ORIGINAL ARTICLE

Duration of Asthma and Lung Function in Life-Long Nonsmoking Adults

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Abstract

Background: The airways of adult or elderly asthmatics are likely candidates for airway remodeling, resulting in persistent airflow obstruction. This population can provide a good model for cross-sectional evaluation of the effect of asthma duration on airflow.
Methods: We evaluated postbronchodilator airflow and lung volumes at baseline and after a short course of oral prednisone in a group of 42 never-smokers with persistent mild or moderate asthma aged 55 years or older. Patients were grouped as having short duration asthma (SDA, < 14 years) or long duration asthma (LDA, ≥ 14 years) according to the median duration of the disease (14 years) of the sample.
Results: There were no significant differences in patient characteristics or asthma severity indices between the groups. After a short course of prednisone, forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to forced vital capacity (FVC) were significantly higher for the SDA group. Only 3 patients presented persistent airflow limitation (FEV_1/FVC% < 75%). An inverse correlation was demonstrated between duration of asthma and postbronchodilator FEV_1 (% predicted) ($r = –0.43$, $P = .01$) and FEV_1/FVC% ($r = –0.50$, $P = .003$).
Conclusion: Our data show a close relationship between duration of disease and loss of lung function, supporting the concept of asthma as a slow, progressive disease at least among those patients with a mild-to-moderate severity. Permanent airflow obstruction in mild or moderate asthma is unusual, but can occur in a small number suffering from the disease for years.

Key words: Asthma. Airway remodeling. Airflow obstruction. Lung function decline.

Resumen

Introducción: La vía aérea de pacientes asmáticos adultos que han padecido la enfermedad durante años es en principio una candidata muy probable a sufrir un proceso de remodelado que conduce a la obstrucción bronquial fija. Este tipo de población es un buen modelo para estudiar la relación entre la duración del asma y la obstrucción persistente al flujo aéreo.
Métodos: Estudiamos los cambios de los flujos y volúmenes pulmonares tras broncodilatador en situación basal y tras la administración de un ciclo corto de prednisona (30 mg durante 8-10 días), en un grupo de 42 adultos nunca fumadores con asma persistente leve o moderada de edad más de 55 años. De acuerdo a la mediana de la duración de la enfermedad (14 años) se dividió la muestra de los pacientes en dos grupos: asma de corta duración (SDA, < 14 años) y asma de larga duración (LDA, ≥ 14 años.).
Resultados: Tras el ciclo corto de prednisona oral los valores del volumen espiratorio forzado en el primer segundo (FEV_1) y la relación de FEV_1 y capacidad vital forzada (FVC) se incrementaron significativamente en el grupo SDA. Solamente 3 pacientes presentaban obstrucción persistente del flujo aéreo (FEV_1/FVC% < 75%). So observó una correlación inversamente significativa entre el tiempo de evolución del asma y los valores tras broncodilatador del FEV_1% ($r = –0.43$, $P = 0.01$) y del FEV_1/FVC% ($r = –0.50$, $P = 0.003$).
Conclusión: Nuestros resultados apoyan claramente una relación entre la duración de la enfermedad y la pérdida de función pulmonar y una visión de la enfermedad como un proceso que conlleva un deterioro de la función pulmonar de lenta progresión. La presencia de obstrucción fija al flujo aéreo es poco habitual pero puede ocurrir en una pequeña proporción de pacientes con asma leve o moderada con largo tiempo de evolución.

Palabras clave: Asma. Remodelado de la vía aérea. Obstrucción bronquial. Deterioro de la función pulmonar.

Introduction

Airway inflammation is generally accepted as a central mechanism in the pathogenesis of asthma. Inflammatory changes have been described even in distal airways and the pulmonary parenchyma [1-3]. An ongoing inflammatory process may lead over time to distortion of bronchial architecture [4]. Airway structural studies in chronic asthma have emphasized morphologic alterations associated with this inflammatory process. The structural changes leading to fibrosis include denuding epithelium, deposition of collagen in subepithelial layers, smooth muscle thickening, bronchovascular permeability, edema, goblet cell hyperplasia, and submucosal gland hypertrophy [5]. These changes make up the airway remodeling process and potentially lead to irreversible airway obstruction [6,7]. Although some of these changes can occur early in the disease process [8,9], the airway of adult or elderly individuals who have had chronic asthma for years are the likely candidates for airway remodeling.

