

The Impact of Intranasal Corticosteroids on Lung Function in Children With Allergic Rhinitis

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Summary. Background: Subjects with allergic rhinitis (AR) suffer from impaired lung function, especially decreased $FEF_{25-75\%}$. The purpose of this study was to examine lung function and the long-term response to INCS in AR patients with impaired lung function, and to characterize the phenotype of these children. Methods: Two hundred two children with AR underwent an allergy evaluation including a skin prick test and spirometry. Children with impaired lung function were treated with daily nasal corticosteroids spray (INCS) and antihistamine as needed. Results: Fifty-three children out of 202 (26.3%) had impaired lung function: 34 of them (64.2%) had $FEF_{25-75\%}$ values under 80% of predicted and normal FEV_1 values, and 19 individuals (35.8%), had both $FEF_{25-75\%}$ and FEV_1 values below 80% of predicted. A positive correlation between FEV_1 and $FEF_{25-75\%}$ values ($r = 0.369$, $P = 0.007$) and a reverse correlation between duration of nasal symptoms and $FEF_{25-75\%}$ values ($r = -0.364$, $P = 0.012$) were found. Post-ronchodilation FEV_1 levels increased from 81.9 ± 8.0 to 87.7 ± 10.4 ($P < 0.0001$). Thirty-five of the 53 children complied with a continuous INCS treatment regimen over a period of 3–12 months, demonstrated increased $FEF_{25-75\%}$ (84.4 ± 13.6 vs. 70.1 ± 7.1 , $P < 0.001$) and FEV_1 (92.3 ± 10.9 vs. 84.4 ± 7.8 , $P < 0.0001$) after INCS treatment. However, $FEF_{25-75\%}$ values were still significantly lower compared to the group of AR children with normal lung function (84.4 ± 13.6 vs. 95.7 ± 8.8 , $P < 0.0001$). Conclusions: INCS improve $FEF_{25-75\%}$ above 80% of predicted values in 2/3 of children with abnormal lung function. However, this improvement does not reach levels of AR children with normal lung function. **Pediatr Pulmonol.** © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

Allergic rhinitis (AR) is a common clinical problem in children. The International study of asthma and allergies in childhood revealed that the mean prevalence of current rhinoconjunctivitis symptoms among children at the age of 6- to 7-year old was 8.5%. For 13- to 14-year old children, prevalence ranged from 1.0 to 45% with a mean of 14.6%.¹ AR is characterized by an inflammatory infiltrate in the nasal mucosa and the release of mediators responsible for the typical symptoms. The goal of medical treatment of children with AR is to reduce nasal symptoms, decrease the underlying inflammation process, prevent the development of comorbidities, and thereby enhance the quality of life for both the child and his/her parents.

Intranasal corticosteroids (INCS) are the most efficacious medication treatment in children and adults, and consequently are recommended as first-line therapy by both National and International task forces for individuals with moderate-to-severe or persistent AR.^{2,3} This treatment was found to reduce the inflammatory process in the nasal mucosa and as a result lessen the symptoms of rhinitis. Previous studies, especially in adults, have shown that subjects with AR suffer from impaired lung function, especially decreased mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{25-75\%}$).⁴ The midflow rates measured during spirometric testing are believed to represent small airway airflow.⁵ Children with AR commonly suffer from bronchial hyperresponsiveness (BHR) which is a pathophysiological characteristic of asthma.^{6,7} Moreover, AR is regarded as a risk factor for

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the development of asthma, especially in the presence of BHR.^{8–11} In a pilot study we found that a substantial proportion of children with AR due to house dust mite have diminished forced expiratory flow at FEF_{25–75%} values and reversible airway obstruction. In a small group of these patients INCS improved pulmonary function.¹² In the current study, we aim to examine lung function and the long-term response to INCS in a large group of AR patients with impaired lung function whose AR stems from a varied array of allergens. Additionally, we aim to describe the phenotype of these children.

