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Severe exacerbations predict excess lung function decline in asthma

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Abstract

Severe asthma exacerbations are periods of intense airway inflammation that have been hypothesized to contribute to structural changes in the airways. If so, accelerated lung function decline over time should be more prevalent in adult patients with asthma who have frequent exacerbations than those without, but this has not been demonstrated so far.

We performed a cohort study investigating the effect of severe exacerbations on the progression of airway obstruction in 93 non-smoking asthmatics with moderate to severe disease prior to starting inhaled corticosteroids. Subjects were followed for at least 5 years (median follow-up was 11 yrs).

Fifty-six subjects (60.2%) experienced at least one severe exacerbation (median rate 0.10/yr). Oral corticosteroid use and more severe airway obstruction at baseline were associated with a higher exacerbation rate. Independent of these variables, asthma patients with frequent exacerbations had a significantly larger annual decline in FEV_1 (median difference=16.9 mls/yr (95% CI: 1.5-32.2). Exacerbation rate significantly predicted an excess decline in FEV_1, so that one severe exacerbation per year was associated with a 30.2 ml greater annual decline in FEV_1.

These data support the hypothesis that exacerbations, indicating intermittent periods of worsening airway inflammation, are associated with excess lung function decline in asthma.

Key words: exacerbations, airways remodeling, prognosis, treatment of asthma

Introduction

Patients with asthma are at risk of developing persistent airflow limitation secondary to structural changes in the airways. Significant obstruction occurs only in a subset, related to age of onset, disease duration, disease severity, environmental exposures, under-treatment and genetic predisposition [1-4]. It has been proposed that worsening of airway inflammation associated with asthma exacerbations represents periods of enhanced structural airway changes, usually termed airways remodeling. The relationship between exacerbations, which are associated with increased airway inflammation, and accelerated lung function loss in adult asthmatics has not been established. Intuitively there might be a causal relationship because of the enhanced activation of many inflammation and repair pathways during exacerbations [3], including elevated expression of proteinases such as matrix metalloproteinases [5,6]. Patients requiring hospitalization for acute asthma and those requiring courses of oral corticosteroids probably have the most severe (and prolonged) worsening of airway inflammation. Thus increased frequency of hospitalizations and severe exacerbations might be associated with an enhanced rate of lung function decline and a greater prevalence of non-reversible airflow limitation. Alternatively, it may be that it is the severity of the underlying chronic inflammation and/or other host factors that are the key determinants of lung function decline, unrelated to hospitalization and severe exacerbation frequency. There are, however, no data on the relationship between exacerbation rate and lung function decline in adults with asthma [3,7].

We have studied the long term effect of exacerbations on annual lung function decline in a historical cohort of moderate to severe non-smoking asthmatics. Only lung function

data before the introduction of inhaled corticosteroids (ICS) were included, so that the effect of the airway inflammation was unmodified by ICS.

Methods

Patients

The characteristics of this cohort have been described previously [8]. In summary a population of 281 adults with predominantly moderate (FEV_1 < 80% predicted) or severe (FEV_1 < 60% predicted) persistent asthma, based on the GINA guidelines, was initially evaluated using a standardized protocol between 1962 and 1975 and closely followed thereafter with spirometry (performed on usual medication, including beta agonists) at every visit or admission. Patients attended the clinic on a regular basis during follow-up (generally once, twice, or four times a year) and if their asthma was deteriorating unscheduled visits were made. Bronchial responsiveness, serum IgE and detailed pulmonary function tests were re-studied in 1990. At enrolment all patients had bronchial hyperresponsiveness to histamine (PC_{20} ≤ 32 mg/ml, using the Tiffeneau method as modified by de Vries and colleagues) [8]. We excluded all subjects with a > 5 pack year smoking history. Subjects without continuous records for at least 5 yrs from the age of 25, at which time lung function has maximized [9] were also excluded. Overall, 93 subjects were included in the current study pertaining to the period before ICS were initiated. Treatment was standardized and directed by the same clinician throughout this period and included allergen avoidance, injected or oral multergan (thiazinamium methyl sulphate, which has anti-cholinergic and anti-histaminic properties), sympathomimetic agents by inhalation, and intermittent oral corticosteroid courses and/or continuous low dose (<15 mg/d) oral corticosteroids. The same water-sealed spirometer (Lode Spirograph D53, Lode instruments, Groningen) was used at initial study and throughout follow-up, and was calibrated daily. Two valid spirometric measures of FEV_1 and slow vital capacity were recorded at each visit. The values for the two FEV_1 measurements had to be within 3% to be considered valid and the highest

value was used in this analysis. All original spirometric curves were checked. The study was approved by the medical ethics committee of the University Medical Center Groningen and written informed consent was obtained from all participants.

