *P. aeruginosa* infection, Aspergillus infection; a diagnosis of ABPA, positive RAST for *Aspergillus fumigatus*; and the following markers of atopy: highest recorded serum IgE and highest recorded total eosinophil count. Information available regarding a family history of asthma in a first degree family member was also documented.

We detailed whether patients were receiving SABA, ICS or combination therapy of LABA with ICS at the time of the selected spirometry test.

Statistics

Descriptive statistics were used, and data is expressed as mean $\pm$ standard deviation or as median and range as appropriate. Among the patients with complete data, we tested differences between subgroups of patients with χ^2 test or Fisher-Exact test (for 2×2 tables) for categorical variables and *t* tests for Normally distributed continuous variables. We used compared means of Normally distributed variables using ANOVA. When distribution of continuous variables (such as age across categories) was not Normal we compared group distribution using the Mann–Whitney test. In measures with levels of missing data we categorized the data and introduced missingness as an independent category to test significance, using χ^2 test. The statistical analysis was performed with SPSS 22.0 for Windows. Statistical significance was defined by a two-sided alpha level of 0.05.

The Rabin Medical Center and Hadassah Medical Center Research Ethics Committees granted approval for this retrospective study (Rabin ERB number: 0427-13-RMC; Hadassah ERB number: 0592-12).

Results

Of the 190 CF patients that fulfilled the inclusion criteria, 103 were from the Graub CF Center at Schneider Children's Medical Center and 87 from the CF Center at Hadassah-Hebrew Medical Center. Median age was 14.4 years with a range of 4–76 years, and 110 (58%) were males.

Reversibility of airway obstruction

As shown in Table 1, 75 (39%) patients had reversibility of airway obstruction as expressed by $\geq 12\%$ increase in FEV₁% of predicted following bronchodilators.

Patients with a Δ FEV₁% predicted $\geq 12\%$ were aged 14.4 (4–53) years, median (range) compared to age 20.3 (4–67) years for those with Δ FEV₁% predicted $< 12\%$ ($p = 0.001$). Distribution of ages was also significantly different between these two groups ($p < 0.001$) (Fig. 1a). Similarly, patients with Δ MEF_{25–75%}% predicted $\geq 30\%$ were younger than those with Δ MEF_{25–75%}% predicted $< 30\%$, with age 11.09 (4–53) years, and 16.98 (4–67) years, median (range) respectively ($p = 0.026$). The distribution of ages was also significantly different between these two groups ($p = 0.002$) (Fig. 1b).

There was no significant association of bronchodilator reversibility with gender, with respect to either a change in FEV₁ $\geq 12\%$ ($p = 0.06$) or MEF_{25–75%} $\geq 30\%$ ($p = 0.3$). When subdividing the population into patients aged 12 years or below, 12–45 years or above 45 years, there was no association with gender in any of the age groups.

Association with features of asthma and atopy

As shown in Table 1, no difference was found in rates of asthma among 1st degree family members between those with or without reversible airway obstruction. Although data was only available with regard to 86 of 190 patients, these did not vary from the 104 with no information regarding asthma family history, with regard to reversibility of airway obstruction (Δ FEV₁% predicted $\geq 12\%$, Δ MEF_{25–75%}% predicted $\geq 30\%$ following bronchodilator, $p = 0.82$ and $p = 0.65$ respectively).

Laboratory parameters of atopy were available for the entire clinic cohort. There was no difference in the median values or distribution of markers of atopy, including maximal recorded

Ig-E levels or total eosinophil count between those with or without reversible airway obstruction (Table 1 and Fig. 2).

Association of reversible airways obstruction with genotype and clinical characteristics

Subjects with 2 class I–III *CFTR* mutations, compared to those with at least one class IV or V mutation and residual *CFTR* function, had more reversibility with regard to Δ FEV₁% predicted $\geq 12\%$, ($p = 0.02$) but not with regard to Δ MEF_{25–75%}% predicted $\geq 30\%$ ($p = 0.67$) (Table 2). We did not find a difference in the prevalence of reversible airway obstruction for those with FEV₁ $\leq 40\%$ predicted, compared to those with FEV₁ $> 40\%$ predicted. Bronchodilator reversibility was not associated with a steeper slope of decline for FEV₁.

