

Respiratory pathophysiologic responses

Objective indicators of severity of asthma

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Subjects with asthma who are intensively treated in residential care facilities frequently demonstrate marked clinical improvement in their disease, with fewer attacks and improved well being. Despite their improved status, it is known that pulmonary function test results often remain abnormal in patients with asthma. This prospective study on children with asthma receiving residential care was carried out to determine which pulmonary function parameter best reflected clinical improvement through correlation with the duration of complete freedom from wheezing. Evaluated in 42 children were spirometry values including forced vital capacity, forced expiratory volume in 1 second, peak expiratory flow rate, forced expiratory flow (between 25% and 75% of forced vital capacity), and lung volumes as reflected by residual volume/total lung capacity. Bronchial hyperreactivity as reflected by bimonthly provocative concentration causing a 20% fall in FEV₁ in response to methacholine inhalation was evaluated in 18 patients. All pulmonary function test results were correlated with days since last wheezing episode. Results indicate that only peak expiratory flow rate ($r = 0.91$; $p < 0.001$), forced expiratory volume in 1 second ($r = 0.69$; $p < 0.01$), and forced expiratory flow ($r = 0.62$; $p < 0.05$) demonstrated significant correlation with the number of days since last wheezing episode. Of particular interest was the failure of bronchial hyperreactivity to improve despite intensive therapy with bronchodilators and corticosteroids. Persistence of bronchial hyperreactivity despite intensive therapy with corticosteroids suggests that in at least some children with severe asthma, bronchial hyperreactivity may be especially long-lived, may be perpetuated by inhaled β_2 agonists, or may exist independently of airway inflammation. (J ALLERGY CLIN IMMUNOL 1994;94:517-22.)

Patients with severe bronchial asthma admitted to centers for residential care often show marked clinical improvement in their asthma during residence.¹ Improvement is seen in the decrease or disappearance of episodes of wheezing and dyspnea, absence of wheezing during chest auscultation, higher activity level, and lessening of a subjective tolerance of a given degree of airway obstruction. Pulmonary function tests (PFTs) are the accepted objective measure of airway function and might be expected to reflect the clinical improvement of such patients. It has long been known, however, that some PFT abnormalities may persist after an acute asthmatic attack,² may be present in asymptomatic asthma,³ and may

Abbreviations used

BHR:	Bronchial hyperreactivity
CRH:	Children's Rehabilitation Hospital
DLW:	Days since last wheezing
FEF ₂₅₋₇₅ :	Forced expiratory flow between 25% and 75% of vital capacity
FEV ₁ :	Forced expiratory volume in 1 second
PC ₂₀ :	Provocative concentration causing a 20% fall in FEV ₁
PEFR:	Peak expiratory flow rate
PFT:	Pulmonary function test

even persist in adults with a history of childhood asthma.⁴ It is not fully known why PFT abnormalities persist in some patients with asthma who are otherwise free of symptoms. Although some investigators have suggested that persistent PFT abnormalities may presage increased frequency of asthma attacks or more severe disease, this is unproven.⁵

A preliminary review of weekly PFT results in a population of children with asthma in our residential care center revealed erratic correlation

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TABLE I. Pearson correlation matrix

	PC ₂₀	FEV ₁	FEF ₂₅₋₇₅	%R	DLW	Steroid	PF
PC ₂₀	1.00						
FEV ₁	-0.10	1.00					
FEF ₂₅₋₇₅	-0.37	0.86*	1.00				
%R	0.19	-0.23	-0.5†	1.00			
DLW	-0.39	0.69†	0.62	0.04	1.00		
Steroid	0.53	-0.23	-0.22	-0.40	-0.78‡	1.00	
PF	-0.09	0.81‡	0.59*	0.13	0.90	-0.56	1.00

PF, Pulmonary function.