PATIENTS AND METHODS

Patients

The study population recruited from our outpatient allergy clinic, consisted of children with moderate/severe persistent AR with no past medical history suggestive of asthma. A detailed clinical history and complete physical examination including allergy evaluation and spirometry were performed. We also performed spirometry before and after inhalation of a bronchodilator among children with impaired lung function. Exclusion of children with asthma was based on their physician medical report and on a series of questions that were addressed to the parents and children such as: “Did your child suffered from wheezing, dyspnea, chest tightness, exercise-induced symptoms, or recurrent cough outside common cold.” Those who suffered from one of these symptoms or previously treated with anti-asthma medications were excluded from the study. Additional exclusion criteria included: (a) previous or current treatment with intranasal or oral corticosteroids within 4 weeks, and (b) prior use of leukotriene modifier. The diagnosis of AR was made according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines by the presence of two or more of the symptoms of AR (sneezing, watery rhinorrhea, nasal obstruction, and nasal pruritus) lasting more than 1 hr on most days and a concordance between a typical history of allergic symptoms and positive skin prick tests to inhalant allergen.¹³ The study group was treated with INCS treatment (Budesonide or Triamcinolone acetonide) daily and second generation oral antihistamines as needed. The study was approved by the community Helsinki committee at Meir Hospital, Kfar-Saba, Israel.

Skin Prick Test

Sensitization was established by performing SPT reactivity to common inhaled allergens in conjunction with positive and negative controls, 1 mg/ml histamine and 0.9% (w/v) saline, respectively (ALK ABELLO Port, Washington, NY). The panel consisted of house dust mite (*dermatophagoides farine* and *pteronyssinus*), mixed weeds (Pigweed, Lambs quarters, Sagebrush, Plaintain,

Nettle, Wall pellitory, Cocklebur), mixed grass (Bermuda, Jhonson, Orchard, Timothy) mixed trees (Olive, Cypress, Pecan, Oak, Acacia, Cottonwood, Casuarina) mixed molds (*Cladosporium*, *Alternaria*, *Aspergillus*), dog, cat, and cockroach extracts. Reactions to the allergens were read after 15 min. Wheals with a mean diameter ≥ 3 mm larger than those of the negative control were considered positive reactions.¹⁴

Spirometry

Spirometry was performed by using a computer-assisted spirometer (KoKo version 4.11; PDS Instrumentation; Louisville, CO) with an optoelectronic whirl flow meter as described by European Respiratory Society and according to international guidelines.¹⁵ The best spirometric measures of at least three reproducible attempts were recorded for analysis. Values that we used in the analyses were adjusted for age, height, and gender and expressed as percent predicted.¹⁶

Bronchodilation Effect

Conventional reversibility test was performed with two puffs (400 μ g) terbutaline (Ventoline; GlaxoSmithKline; London, UK), a short acting beta agonists (SABA), through a spacer device (Volumatic; GlaxoSmithKline). Subjects then remained seated for 15 min, after which a repeated spirometry was performed in an identical fashion to determine the bronchodilation response. The bronchodilator response (BDR) was positive if there was a rise of 12% or more in forced expiratory volume in the first second (FEV₁) from the baseline measurements.¹⁷

Statistical Analysis

The comparison between the means values of pulmonary function of the different groups was performed using unpaired *t*-test, and within the groups by paired *t*-test. The Pearson correlation coefficient (*r*) was used to assess the correlation between the different parameters. Differences were considered significant if *P*-values were <0.05 .

RESULTS

Patients

Two hundred two children (132 males (65.3%), 70 females (34.7%)), mean age 11.6 ± 3.4 years $\pm$ SD) were recruited from our outpatient allergy clinic and participated in a lung function test. In total, 149 out of 202 (73.7%) had normal pulmonary function tests (PFTs). Consequently, our study group consisted of the 53 children (53/202, 26.3%) who had impaired lung function defined by FEF_{25–75%} and/or FEV₁ under 80% of predicted. This group included 36 males (36/53, 67.9%) and 17 females (17/53, 22.1%). Participants mean age was

11 (SD + 2.63 years). The mean duration of rhinitis at diagnosis was 2.66 (SD = 2.24 years). Thirty-two children (32/53, 60.4%) had only house dust mite allergy. Eleven children (11/53, 20.7%) had allergy to dust mite and inhaled pollens. Five children had dust mite inhaled pollens and animal dander allergy (5/53, 9.4%). Three children (3/53, 5.7%) had allergy only to inhaled pollens. One patient (1/53, 1.9%) had allergy to dust mite and animal dander extract and one patient had allergy to inhaled pollens and animal dander extract (1/51, 1.9%). Forty-nine children (49/53, 92.45%) had persistent moderate/severe AR and 4 children (4/53, 7.55%) had intermittent moderate/severe AR. Fifty-five percent of the children with impaired lung function had, by self report, one parent with asthma and/or AR.