There was no change in the frequency of reversible airway obstruction associated with pancreatic status, with a positive sputum culture for *Aspergillus* or with chronic airway infection with *P. aeruginosa* (Table 2). Seventeen (9%) of the CF patients had ABPA with no significant difference in the response to bronchodilators compared to patients without ABPA ($p = 0.076$) (Table 2).

One hundred and twelve (63%) out of 177 CF patients for which data was available were using bronchodilators (Table 3A). SABA was used by 61 (38%) of 162 for which data was available, whereas LABA as part of combination LABA/ICS therapy was used by 84 (51%) of 165 for which data was available.

Of these 112, only 51 (45.5%) had reversible airway obstruction. Of the 69 patients with reversible obstruction and complete data on bronchodilator use, 51 (74%) were on bronchodilator therapy compared to 18 (26%) not using bronchodilators ($p = 0.046$) (Table 3B). Being on bronchodilator therapy had a negative predictive value (NPV) of 0.44 and positive predictive value (PPV) of 0.74 for having FEV₁ reversibility of $\geq 12\%$ with 0.73 and 0.45 specificity and sensitivity respectively.

Table 1
Bronchodilator reversibility and features of asthma and atopy.

Parameter		All patients	Change in % predicted following bronchodilator			
			Δ FEV ₁ pp $\geq 12\%$	p ^ψ	Δ MEF _{25–75%} pp $\geq 30\%$	p [§]
All patients, n (%)		190	75 (39)		76 (40)	
Gender	Males, n (%)	110 (58)	49 (44.5)	0.06	42 (38)	0.3
	Females, n (%)	80 (42)	26 (39.5)		34 (43)	
IgE*, IU/ml		68 (0–6655)	93 (0–6655)	0.133	97 (0–4550)	0.073
median (range)						
Eosinophils*/μl		500 (100–3800)	515 (100–2400)	0.33	500 (100–3800)	0.497
median (range)						
Asthma F/H [¶]	Yes	53 (62)	19 (36)	0.82	21 (40)	0.65
	No	33 (38)	13 (39)		15 (46)	

Δ FEV₁ pp = Improvement in %predicted forced expiratory volume in 1 s following bronchodilators.

Δ MEF_{25–75%} pp = Improvement in %predicted maximal mid-expiratory flow following bronchodilators.

Values are n (%) unless otherwise indicated; *refers to maximal value recorded in the patient's chart.

^ψp value comparing Δ FEV₁% predicted $\geq 12\%$ to n with Δ FEV₁% predicted $< 12\%$.

[§]p value comparing Δ MEF_{25–75%}% predicted $\geq 30\%$ to n with Δ MEF_{25–75%}% predicted $< 30\%$.

[¶]Asthma F/H: asthma in a first degree family member, according to patient history, where available. These 86 did not differ from the 104 with no information, with regard to prevalence of reversibility of airway obstruction for the entire group (Δ FEV₁% predicted $\geq 12\%$, Δ MEF_{25–75%}% predicted $\geq 30\%$ following bronchodilator, $p = 0.43$ and $p = 0.8$ respectively).