**p* > 0.001.†*p* > 0.05.‡*p* > 0.01.

with clinical improvement of the asthma as described above. This finding led us to do this prospective study of a group of children with asthma during residential care by sequential weekly PFTs. PFT results were correlated with observed clinical improvement. In a subgroup of patients, the observations were extended to include methacholine bronchial provocation tests, carried out at 2-week intervals during residential care.

This study addresses the question of the degree to which specific PFT results and methacholine bronchial challenge results correlate with duration of clinical control of asthma.

METHODS

Subjects and setting

Subjects were 42 children and adolescents, aged 7 to 16 years, admitted to residential care at Children's Rehabilitation Hospital (CRH) because outpatient treatment did not adequately control their symptoms. Outpatient treatment failure was defined as occurrence of life-threatening asthma, frequent acute-care hospitalizations, continuous or frequent corticosteroid use, excessive school absenteeism, or extended inactivity. During the course of the residential program, which is 8 to 12 weeks in length, the subjects began receiving therapeutic doses of theophylline, orally administered corticosteroids in doses usually beginning at 0.5 mg/kg/day, and therapeutic doses of inhaled corticosteroids. Inhaled nebulized β_2 -agonists and cromolyn sodium were administered four times per day. The hospital environment is maintained as "hypoallergenic," and smoking, perfumes, and scented toiletries are not permitted. Children partake in a full range of daily activities in the hospital, attend school, and participate in an aerobics program to increase their physical fitness. Every attempt is made to reduce the oral steroid dose as clinical improvement occurs. A subgroup of 18 subjects underwent sequential methacholine bronchial provocation throughout the 8- to 12-week stay at CRH.

Pulmonary function testing

Complete PFTs, including spirometry and lung volumes, were performed on all subjects at the same time of day every week of hospitalization by pediatric respiratory therapists. Bronchodilator medications were withheld from the previous night on days when complete PFTs were done. Peak expiratory flow rates (PEFRs) were measured four times daily immediately before nebulizer treatments by nursing staff trained to perform these studies. All effort-dependent tests are repeated three times or until they could be done reproducibly. Spirometry was measured in an Ohio 822 spirometer (Ohio Medical Products, Madison, Wis.). Lung volumes were determined with a variable pressure body plethysmograph (Warren E Collin Inc., Braintree, Mass.). Methacholine challenge was performed at 2-week intervals with the method of Chai et al.⁶ In brief, after all medication had been withheld for at least 12 hours, each subject had spirometry performed to ensure adequate initial forced expiratory volume in 1 second (FEV₁). The patients then inhaled 5 inspiratory capacity breaths of normal saline solution from a DeVilbiss No. 646 nebulizer (DeVilbiss Company, Somerset, Pa.) connected to a Rosenthal dosimeter set to open for 0.6 seconds and powered by an air source at 20 psi. The FEV₁ recorded 3 minutes after saline inhalation constituted the subject's baseline FEV₁ value. If this baseline FEV₁ showed a drop of less than 20% from the initial FEV₁, the subjects proceeded to take 5 inhalations of twofold increasing concentrations of methacholine (Provocholine; Hoffman-LaRoche, Nutley, N.J.), beginning with 0.075 mg/ml and increasing to a maximum of 25 mg/ml. FEV₁ was determined 3 minutes after each series of inhalations, and a 20% decrease from baseline was considered a positive challenge result. The PEFR was recorded four times daily on a Wright peak flow meter (Ferraris Medical, Inc., Holland, N.Y.); three challenges were performed, and the best result of these was recorded. Written informed consent for sequential methacholine challenge was obtained from parents or legal guardians of the subjects. This protocol was approved by the