Thirty-four children out of fifty three (34/53, 64.2%) had $FEF_{25-75\%}$ values under 80% of predicted and normal FEV_1 values (>80% predicted) (Group A) and 19 individuals out of 53 (19/53, 35.8%) had both $FEF_{25-75\%}$ and FEV_1 values below 80% of predicted (Group B). $FEF_{25-75\%}$ values in group A tended to be higher compared to children in group B (71.4 ± 5.4 vs. 67.7 ± 7.2 , $P = 0.05$) (Fig. 1A). FEV_1 values in children with normal lung function were found to be significantly higher compared to children in group A (95.7 ± 8.8 vs. 87.14 ± 5.5 , $P < 0.001$) and FEV_1 values in children in group A were significantly higher compared to children in group B (87.14 ± 5.5 vs. 73.9 ± 4.3 , $P < 0.001$) (Fig. 1B).

We found a positive correlation between FEV_1 and $FEF_{25-75\%}$ values in children with abnormal lung function (Group A and B) ($r = 0.369$, $P = 0.007$) (Fig. 2A) and a reverse correlation between nasal symptoms duration and $FEF_{25-75\%}$ values ($r = -0.364$, $P = 0.012$) (Fig. 2B).

Test of Bronchodilation

The degree of reversibility was determined as the difference between pre-SABA and post-SABA therapy

FEV_1 . FEV_1 levels increased from 81.9 ± 8.0 to 87.7 ± 10.4 , $P < 0.0001$ (Fig. 3). An increase of 12% or greater in FEV_1 was present in 24% of these children.

The Effect of Intranasal Corticosteroids on PFTs

Thirty five of our patients with impaired lung function (35/53, 66%) complied with a 3–12 months treatment protocol of INCS. These patients had statistically significant increased $FEF_{25-75\%}$ (84.4 ± 13.6 vs. 70.1 ± 7.1 , $P < 0.001$) and FEV_1 (92.3 ± 10.9 vs. 84.4 ± 7.8 , $P < 0.0001$) after treatment with INCS. However, in 12/35 (34.2%) of the children, the elevation in $FEF_{25-75\%}$ did not reach 80% of predicted. Furthermore, $FEF_{25-75\%}$ values were still significantly lower, after INCS treatment, compared to the group of AR children with normal lung function (84.4 ± 13.6 vs. 95.7 ± 8.8 , $P < 0.0001$) (Fig. 4). Nine children out of the 35 (25.7%) needed further treatment, in order to influence both nasal symptoms and lung function and were treated with montelukast. Interestingly, in most subjects treated with INCS, but without significant improvement of nasal symptoms, there was no evidence of an improvement in lung function. During the follow-up period, two patients developed a clinical picture of asthma and were among those treated with montelukast. One had $FEF_{25-75\%}$ and FEV_1 values below 80% of predicted and the other one $FEF_{25-75\%}$ values under 80% of predicted and normal FEV_1 values.

DISCUSSION

Allergic rhinitis is classically considered to result from an IgE-mediated allergy associated with inflammation of the nasal mucosa at variable intensity. Therefore, INCS sprays are a rational treatment choice for persistent moderate to severe AR. The assessment of AR control focuses on three main domains: (1) rhinitis symptoms

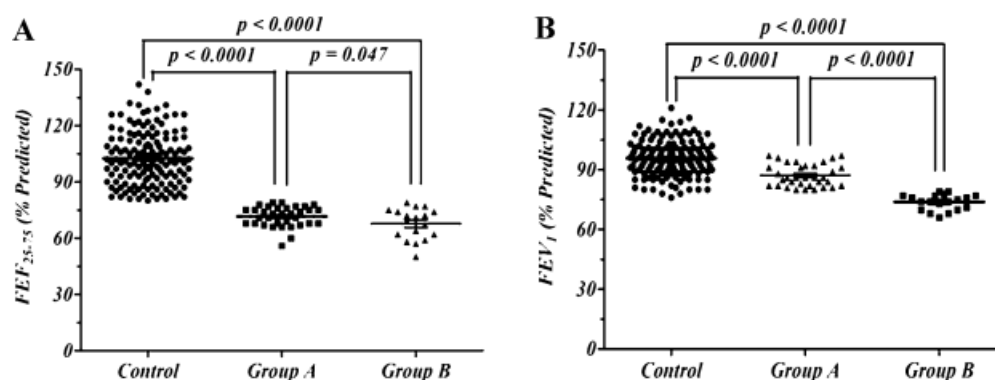


Fig. 1. FEF_{25-75} and FEV_1 values of children with allergic rhinitis. **A:** Children with normal lung function (Control) had higher levels of $FEF_{25-75\%}$ compared to children in group A ($FEF_{25-75\%}$ values under 80% of predicted and normal FEV_1 values >80% predicted) and Group B (patients with both $FEF_{25-75\%}$ and FEV_1 values below 80% of predicted). **B:** Children with normal lung function (Control) had higher levels of FEV_1 values compared to group A and B.