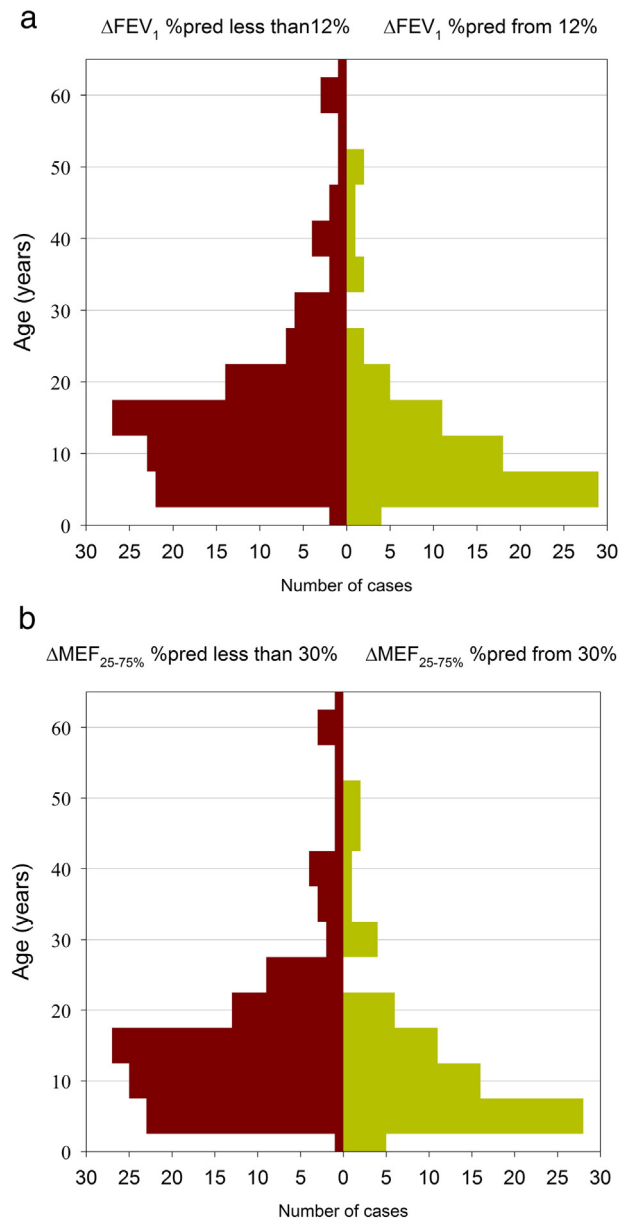


Fig. 1. Age distribution of CF patients as associated with reversible airway obstruction: a. Age distribution stratified by change in FEV₁% predicted (Δ FEV₁%pred) post bronchodilator showed a younger age distribution for the patients in the group with bronchodilator reversibility ($p \leq 0.001$). b. Similarly, there was a younger age distribution for patients with change in MEF_{25-75%}% predicted (Δ MEF_{25-75%}%pred), post-bronchodilator of $\geq 30\%$ ($p = 0.026$).

With regard to patients with reversibility of small airway obstruction after bronchodilators, 58 (80%) were on bronchodilator therapy ($p < 0.001$). ICS use was also common among CF patients, with 112 (63%) of 179 patients for which data was available, on therapy. Of 70 patients with reversible obstruction, 48 (68%) were on ICS therapy compared to 22 (32%) not using ICS ($p = 0.0.2$). Of all patients taking ICS (112 patients), only 48 (43%) had reversible airway obstruction ($p = 0.2$) (Table 3C). Being on ICS therapy had a NPV of 0.41 and a PPV of 0.69 for having FEV₁ reversibility of $\geq 12\%$, with 0.67 and 0.43 specificity and sensitivity respectively.

Of 72 patients with reversible small airways obstruction, 54 (75%) were on ICS therapy whereas only 54 (48%) of all

patients treated with ICS had reversible small airway obstruction ($p = 0.007$) (Table 3C and D).

Discussion

This study demonstrates that reversible airway obstruction is a common finding in CF and that reversibility is associated with younger patient age. We found no increased prevalence of reversible obstruction in those with atopy or a family history of asthma. With regard to CF characteristics, reversibility was more common among patients with 2 class I–III *CFTR* mutations compared to those with at least 1 class IV or V mutation, but there was no association with clinical measures of severity such as