Severe exacerbations

Severe exacerbations were defined as hospitalizations for asthma worsening or as a significant and reversible reduction in FEV_1. These significant reductions in FEV_1 were initially identified on standardized graphical displays of the entire data set for each patient and were detected as a clear relatively abrupt decline in FEV_1, using a horizontally expressed scale, similar to the concept described by Reddel and coworkers for peak expiratory flow records in asthma [10]. If these FEV_1 reductions were $\geq$ 20% and 500 ml declines in FEV_1 from the mean value over the 2.5 years on each flank of the reduction (excluding exacerbation and admission FEV_1 measurements), it was defined as an exacerbation. Review of dates of visits showed that exacerbations based on FEV_1 reductions were unscheduled office visits. A maximum of one exacerbation per 3 month period was counted.

Statistical Analyses

Calculations were conducted in SPSS version 12 (SPSS inc.) and S-plus 6 (Insightful Corporation, Seattle, WA, USA). The 93 patients were divided into two groups based on the median exacerbation rate (=0.10 per year). Subjects with an exacerbation rate above median were defined as having 'frequent exacerbations', whereas subjects with an exacerbation rate below median were defined as having 'infrequent exacerbations'. Baseline variables between these groups were compared using Chi^2 test for categorical variables, and T-tests or Mann-Whitney U tests as appropriate for continuous variables. To analyze the effect of hospitalizations and severe exacerbations on the annual decline

of FEV_1 we used a linear mixed effects (LME) model [4]. Lung function data obtained *during* hospitalizations/exacerbations were not used in the analyses. In the linear mixed effect model an indicator variable for group was included to estimate the difference in FEV_1 decline between groups. Height, gender, the first available FEV_1 after age 25 years (centered at 2.7 L), and their interaction with time, and oral corticosteroid use as a time-varying variable were included in the model [11].

Results

The characteristics of the study population are presented in Table 1. The median duration of follow-up was 11 years in the ICS-untreated period. During this time 186 severe exacerbations based on hospitalization or change in FEV_1 (see *Methods)* were identified: 33 hospitalizations and 153 exacerbations based on change in FEV_1. Fifty-six subjects (60.2% of the cohort) experienced at least one severe exacerbation, with a median rate of 0.10 per year. An illustrative graph of FEV_1 measures over 35 years in one patient is shown in Figure 1.

The mean (standard deviation) values of the recorded FEV_1 values were 62.0 (22) % predicted (2.35 (1.04) L) during hospitalizations, 39.7 (14.4) % predicted (1.37 (0.58) L) during exacerbations, and 71.4 (19.5) % predicted (2.47 (0.88) L) at all other measurement points. The characteristics of the subjects subdivided by median exacerbation rate are shown in Table 2.

Subjects with frequent exacerbations had more severe airway obstruction at baseline, and were house dust mite negative more often compared to subjects with infrequent exacerbations. Severity of airways hyperresponsiveness, bronchodilator reversibility, blood eosinophil count and age of symptomatic onset of asthma were not significantly different between the groups. Although subjects with frequent exacerbations were more often females and non-atopic compared to subjects with infrequent exacerbations, these differences were not statistically significant. The percentage of subjects with adult onset symptoms was also not different between the two groups (see Table 2).

We analyzed a total of 1,939 FEV_1 measurements from the 93 patients during the ICS-untreated period, excluding lung function measurements during exacerbations or admissions. Decline in FEV_1 was 14.6 mls/yr (95% confidence interval (CI): 1.9 - 27.3)

in those with infrequent exacerbations and 31.5 mls/yr (95% CI: 18.2 - 44.8) in asthmatics with frequent exacerbations, the difference between the groups being 16.9 mls/yr (95% CI: 1.5 - 32.2; p= 0.03) (see Figure 2). After 11 years, FEV_1 % predicted was 64.3 (18.9) % (2.08 (0.720 L) in the group with frequent exacerbations compared to 77.2 (± 19.1) % (2.69 (0.93) L) in those with infrequent exacerbations (p=0.002). A higher exacerbation rate (expressed as a continuous variable) was associated with an excess decline in FEV_1, so that one severe exacerbation per year was associated with a 30.2 ml greater annual decline in FEV_1 (95% CI: 3.7 - 56.7). Additional adjustment for body mass index did not alter the relationship between exacerbations and FEV_1 decline, nor did exclusion of the 2 subjects who had irreversible airway obstruction at baseline. Inclusion of house dust mite positivity in the LME model slightly decreased the difference in FEV_1 decline between subjects with frequent and infrequent exacerbations (from 16.9 to 13.8 ml/yr).