We hypothesized that this population of senior asthmatic patients would provide a good model for a cross-sectional study of the effect of duration of the course of disease on airflow. Characterization of asthma in older patients is made more difficult by the possible presence of other obstructive diseases [2,10]. Cigarette smoking is, clearly, a major diagnostic confounder as both smoking and asthma are independently associated with a more rapid decline in forced expiratory volume in 1 second (FEV_1) and they have additive effects [11,12]. Therefore, the confounding effects of tobacco exposure were eliminated in search of a model that would allow us to study the natural history of asthma.

Inhaled corticosteroids, which suppress airway inflammation and have changed the natural course of the disease, are highly efficient in reducing symptoms and exacerbations. Nonetheless, there are unmet needs in asthma therapy. It is not clear whether or not inhaled corticosteroids are able to stop or reverse the airway remodeling process [13]. Although there are studies, generally in small numbers of patients, that show improvement in certain structural changes such as subepithelial fibrosis [14], many studies with large numbers of patients have found a progressive loss of lung function in spite of this therapy [12,15,16].

We present the result of postbronchodilator airflow and lung volume measurements and their changes after a short course of oral corticosteroids in a well-defined group of never-smokers with long-standing asthma. All were using inhaled corticosteroids, although some had begun such therapy years after diagnosis. We hypothesized that some degree of irreversible airflow limitation, defined by measurements of physiologic outcomes after bronchodilator and intense anti-inflammatory therapy, would be present in these patients and correlated with the duration of the disease. To avoid the bias of severity or poor responsiveness to steroids, we excluded patients with severe asthma defined by daily need of oral steroids to control symptoms.

Methods

Subjects

Every adult with persistent asthma older than 55 years evaluated in a tertiary care pulmonary function laboratory between October 2003 and June 2004 were recruited for the study. Only never-smokers, defined as those patients who reported no pack-years of cigarette use were included. Patients with severe asthma defined as those requiring oral corticosteroids on a daily basis were excluded from the study. The diagnosis of asthma was performed according to international guidelines [17]. Only 33% of the patients were considered allergic defined by the presence of positive skin tests and specific immunoglobulin E (CAP System, Phadia, Uppsala, Sweden). The majority of the patients were sensitized to mite alone or in combination with dog or cat epithelia. Only 3% of patients were sensitized to *Alternaria alternata*. As part of the initial general evaluation, we assessed changes in lung function after a short course of oral steroids in order to know each patient's "personal best" for determining the objectives of their individual maintenance therapy. A total of 51 patients were initially selected. Five refused to take the course of oral steroids. Another 3 patients had advanced osteoporosis and oral steroids were contraindicated. One patient was not able to perform reproducible spirometric maneuvers. Thus, 42 patients were finally included. Medical records from the patients' own clinics where the diagnosis had been made and regular follow-up had been performed were exhaustively reviewed to obtain information on the onset, year of diagnosis and treatments administered. The median duration of asthma was 14 years, and this figure was used to split the cohort into 2 groups, comprising those with long duration of asthma (LDA) who had a clinical course of more than 14 years and those with short duration of asthma (SDA) whose clinical course was 14 years or less.

Table 1 presents patient characteristics, including medications used at the beginning of the study. Most patients required low to medium doses of inhaled corticosteroids alone or in combination with long-acting β_2-agonists (82% of the patients) for control of symptoms. The documented total years of use of inhaled corticosteroids was recorded and quoted as a percentage of the asthma duration.

Pulmonary Function Testing

All measurements were performed when patients had been clinically stable for at least 4 weeks on their usual therapy. Every patient underwent postbronchodilator (4 puffs of salbutamol, Ventolin, administered through a spacer) spirometry and body plethysmography (Master Body, Jaeger, Berlin, Germany) according to standard methods. Reference values used were those proposed by the European Respiratory Society [18], except for FEV_1, FVC, and FEV_1/FVC for which the values proposed by Castellsague et al [19] were used. Persistent airflow limitation was defined by a postreatment FEV_1 or FEV_1/FVC less than 75% of predicted with a total lung capacity (TLC) more than 75% predicted.