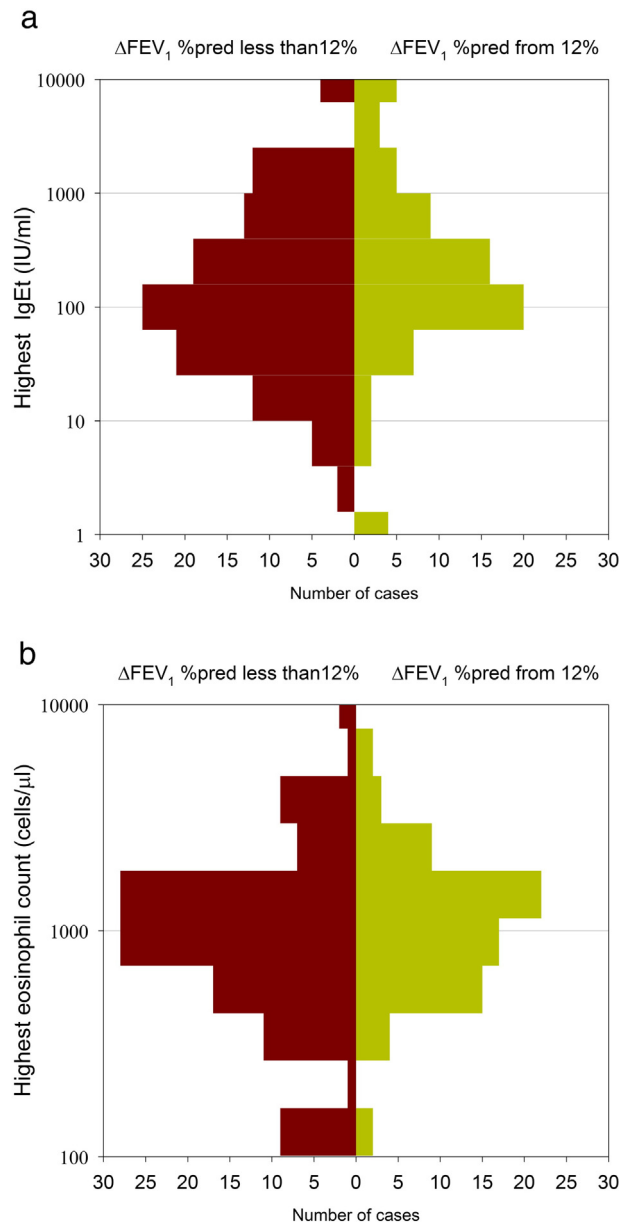


Fig. 2. Markers of atopy stratified by reversible airway obstruction: a. Highest recorded IgE, distribution stratified for change in FEV₁% predicted (Δ FEV₁ %pred). There was no difference between those with or without reversible airway obstruction ($p = 0.08$), Mann–Whitney U test. b. Highest recorded eosinophil count (cells/ μ L), distribution stratified for change in FEV₁% predicted (Δ FEV₁ %pred). There was no difference between those with or without reversible airway obstruction ($p = 0.38$), Mann–Whitney U test.

pancreatic insufficiency, chronic *P. aeruginosa* or Aspergillus infection.

The strength of this study is its focus on the objective measure of maximal recorded reversibility of airway obstruction over the entire course of a patient's history. Our findings in two CF centers strengthen those of previous, mostly smaller studies, demonstrating the high prevalence of bronchodilator response [14] which is unlikely to be related to atopic asthma [15,16]. Most importantly, our study identifies a lack of consistency between the presence of reversible obstruction and the decision to treat with bronchodilators and ICS in CF.

Our observation that reversibility of obstruction decreases with age in CF could possibly be due to increased bronchomotor tone

and bronchospasm in early stages of the disease, which decreases as chronic inflammation and destruction of the airway wall increase over time. Wheezing phenotype was described in 25% of CF infants [17] and decreased $V_{\max}$ FRC, normalized with metoprolol has been demonstrated [18], suggesting the importance of increased bronchomotor tone and bronchoconstriction in CF airway obstruction at this age. Similarly, Sanchez et al. showed that at least 40% of young children with mild CF already had moderate to severe nonspecific airway hyperreactivity, possibly due to subclinical lung damage, or related to an intrinsic feature of CF [19]. A recent study of 4480 young children with CF has shown that early childhood wheezing is common and associated with lower lung function in mid-childhood [20].

Table 2
Association of reversible airways obstruction and CF clinical parameters.

CF parameter		Patients n (%) Total n = 190	Change in % predicted following bronchodilator			
			Δ FEV ₁ pp $\geq 12\%$	p	Δ MEF _{25–75%} pp $\geq 30\%$	p
<i>CFTR</i> genotype n = 178	Severe mutation	121 (68)	55 (45.5)	0.02	51 (42)	0.67
	Residual function	57 (32)	14 (24.6)		20 (35)	
Pancreatic function n = 188	Pancreatic insufficient	103 (55)	55 (42)	0.4	36 (35)	0.18
	Pancreatic sufficient	85 (45)	36 (35)		38 (45)	
ABPA n = 187	Yes	17 (9)	10 (59)	0.1	6 (35)	0.8
	No	170 (91)	64 (38)		66 (40)	
Aspergillus infection n = 184	Yes	55 (30)	25 (45)	0.5	26 (47)	0.3
	No	129 (70)	50 (39)		48 (37)	
<i>P. aeruginosa</i> infection n = 179	Yes	71 (40)	30 (42)	0.4	27 (38)	0.7
	No	108 (60)	41 (38)		43 (40)	

Values are n (%) unless otherwise indicated; ABPA = Allergic bronchopulmonary aspergillosis, *P. aeruginosa* = *Pseudomonas aeruginosa*; Δ FEV₁ pp = Improvement in %predicted forced expiratory volume in 1 s following bronchodilators; Δ MEF_{25–75%} pp = Improvement in %predicted maximal mid-expiratory flow following bronchodilators.