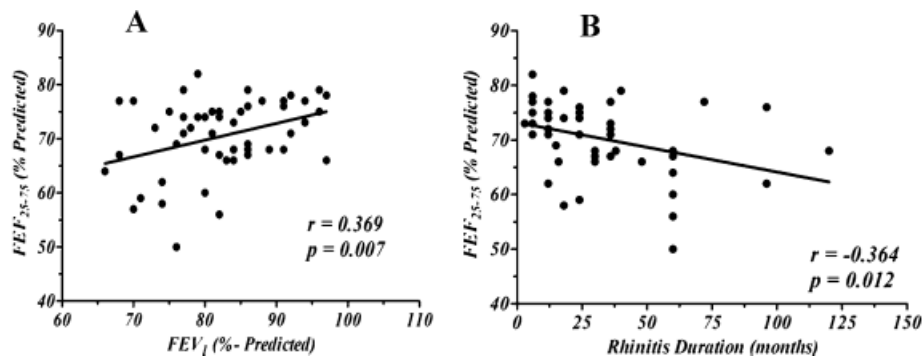


Fig. 2. A: Correlations between levels of $FEF_{25-75\%}$ and FEV_1 in children with AR and impaired lung function. (Pearson Rank correlation test). **B:** Correlations between levels of $FEF_{25-75\%}$ and nasal duration in children with AR and impaired lung function (Pearson Rank correlation test).

(sneezing, nasal congestion, and mucous discharge), (2) limitation of activities (social life, sleep, school performance), and (3) comorbidity disorders (asthma, chronic middle ear effusions, sinusitis, and lymphoid hypertrophy with obstructive sleep apnea). One of the main concerns in AR patients is the development of asthma. AR and asthma are similar chronic inflammatory diseases affecting upper and lower airways, which appears to have bidirectional interactions by both neurological and inflammatory mediators.^{18,19} Overall, pediatric patients with AR have a three to fourfold increased incidence of asthma compared to children without AR.²⁰ Surveys have shown that approximately 60–80% of children with asthma have symptoms of AR.²¹ In monosensitized children with AR subcutaneous specific immunotherapy therapy prevents the development of new sensitizations and may prevent the development of asthma.^{22,23}

In agreement with other studies, males comprised a larger portion of our patient group than females, suggesting that male gender may be at greater risk for

AR in childhood than female.^{24,25} Similarly, prior to the age of 14 years, the prevalence of asthma is nearly twice as great in males than in females.²⁶ The best established risk factor for AR is a family history of allergy, especially AR.²⁷ In our study, 55% of the children with impaired lung function had at least one parent with asthma and/or AR. INCS are extremely effective in reducing the nasal symptoms of sneezing, itching, rhinorrhea, and nasal congestion as well as ocular symptoms.^{28–30}

In adult patients with AR and asthma, INCS treatment was found to improve bronchial responsiveness.^{31–33} However, one of the interesting questions is whether INCS is sufficient to improve lung function impairment or whether more standard asthma treatments for example, inhaled corticosteroids or anti-leukotrienes are warranted in these children. According to our findings, children with AR can be classified into three groups: (1) children with normal lung function, (2) children with decreased

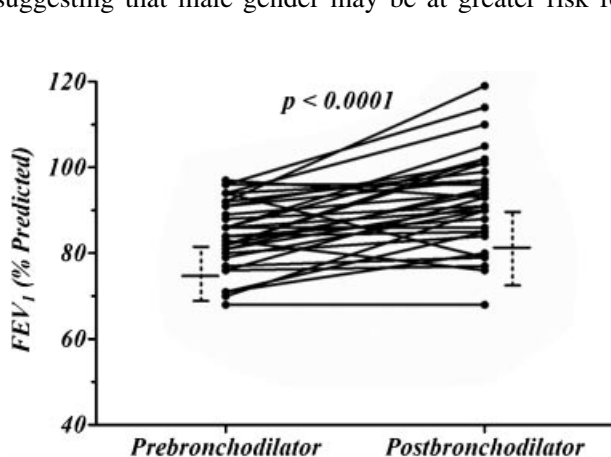


Fig. 3. Reversibility of FEV_1 values in children with AR and impaired lung function. Following administration of terbutaline metered dose inhaler (400 μ g), the average FEV_1 levels increased significantly, from 81.9 ± 8.0 to 87.7 ± 10.4 , $P < 0.0001$.