After 8 to 10 days of therapy with 30 mg of prednisone administered in the morning, postbronchodilator measurements were performed. Ten tablets of prednisone were given to each patient, and they were asked to return the tabs remaining as a method of assessing compliance, which was expressed as a percentage.

Table 1. Patient Characteristics and Medications*

	Total	LDA	SDA
No.	42	20	22
Age, y†	60 (55-78)	64 (56-78)	58 (55-73)
Sex, % female	72	75	65
Duration, y†	14 (3-40)	22 814-40)	9 (3-13)
Allergic asthma, %	33	36	25
Mild persistent asthma, %	23	30	18
Moderate asthma, %	77	70	82
Therapy (%)			
ICS	18	24	15
ICS + LABA	82	76	85

* LDA indicates long duration of asthma; SDA, short duration of asthma; ICS: inhaled corticosteroids, LABA: long-acting β-agonists.
† Data are expressed as median (range).

Table 2. Dynamic Lung Volumes and Resistance at Baseline and After Treatment With Oral Steroids and Bronchodilators

	Baseline		Treatment	
	LDA	SDA	LDA	SDA
FEV_1 L	89 ± 4.1	93 ± 5.8	102 ± 0.2	116 ± 4.6*
FVC L	108 ± 4.6	111 ± 5.3	122 ± 4.7	127 ± 4
FEV_1/FVC	86 ± 6.8	93 ± 4.5	91 ± 3.1	103 ± 4.6*
sRaw, kPa·s	2.34 ± 0.38	1.57 ± 0.18	1.01 ± 0.13	0.71 ± 0.02*

* Results are expressed as mean (±SEM) percentages of predicted values. FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; sRaw, specific airway resistance.
† $P < .01$ compared to baseline.

Statistical Analysis

In order to avoid the effects of age and anthropomorphic characteristics, the physiologic measurements were recorded as a percentage of predicted value. Regression analyses were performed to explore the relationship between pulmonary physiology and duration of asthma. Measurements obtained in both groups (LDA and SDA) were compared with a *t* test and a value of $P < .05$ was considered significant. All analyses were performed with the statistical package SPSS version 9.0 (Chicago, Illinois, USA).

Results

Patient Characteristics

There were no significant differences between the groups except for the defining characteristic, duration of the disease (Table 1). All patients had persistent asthma classified as moderate in most cases.

The median age at the onset of the disease was 42 years (range, 15-70 years). The median duration of asthma was 22 years for LDA patients and 9 years for SDA subjects. Most had received inhaled corticosteroids regularly during the course of their disease (median time on corticosteroids, 62% of the duration of disease; interquartile range [IQR], 35%-89% of the duration).

Dynamic Lung Volumes and Airflow Resistance

The main parameters are presented in Table 2. No difference between groups was observed at baseline, when 18% of patients had FEV_1 or FEV_1/FVC values less than 75% of predicted. After the short course of prednisone, postbronchodilator values of FEV_1 and FEV_1/FVC were significantly higher for the SDA group; the opposite pattern was observed for specific airway resistance. SDA group patients tended to exhibit greater increases in FEV_1 values (median increase, 17%; IQR, 5%-49%) than did LDA group patients (median increase,11%; IQR, 3%-11%), although the difference did not reach statistical significance. Three patients, all from the LDA group, showed irreversible obstruction (FEV_1/FVC%, 73%, 74%, and 74%, respectively). The median compliance with the prednisone course was 90% (70%-100%).

Static Lung Volumes

Results for static lung volumes are presented in Figure 1. All measurements were in the normal range according to the reference values used. As expected there was a small decrease in these volumes after therapy but no differences between the groups.