Our findings of severe genotype associated with reversible airway obstruction suggest a possible role of chronic loss of *CFTR* in association with a hyper-contracted state. Indeed, recent studies have detected *CFTR* in smooth muscle, and functional studies suggest that *CFTR* may play a role in muscle relaxation. A recent review discusses the interplay of likely direct effects of absent *CFTR* with progressive CF infection and inflammation upon airway smooth muscle proliferation and hyper-responsiveness [4]. Recent insights are provided by the porcine CF model which showed that neonatal *CFTR*^{−/−} pigs

have reduced tracheal and main stem bronchial caliber with prominent trachealis smooth muscle and altered bundle orientation [21]. These changes were found at a stage where no infection or inflammation is present, suggesting that they were directly attributable to loss of *CFTR* rather than the result of remodeling. Indeed, *CFTR* has been localized to smooth muscle within the airway, intestine and other organs and activation of the *CFTR* channel in rat trachealis muscle results in airway dilation [22]. Absence of *CFTR* may result in a hypercontracted state of human airway smooth muscle as well [23]. The commonality of smooth

Table 3
Bronchodilator and inhaled corticosteroid use by CF patients.

A. Percent of patients on bronchodilator therapy who have airway reversibility (n = 177)			
On bronchodilator therapy	Δ FEV ₁ % predicted $\geq$ 12%	Δ MEF _{25–75%} % predicted $\geq$ 30%	
Yes, 112 (63)	51 (45.5)	58 (52)	
No, 65 (37)	18 (28)	14 (22)	
p value	0.046	<0.001	
B. Percent of patients with reversible airway obstruction on bronchodilator therapy (n = 177)			
Reversible airway obstruction	On bronchodilator therapy	Not on bronchodilator therapy	p value
Δ FEV ₁ % predicted $\geq$ 12% n = 69	51 (74%)	18 (26%)	0.046
Δ MEF _{25–75%} % predicted $\geq$ 30% n = 73	58 (80%)	15 (20%)	<0.001
C. Percent of CF patients on ICS therapy with reversible airway obstruction, n = 179			
On ICS therapy	Δ FEV ₁ % predicted $\geq$ 12%	Δ MEF _{25–75%} % predicted $\geq$ 30%	
Yes, 112 (63)	48 (43)	54 (48)	
No, 67 (37)	22 (33)	18 (27)	
p	0.2	0.007	
D. Percent of CF patients with reversible airway obstruction on ICS therapy, n = 179			
Reversible obstruction	On ICS therapy	Not on ICS therapy	p value
Δ FEV ₁ % predicted $\geq$ 12% n = 70	48 (68%)	22 (32%)	0.2
Δ MEF _{25–75%} %predicted $\geq$ 30% n = 72	54 (75%)	18 (25%)	0.007

ICS = Inhaled corticosteroids; Δ FEV₁% predicted = Improvement in %predicted forced expiratory volume in 1 s following bronchodilators, Δ MEF_{25–75%} % predicted = Improvement in %predicted maximal mid-expiratory flow following bronchodilators.

muscle changes in CF humans, pigs and mice suggests an emerging role for *CFTR* in smooth muscle functioning and direct alterations in contractile signaling where *CFTR* is deficient.

Airway hyperreactivity is common in CF and bronchodilator response is greater in those with a positive methacholine (MCh) challenge test [15,26]. However, the basis for this response appears to differ from that in asthma. Mitchell et al. found a positive response to MCh in 51% of CF compared with 98% of asthmatic patients with different dose–response curves and time course suggesting different pathophysiologic mechanisms in each disease [26]. There is evidence that in CF, as opposed to asthma, airway hyperreactivity is neurally mediated. Increased vagal bronchomotor tone was suggested as a possible mechanism by van Haren et al. who demonstrated, that in CF, unlike in asthma, bronchodilation following exercise was correlated with a bronchodilator response to ipatropium bromide [24]. In support of this altered autonomic reactivity is the finding that obligate CF heterozygotes had more reactive pupils to both phenylephrine and carbachol [25].