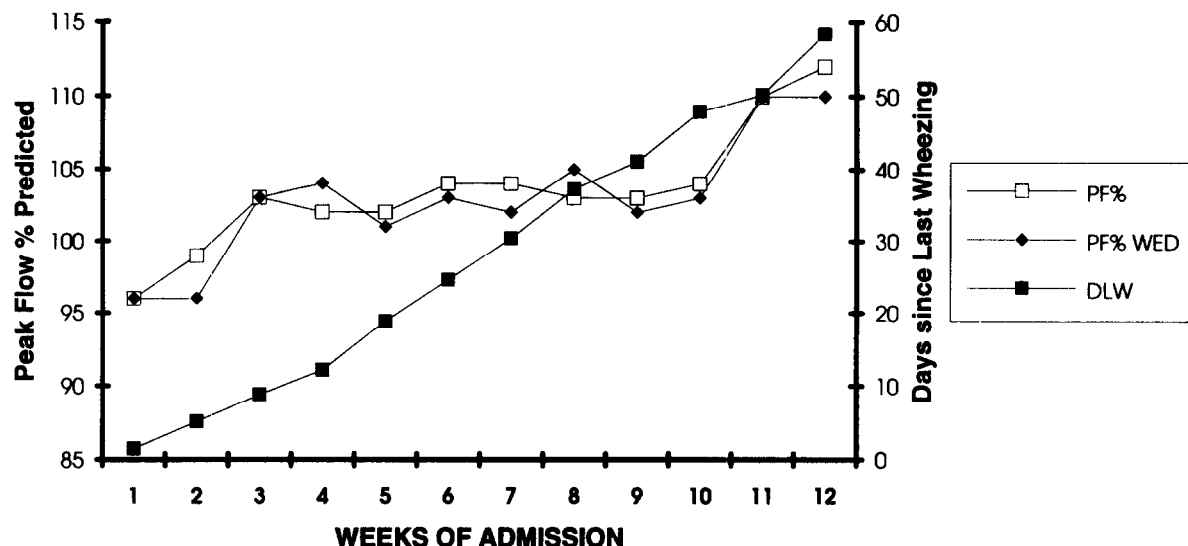


FIG. 1. Comparison of DLW, mean daily PEFR (PF%), and PEFR performed on Wednesday at 8:00 AM (PF% WED) over 12 weeks of hospitalization.

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Index of clinical improvement

As noted above, there is usually considerable subjective and clinical evidence of patients having fewer symptoms of asthma throughout their stay at CRH. We selected the number of days since the last recorded wheezing episode (DLW) as the criterion with which the PFT results were correlated. In the CRH setting subjects with asthma are closely monitored, and a physician is always present. Patients undergo auscultation of the chest by stethoscope at least three times each day by a physician or nurse. The philosophy of the CRH residential asthma program emphasizes early and aggressive treatment of objective asthmatic symptoms to prevent progression. Cough, subjective feelings of tightness, and restriction of physical activity are closely evaluated and treated as deemed appropriate. Any such symptoms that result in extra treatments would thus be recorded as a treated wheezing episode.

Statistical methods

Correlations between improvement in pulmonary function parameters and DLW were assessed by determining the Pearson's correlation coefficient. A p value of less than 0.05 was accepted as a significant correlation.

RESULTS

Correlation data between all variables considered are presented in Table I. It can be seen from these data that the highest degree of correlation observed was between DLW and PEFR. This correlation produced a Pearson r value of 0.91

and a p value of less than 0.001. Lesser but significant degrees of correlation were observed for FEV_1 and FEF_{25-75} , which demonstrated r values of 0.69 and 0.62 and p values of less than 0.01 and less than 0.05, respectively. Other PFT parameters did not correlate significantly with DLW. As expected, the oral steroid dose was negatively correlated with DLW. Because the PEFR data analyzed reflected the average of measurements taken four times each day, whereas other PFT determinations were taken weekly, the possibility that frequency of determination led to a higher degree of correlation was considered. Fig. 1 demonstrates the correlation with DLW observed when PEFR data from all determinations were compared with the single weekly PEFR measurement arbitrarily selected to be that determined on Wednesday at 8:00 AM. It can be seen that the frequency of PEFR determination had little effect on correlation with DLW.