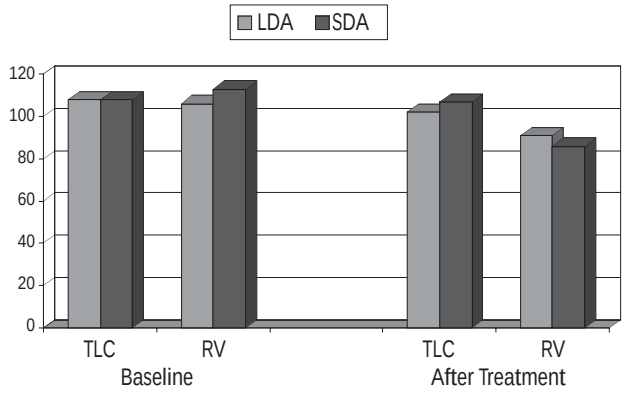

Figure 1. Static lung volumes at baseline and after treatment with oral steroids (prednisone 30 mg over 8 to 10 days) and a bronchodilator

Interaction Between Physiologic Outcomes and Duration of the Disease

To explore the relationship between airflow limitation and duration of asthma we performed a correlation analysis with data from the whole study cohort. An inverse correlation was observed between asthma duration and both postbronchodilator FEV_1% ($r = –0.43$, $P = .01$) and FEV_1/FVC% ($r = 0.50$, $P = .003$) values recorded only after the patients were given the short course of oral steroids (Figure 2). When this analysis was restricted to the women of the total sample the correlations between duration of disease and airflow after the short course of prednisone were somewhat stronger (FEV1/FVC %, $r = –0.64$, $P = 0.002$) (Figure 3). The correlation disappeared when only the men were included, but that sample size was very small (n = 12). There were no correlations between asthma duration for any of the static lung volumes at any moment.

Discussion

In the present study classical measures of airflow obstruction correlated with years of duration of the disease in a well defined group of patients with persistent mild or moderate asthma.

Factors and mechanisms associated with the accelerated decline in lung function seen in asthmatics are not well understood [13]. The current working hypothesis is that chronic inflammation promotes restructuring of the airways, which in turn results in a rapid decline in lung function. Airway inflammation in asthma is characterized by infiltration of the airway by a variety of cell types (eg, mast cells, lymphocytes, and eosinophils) that release potent mediators, including growth factors, leading to structural changes in the bronchial wall (tissue remodeling) [20]. The process begins early in the development of the disease, so it can be hypothesized that remodeling may occur in parallel or could even be a prerequisite for the development of airway inflammation [5].

Permanent airflow obstruction is generally associated with severe asthma, and as was expected, many of our patients suffering from mild or moderate disease had near-normal lung function values. At baseline 18% patients had FEV_1 or FEV_1/FVC % less than 75% of predicted. It is remarkable that after the course of oral corticosteroids, 3 patients in the LDA group had signs of permanent obstruction. All of them had suffered from asthma for more than 20 years.

All our patients had been treated regularly with inhaled corticosteroids, but this therapy seemed unable to prevent the development of permanent airway obstruction. Other reasons can be argued as the cause of this observation, since we must recognize that the patients had not been followed prospectively and we had no measurements of pulmonary function from disease onset. In any case lower values in dynamic lung volumes are clearly related to more distorted functional or mechanical properties of the airways and lung parenchyma, which appear over a period of years of active disease. Our decision not to include severe asthma patients was a deliberate strategy in order to avoid the bias that the effect of severity would produce on airflow [16].

Normal values of lung volumes measured by body plethysmography were somewhat unexpected as residual volume has been presented as a surrogate marker of distal airway inflammation [3]. On the other hand, our data are consistent with previous reports in which normal values are generally present even in patients with refractory asthma providing they have normal or near-normal forced spirometry [16].