Given that even a low level of smoking could conceivably influence exacerbation rates, we additionally repeated our analyses restricted to subjects with 0 packyears. This did not change the estimated FEV_1 decline in both the infrequent and frequent exacerbator groups (low: 6.5 ml/yr, high: 31.5 ml/yr). These results suggest there is no confounding or modification of the original associations by smoking history.

Discussion

This study is the first to show that asthmatics with frequent exacerbations experience excess decline in FEV_1 and more severe airway obstruction after 11 years follow-up. Our findings show that exacerbations represent periods of accelerated structural changes in the airways, otherwise known as airways remodeling. The results provide additional rationale for the notion that prevention of exacerbations should be a primary endpoint in trials of asthma therapy.

Since we have only studied the effects of severe exacerbations on lung function decline, and did not include mild exacerbations, the results of this study might actually be an underestimation of the true overall effects. Moreover, the overall effects of exacerbations might have been underestimated because some patients were on continuous low dose oral corticosteroids. Additionally, the fact that all patients were studied during the relative plateau phase of their FEV_1 between the age of 25 and 40 yr, thus missing the lung function decline phase that is usually seen at elderly age, might also have led to underestimation of the overall effect of exacerbations on lung function decline. Since we excluded FEV_1 measures during exacerbations in our analysis of rate of decline in FEV_1, our findings cannot simply be a reflection of the increased airflow variability of poor asthma control, or of greater intrinsic severity in those with frequent exacerbations. The decline in FEV_1 in infrequent exacerbators was not significantly different from the general Dutch population after age 30 (i.e. 18.7 ml/yr) [12]. Notwithstanding this, the earlier age of initiation of analysis in this asthma cohort (age ≥25.0 yr) and relatively short period of follow-up compared to the observations in the general Dutch population may have underestimated lung function decline, accelerated decline in FEV_1 being primarily detected in midlife and older asthmatic subjects [2]. Our study has also shown that females tend to be frequent exacerbators more often; this is

supported by previous findings in studies of asthmatics in which females required hospitalization more frequently [13].

Testing the hypothesis of this study required evaluation during long-term treatment without inhaled corticosteroids, hence the need to perform a retrospective cohort study. A prospective cohort study in patients not on ICS is unlikely to occur for ethical reasons. Although the results of this study do not necessarily reflect outcomes under current best practice guidelines, in reality many patients still do not have access to, or use ICS, on a regular basis, and are therefore at risk of accelerated decline in lung function. Ideally we would have liked to exclude all subjects on continuous oral corticosteroids, but this was not feasible because of sample size constraints. Likewise, adjustments for additional possible confounders effecting decline such as effects of occupational exposures and co-morbidities could not be made.

Unlike COPD, asthma is not a disease generally acknowledged as being associated with either significant irreversible airway obstruction or an accelerated decline in FEV_1. However, treatment-resistant impairment in airflow rates at diagnosis of asthma is frequently apparent, and usually inferred as secondary to structural change in the presymptomatic phase [3]. Multiple factors have been associated with excess decline in lung function in adult patients with asthma, including more severe airways hyperresponsiveness and baseline airway obstruction [1], older age [2,14], adult onset of asthma [15], and within adults, onset at an older age [16]. Prior studies of adult asthmatic populations provided insufficient data to distinguish whether it is chronic severity, exacerbation frequency or associated factors such as smoking that dictates progression of lung function decline [17]. Although an accelerated longitudinal decline in lung function may reflect ongoing structural changes, a labile component secondary to

airway plugging, airway wall edema and inflammatory cell infiltrates in those with relative corticosteroid resistance can not easily be excluded [18].