The provocative concentration causing a 20% fall in FEV_1 (PC_{20}) on methacholine challenge, measured sequentially in a subgroup of 18 patients with asthma, could not be shown to correlate with DLW to any significant degree. The mean PC_{20} for these subjects over the time that they were in residential care is shown in Fig. 2. It can be appreciated from this figure that these subjects demonstrated no change in their methacholine PC_{20} , even though all subjects were receiving inhaled corticosteroids and 17 of 18 were also receiving systemic corticosteroids. The average admission dose was 0.46 mg/kg/day of pred-

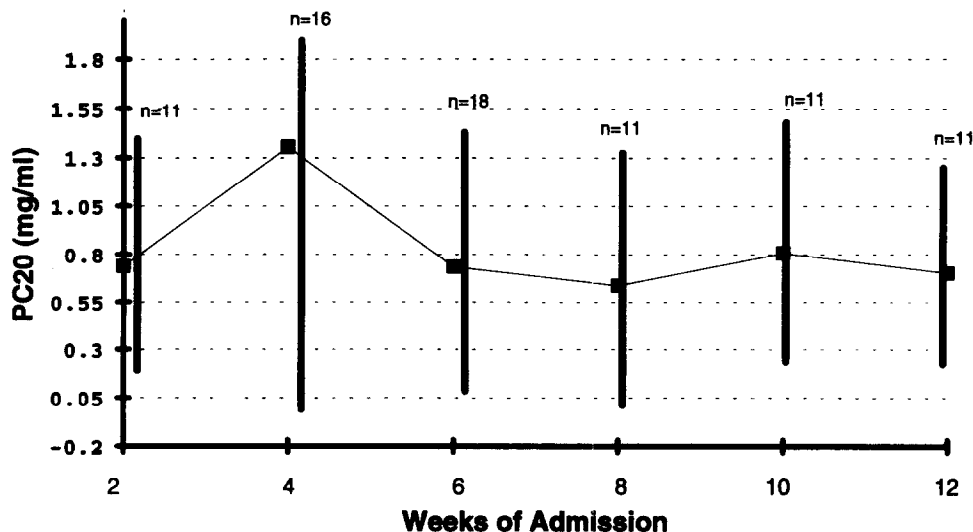


FIG. 2. Mean PC₂₀ (FEV₁) bimonthly values and standard deviations throughout the hospitalization.

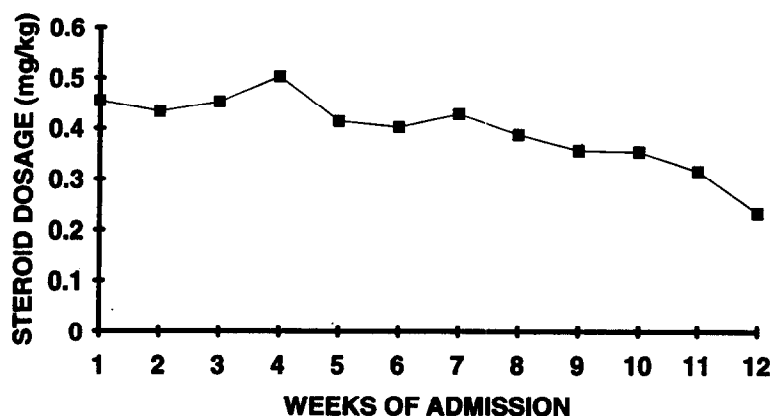


FIG. 3. Mean oral corticosteroid dosage (in milligrams per kilogram per day) throughout the 12-week hospital stay ($n = 42$).

nisone or equivalent corticosteroid, with gradual taper to clinical response as demonstrated in Fig. 3.