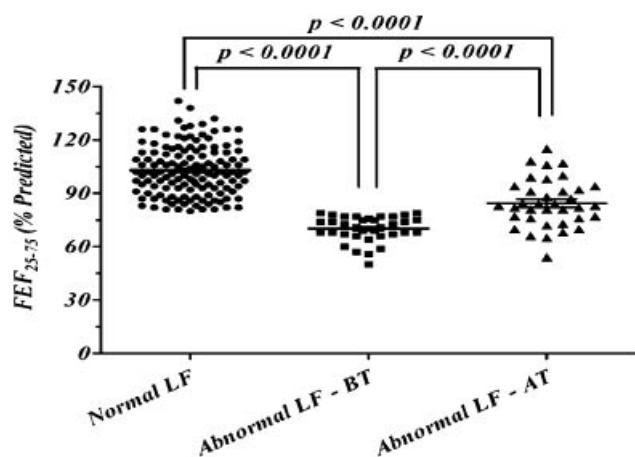


Fig. 4. Comparison of $FEF_{25-75\%}$ values between children with AR and normal pulmonary function and children with AR and impaired lung function at baseline and after treatment with daily INCS.

FEF_{25–75%} values and normal FEV₁ values, (3) children with decreased of both FEF_{25–75%} and FEV₁ values. The children with impaired lung function were additionally characterized by high prevalence of a positive bronchodilation test. The bronchodilation test is used to detect reversible airways obstruction, which is considered to be important for diagnosis of asthma.³⁴ Taken together our findings suggest a continuum in children with AR, from normal lung function toward development of asthma.

The use of INCS increases FEF_{25–75%} levels in children with AR. However, the improvement of FEF_{25–75%} did not reach above 80% of predicted in one third of individuals and in the remaining children, although they reached FEF_{25–75%} above 80% of predicted, they were still lower statistically compared to those presented with normal lung function.

Interestingly, most of the children who did not benefit in terms of nasal symptoms improvement from INCS were those who did not had elevation of FEF_{25–75%} values and were those who needed additionally treatment with montelukast. The question of additional medical treatment in order to further improve lung function in these children is complicated. Children with impaired FEF_{25–75%} fail to meet the clinical or spirometric criteria to be treated as asthma patients as specified by the current global initiative for asthma (GINA) guidelines. Additionally, they don't have any complaints of respiratory difficulties. On the other hand, small airways impairment in these individuals has long been considered to be important in asthma. The presence of inflammation in small airways has been well established in post-mortem tissue examinations.³⁵ Asthmatic patients might have ventilation defects in the presence of a normal FEV₁.³⁶ Ferguson³⁷ observed that in children with asthma but lacking symptoms, FEF_{25–75%} was decreased in a larger proportion of patients than PEFR or FEV₁, suggesting that FEF_{25–75%} is a more sensitive indicator of chronic airflow obstruction.

Published reports also suggests that FEF_{25–75%} is more sensitive as an indicator of symptomatic asthma than FEV₁ in children.^{38,39} Recently, Simon et al.⁴⁰ found in asthmatic subjects with normal FEV₁ levels, that FEF_{25–75%} was correlated with bronchodilator responsiveness. One can assume that AR individuals with abnormal pulmonary function and airway reversibility are at great risk of developing asthma, as was the case in two of our patients. Therefore, it seems that further studies for longer follow-up periods should be conducted in order to better understand this issue. A reasonable suggestion at this time, is to recommend specific allergic immunotherapy in AR, especially in patients with impaired lung function. There are some limitations in this study. It cannot be excluded that some children with AR had underline asthma. Using Bronchial provocation tests such as methacholine test could further characterize our

patient's condition. It is an open study without a control group and finally, a longer follow-up could identify more children with AR that will develop asthma.

CONCLUSIONS

We can conclude that impaired lung function appears in substantial group of children with AR. FEF_{25–75%} values were negatively correlated with nasal symptom duration. Although INCS improved FEF_{25–75%} above 80% of predicted values in two thirds of the children with abnormal lung function that we studied, this improvement did not reach levels of AR children with normal lung function. This suggests that some of children may need additional treatment in order to improve lung function.

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