Donaldson and coworkers [19] reported an 8ml/yr greater decline in FEV_1 over a four year period in patients with moderate or severe COPD who had frequent exacerbations compared with those who had less frequent exacerbations. The differences in rates of decline are less than the effect of exacerbations found in our study, with an overall decline of 36 ml/yr paralleling the effect we have detected in individuals with frequent exacerbations (being 31.5 mls/yr). In our study the association was not due to the modest smoking history reported by some subjects.

Our analyses, based on a period when only symptomatic treatment with or without maintenance oral steroids was utilized, may have yielded a different result if periods of regular ICS use had been included. During the time period of the study it was not possible to attribute exacerbations to specific triggers such as infections or allergens, although triggers may vary in their effect on airway function. During regular ICS treatment, a greater proportion of exacerbations may represent infection-induced neutrophilic inflammation, unresponsive to inhaled corticosteroids [20], and may influence airway structure in a different manner to exacerbations during a period of long term poor asthma control without regular ICS, with a greater frequency of eosinophilic inflammatory events. However, conversely, neutrophilic inflammation has been proposed to be in itself more deleterious to airway structure [21]. Although regular oral corticosteroids use during follow up was more common in the group with frequent exacerbations (results not shown), a significantly greater decline was still seen after adjusting for this use. Regular oral corticosteroid use is expected to suppress eosinophilic airway influx but conceivably could have increased neutrophil influx and

thus airway damage; alternately regular oral corticosteroid use could have lead to a delay in the recognition of exacerbations and thus worsened airway structural change.

In conclusion, our data support the hypothesis that intermittent periods of worsening airway inflammation during exacerbations, when there is elevated expression of many molecular pathways that may enhance airway remodeling, lead to excess decline in lung function in asthma.

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Figure 1.

FEV_1 records over 35 years in a subject with 4 exacerbations indicated (asterisks), as defined in *methods.* Low dose continuous oral corticosteroids (3 to 13 mg prednisolone each day) were in use for the first 20 years of follow-up, prior to the introduction of inhaled corticosteroids (indicated as ICS)

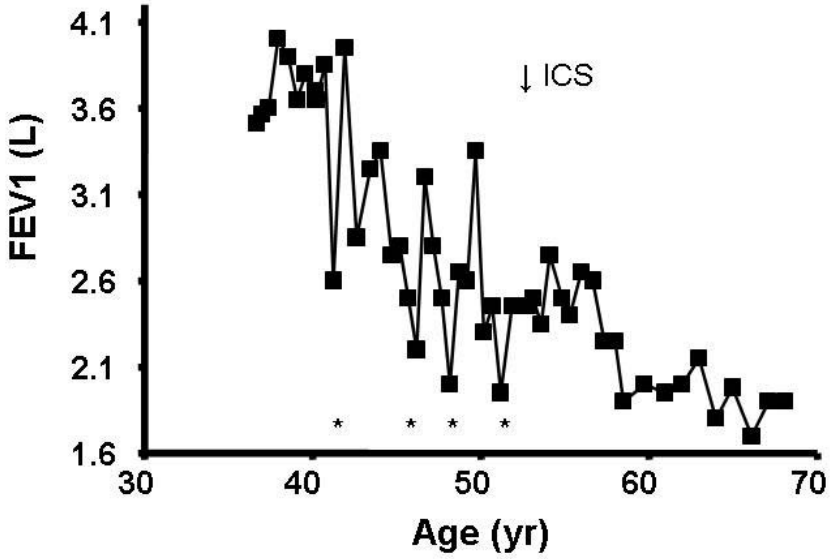

Figure 2.

Estimated annual FEV_1 decline in the group with infrequent exacerbations (closed square) and the group with frequent exacerbations (open square). The analysis is adjusted for gender, height, the first available FEV_1 after age 25 and the use of oral corticosteroids. * The difference between the groups is significant ($P < 0.05$).