DISCUSSION

It has been stated that the main goals of asthma therapy are to control symptoms, to prevent acute attacks, and to maintain lung function as close to normal as possible.⁷ To these goals must be added that of permitting normal, age-appropriate activities. The investigators believed that prolonged duration of symptom control in patients carrying out full activities is the essence of the therapeutic goals. This study was conducted to determine which PFT results best correlate with duration of control of asthma in a setting where there is

frequent clinical assessment and full physical activity. It is apparent that of all PFT parameters evaluated including spirometry, lung volumes, and assessment of bronchial hyperreactivity (BHR), the PEFR shows the highest degree of correlation with DLW. Among other PFT parameters, only FEV₁ and to a lesser extent FEF₂₅₋₇₅ showed statistically significant DLW correlation. Both PEFR and FEV₁ are thought to primarily reflect large airway function, and because acute asthmatic wheezing episodes are precipitated by large airway spasm, this finding is perhaps to be expected. The FEF₂₅₋₇₅ improvement correlated only weakly with DLW, whereas other PFT determinations, including residual volume/total lung capacity and methacholine sensitivity, are not sig-

nificantly correlated. These findings suggest that these parameters, some of which reflect small airway function, may not respond to intense anti-asthmatic therapy to the same degree as PEFR and FEV₁. The clinical significance of these findings is not entirely clear, but the persistence of small airway abnormalities, despite therapy with both inhaled and systemic corticosteroids, suggests that these abnormalities may not be due to inflammation alone. This observation supports the widespread use of inexpensive peak flow meters as a means of monitoring asthma control in outpatients. As shown in Fig. 1, PEFR improvement occurred in a stepwise pattern. The cause of this phenomenon is not clear but may reflect aspects of asthma that are resistant to short-term therapy.

Current views of BHR have suggested that "It correlates with and is likely caused by airway inflammation."⁸ We attempted to demonstrate whether the combination of inhaled and systemic corticosteroid therapy would significantly reduce BHR; this was not the case. Other investigators have observed persistent BHR in patients treated with corticosteroids and those in residential care. Lundgren et al.⁹ used bronchial biopsy to demonstrate suppression of inflammation after prolonged treatment with inhaled corticosteroids but noted that BHR remained. Platts-Mills et al. studied nine subjects with asthma receiving inhaled corticosteroids while living in an allergen-free environment for 2 months. Of these subjects, all improved clinically, but five showed significantly increased provocative dose causing a 30% fall in FEV₁ to histamine inhalation, and four did not. These authors speculated that in some patients with asthma nonspecific BHR, once established, may be extremely difficult to reverse. Kerrebijn¹⁰ reported that among children with asthma in residential care for 1 year in Davos, Switzerland, all subjects showed clinical improvement, but two groups could be identified. In one group the BHR, as defined by histamine bronchial provocation, improved toward normal, whereas in the second group it remained markedly abnormal. The author did not state whether these children received corticosteroids. The study we report is thought to be the first to describe subjects treated with both systemic and inhaled corticosteroids who continued to have significant BHR. These observations do not agree with previous reports that corticosteroid therapy is able to down-modulate BHR.¹¹⁻¹³ Several explanations for the persistent BHR observed in our subjects are possible. First, BHR may be a long-lived residual of airway

inflammation such that a 3-month period of treatment and observation is insufficient to document its resolution despite vigorous antiinflammatory treatment. Alternatively, this persistent BHR may reflect the ongoing use of inhaled β_2 -agonists in these subjects. Recent reports have suggested that apart from their bronchodilator effects, continuously inhaled β_2 -agonists may have an aggravating effect on bronchial asthma and increase BHR.¹⁴⁻¹⁹ Because all of the children with asthma in this study received inhaled β_2 -agonists, the BHR observed may reflect that undesirable effect. Studies are currently in progress to determine whether this effect is present. Finally, it may be that at least this population of children with severe asthma demonstrates BHR that is relatively independent of airway inflammation. It would follow from this observation that bronchodilators have a more important role in the treatment of patients with severe asthma than in those with milder disease and that methacholine bronchial provocation is a useful indicator of their need. As noted above, recent investigation of the pathophysiology of bronchial asthma has focused on the major role of airway inflammation in the BHR of this disease.^{20, 21} Despite these developments, a recent comprehensive review of asthma pathophysiology and treatment concluded that in asthma, "The mechanisms governing the airway hyperresponsiveness remain undiscovered."²² The BHR findings reported in this study support this view.

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