Since most of our patients were on long-acting β_2-agonists we did not perform pre- and postbronchodilator measurements at baseline. As a result we do not know whether the changes in lung function tests are more due to the action of the bronchodilator, prednisone, or the combination of both, although the general clinical assumption leans toward the last possibility. However, it is noteworthy that the relationship between FEV_1 or FEV_1/FVC with asthma duration was only detected after corticosteroid therapy, suggesting that these parameters were strongly related to structural abnormalities which were unresponsive to anti-inflammatory treatment. Some authors [6, 21], but not all [22, 23], have observed an inverse relationship between the thickness of the subepithelial reticular layer and lung function parameters. Furthermore, bronchial alterations seen in high resolution computed tomography of the lung, such as wall thickening, have been inversely correlated with FEV_1 [16]. Again, not all studies have documented such a relationship [24]. The discrepancies between studies observing the correlation between lung function and pathology findings, such as the thickness of the subepithelial reticular layer, probably mean that the restructuring of the airways as measured in large airway biopsies is insufficient for representing small airway remodeling. Hogg et al [25] sampled the small airways of patients with chronic obstructive pulmonary disease,

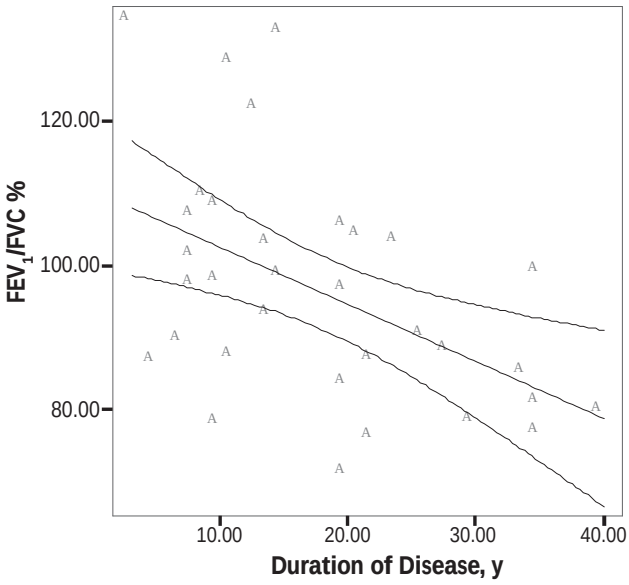

Figure 2. Ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/ FVC) after treatment at the end of the study plotted against asthma duration. Linear regression with 95% mean prediction interval.

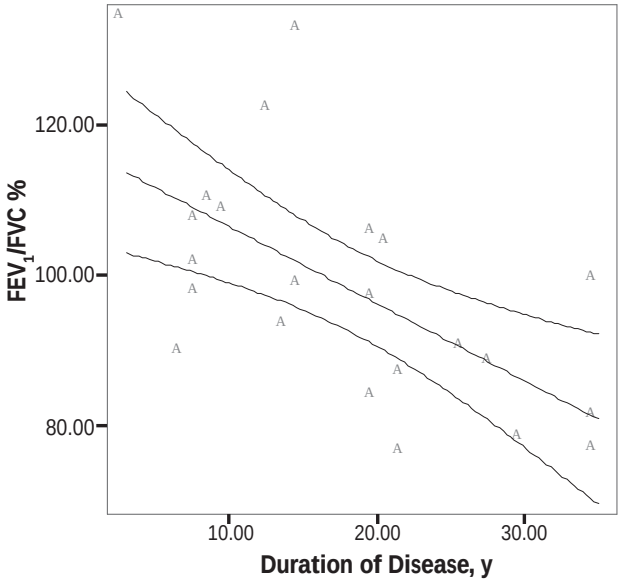

Figure 3. Ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) after treatment at the end of the study and asthma duration in women. Linear regression with 95% mean prediction interval.

showing an association between airway structure and lung function.

More than 70% of the patients in our study were women. A substantially greater loss in lung function over time has been reported in adult female asthmatics, associated with the inability of inhaled corticosteroids to reduce the decline of lung function [26]. Our data are somewhat in agreement with these observations, although the scarce number of men included make it impossible to obtain clear data supporting a different rate of decline in lung function related to gender.

In conclusion our data showed a close relationship between the duration of disease and loss of lung function, supporting the concept of asthma as a slow, progressive disease at least among those patients with a mild-to-moderate degree of airflow limitation. Permanent airflow obstruction in mild or moderate asthma is unusual, but can occur in a small number who suffer from the disease for years. Most patients have a slight loss of lung function, probably associated with the remodeling process, which reflects structural changes not responding to anti-inflammatory therapy.

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