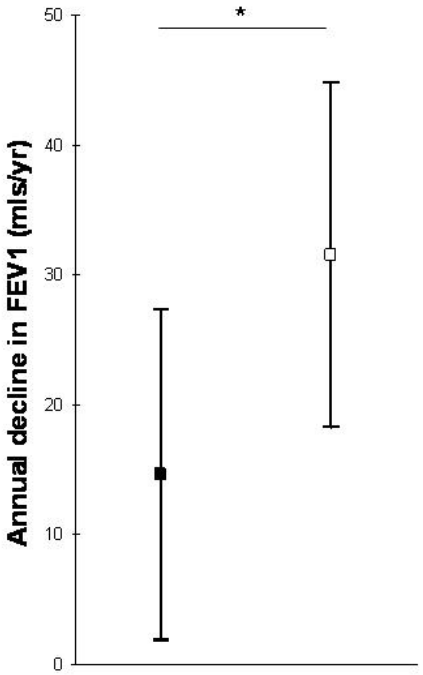
*
50
40
30
20
10
0
Annual decline in FEV1 (mls/yr)

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Table 1: Baseline characteristics of the 93 subjects with asthma	
Female, n (%)	53 (57.0)
Age start analyses (yrs), median (IQR*)	27 (25-36)
Height (cm), mean (sd)	171 (9)
FEV_1 (L), mean (sd)	2.69 (0.91)
FEV_1 (% predicted), mean (sd)	72 (19)
Reversibility (% predicted), mean (sd)	24 (12)
VC (L), mean (sd)	4.32 (1.11)
FEV_1/VC (%), mean (sd)	62 (14)
PC_{20} ≤ 8mg/ml, n (%)[#]	66 (71.0)
Blood eosinophils ≥ 220 x 10^9/L,n (%)	69 (75.0)
HDM positive,n (%)	74 (79.6)
Atopic, n (%)	84 (90.3)
Age symptom onset (yrs), median (IQR)	4 (2-17)
Untreated period ** (yrs), median (IQR)	17 (11-24)
Duration analyses (yrs), median (IQR)	11 (8-16)
OCS duration (yrs), median (IQR)	0.0 (0.0-0.2)

(*IQR = interquartile range, [#] PC_{20} ≤ 8 mg/ml histamine is a measure of severity of bronchial hyperresponsiveness since all subjects had a PC_{20} ≤ 32 mg/ml histamine and were thus diagnosed as being hyperresponsive, HDM = house dust mite, OCS = oral corticosteroid, ** =years with asthma prior to first attendance at asthma center)

Table 2: Characteristics of subjects subdivided by median exacerbation rate			
	Infrequent exacerbators; < 0.10 exacerbations/yr (n=46)	**Frequent exacerbators: > 0.10 exacerbations/yr (n=47)**	**p-value**
Female, n (%)	22 (47.8)	31 (66.0)	0.08
Age start analyses (yrs), median (IQR)	26 (25-37)	28 (26-36)	0.32
Height (cm), mean (sd)	173 (9)	169 (8)	0.04
FEV_1 (L), mean (sd)	3.01 (0.90)	2.37 (0.81)	0.001
VC (L), mean (sd)	4.53 (1.12)	4.11 (1.07)	0.06
FEV_1/VC (%), mean (sd)	66 (13)	57 (13)	0.001
FEV_1 (% predicted), mean (sd)	78 (17)	66 (19)	0.002
Reversibility (% predicted), mean (sd)	24 (14)	25 (11)	0.64
$PC_{20} \leq 8$mg/ml, n (%)*	30 (65.2)	36 (76.6)	0.23
Blood eosinophils $\geq 220 \times 10^9$/L, n (%)	34 (73.9)	35 (76.1)	0.81
HDM positive, n (%)	41 (89.1)	33 (70.2)	0.02
Atopic, n (%)	44 (95.7)	40 (85.1)	0.09
Age symptom onset (yrs), median (IQR)	4 (3-16)	4 (1-20)	0.53
Adult symptom onset(> 18 yrs), n (%)	10 (21.7)	12 (25.5)	0.67
Untreated period** (yrs), median (IQR)	15 (11-20)	19 (10-25)	0.13
Duration analyses (yrs), median (IQR)	11 (9-18)	10 (7-16)	0.34
OCS years#, median (IQR)	0.0 (0.0-0.5)	0.3 (0.0-0.5)	0.368
OCS duration (yrs), median (IQR)	0.0 (0.0-0.20)	0.2 (0.0-0.3)	0.29

HDM = house dust mite
OCS = oral corticosteroids

* $PC_{20} \leq 8$ mg/ml histamine is a measure of severity of bronchial hyperresponsiveness since all subjects had a $PC_{20} \leq 32$ mg/ml histamine and were thus diagnosed as being hyperresponsive

** Years with asthma prior to first attendance at asthma center

1 OCS year is 1 year use of 5 mg prednisolone daily, 2 OCS years is 2 years of 5 mg daily or 1 year of 10 mg daily etc