In the current study, we were not able to show an association of airway hyperreactivity with lower lung function as expressed by FEV₁ below 40% predicted. This is in contrast with others who found an association with decreased pulmonary function, lower Shwachman-Kulczycki score, more pulmonary exacerbations and a more rapid decline in FEV₁ [15]. Mellis and Levison described bronchoconstriction following histamine inhalation in 24% of CF subjects compared to more than 90% of asthmatic subjects with no correlation in CF patients to atopy but an association with abnormal baseline lung function. They concluded that hyperreactivity probably reflected more severe underlying CF lung disease rather than the presence of coexistent asthma [26].

An interesting feature in this study was a lack of correlation between reversible bronchial obstruction and either a family history of asthma or markers of atopy. Warner et al. found that CF patients had a higher incidence of positive allergen skin tests and other markers of atopy when compared to non-asthmatic children, as well as a high number of first degree relatives with a history of atopy [27], and Balfour-Lynn et al. proposed that a strong family and personal history of atopy may suggest the diagnosis of asthma in CF patients [2]. In contrast to these studies, our findings which focus more on the objective measure of post-bronchodilator improvement in FEV₁ and MEF_{25–75%} suggest that reversible bronchospasm in CF may be due other mechanisms, possibly directly related to CF lung disease as discussed above.

Unlike the case for asthma, there are no guidelines today regarding which CF patients should be on bronchodilators, ICS or combination therapy. In a large survey of the Epidemiologic Study of CF in the USA, more than 82% of 18,000 patients used inhaled bronchodilator therapy on a daily basis [28]. An important aspect of our study was the observation that many patients with reversible airway obstruction were not treated with either bronchodilators or inhaled corticosteroids. Conversely, of those on therapy, many did not have reversible airway obstruction. It is not clear what criteria drove therapeutic decision-making in these cases. Bronchodilators are known for their ability to enhance mucociliary clearance [29] and thus could potentially be beneficial for CF patients even when

there is no reversible airway obstruction. Indeed, a benefit for long-term bronchodilators use in CF patients has been demonstrated with or without reversible obstruction [30,31]. However, bronchodilation may theoretically worsen dynamic airway collapse due to decreased airway muscle tone, particularly in patients with severe bronchiectasis [32].

We found that a majority of our patients were receiving long term ICS therapy although significant benefit has not been conclusively demonstrated according to a Cochrane Database Systemic Review from 2014 [33]. On the one hand, data from the Epidemiologic Study of CF has demonstrated a significant reduction in the rate of FEV₁ decline, with ICS use [34]. Other studies failed to find a significant change in FEV₁ after ICS therapy [35]. In addition, there was no difference in the number of respiratory exacerbations, days of intravenous antibiotic therapy or days of hospitalization [35,37]. A study by Balfour-Lynn et al. had to be based on safety of ICS withdrawal rather than a prospective institution of ICS therapy, due to the large proportion of patients already on long term therapy [36]. It should be noted that bronchodilator reversibility could have been masked in the patients on long term ICS in our study. Nevertheless, a third of patients with reversibility were not receiving ICS. Clearly, there is an urgent need for multicenter, prospective trials to evaluate the efficacy and safety of both bronchodilator and ICS therapy in CF.

Limitations of our study are those of a retrospective study design. Subject numbers available varied for the different parameters investigated. Whereas data regarding laboratory parameters of atopy were available on all subjects, information regarding asthma family history was only available on half the patients. In addition, the number of spirometry results pre and post-bronchodilator varied between patients and we selected the point in time of maximal change in FEV₁% or MEF_{25–75%} predicted for comparison of all CF parameters. The retrospective nature of the study also hampered our ability to assess slope of decline in lung function, as measurement of maximal reversibility may not have been during baseline conditions. Finally, the spectrum of *CFTR* mutation classes in our centers includes a larger proportion of mutations with residual function compared to the European and USA CF data registries. Nevertheless, the fact that bronchodilator reversibility was associated with more severe genotype in our study would make the findings broadly applicable.

Reversible airway obstruction appears to be a central feature of CF lung disease, particularly in younger patients and those with severe genotype. At present the associated pathophysiology is poorly understood and this parameter appears to have little impact on therapeutic decision-making regarding bronchodilators and ICS. We recommend a prospective multi-center study identifying CF patients with reversible airways obstruction, associated bronchial hyperreactivity as well as response to targeted bronchodilator and ICS therapy.

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