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Nonreversible airflow obstruction in life-long nonsmokers with moderate to severe asthma

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ABSTRACT: The aim of this longitudinal study was to assess the frequency of nonreversible airflow obstruction (NRAO) among adults with moderate to severe asthma, and to compare the decline of forced expiratory volume in one second (FEV_1) in asthmatics with reversible and nonreversible airflow obstruction.

Ninety-two (31 males) life-long nonsmokers with asthma participated in a 10-yr follow-up study; mean age 37 yrs (range 18–64) and duration of asthma 16 yrs (range 2–60) at enrolment. Case history, including use of asthma medication, was obtained, and pulmonary function, including diffusion capacity, was measured using standard techniques. At enrolment, all patients had typical symptoms and reversible airflow obstruction. (NRAO) was defined as FEV_1 <80% predicted and change in ΔFEV_1 after 5 mg salbutamol <9% pred.

A total of 21 (23%) patients (mean age at enrolment 32 yrs) fulfilled the criteria for NRAO at the time of follow-up; current therapy was inhaled steroids (n=21, mean daily dose 1.5 mg), oral steroids (n=14), theophylline (n=20), oral β_2-agonist (n=6) and inhaled β_2-agonist. The patients with NRAO (n=21) had a steeper decline in FEV_1 than the remaining patients (n=71, reversible airflow obstruction (RAO)), mean±SD 53±23 mL·yr^{-1} and 36±21 mL·yr^{-1}, respectively (p<0.003). Increasing degree of bronchodilator reversibility (ΔFEV_1% pred) at enrolment (p=0.002) and long-term treatment with oral corticosteroids (p=0.009) were associated with an increased risk for the presence of NRAO at follow-up. The comparison of data for NRAO and RAO patients (at follow-up) revealed no significant differences in mean values for total diffusion capacity ($T_{L,CO}$), diffusion constant (K_{CO}), or total lung capacity.

The findings suggest that a subgroup of asthmatics may experience very steep rates of decline in forced expiratory volume in one second leading to severe nonreversible airflow obstruction, whereas no indication was found that long-standing asthma may lead to the development of emphysema.

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Bronchial asthma has traditionally been considered as a disease characterized by reversible airflow obstruction (RAO) with no long-term, permanent damage to the airways. However, evidence from a number of longitudinal population studies of adults might indicate that the rate of decline of lung function in patients with asthma is steeper than that in the nonasthmatic population [1–3], which may suggest that some patients with asthma are at risk for disease progression to clinically important lung function impairment. Furthermore, findings from cross-sectional studies of hospital-based samples of asthmatics suggest that asthma alone can cause persistent, nonreversible airflow obstruction (NRAO) [4–8], and that the degree of obstruction is a function of the duration and severity of previous asthma. The evidence so far from longitudinal studies of asthmatics concerning the possible disease progression to NRAO is very scarce, although PANHUYSEN *et al.* [9] recently reported from a 25 yr follow-up study of adult asthmatics that 14% of the patients had developed NRAO. However, as smoking is generally agreed to be the single most important factor for the development of persistent airflow obstruction. *i.e.* chronic obstructive pulmonary disease (COPD), it may be necessary to exclude asthmatics who smoke from studies concerning the possible development of NRAO in order not to misclassify smoking-related lung function impairment as persistent airflow obstruction caused by long-standing asthma.

Although suggested >40 yrs ago by ROYLE [10], the possible disease progression to emphysema in asthmatics remains controversial. However, evidence from studies using surrogate markers for emphysema, such as diffusion capacity and high resolution computed tomography (CT) scans might suggest that a small number of patients with long-standing asthma may develop signs of emphysema [9, 11–14]. As a number of these studies included asthmatics with a significant smoking history, further studies of nonsmoking asthmatics are needed to increase knowledge about the possible relationship between asthma and development of emphysema.

The purpose of the present longitudinal study was to assess the frequency of NRAO among life-long nonsmoking adults with long-standing moderate to severe asthma, and, furthermore, to compare findings concerning decline of forced expiratory volume in one second (FEV_1) and possible development of emphysema between asthmatics with RAO and NRAO.

Materials and methods

Subjects

A cohort of patients, referred to the Allergy Clinic and the Laboratory of Respiratory Physiology at the University Hospital in Copenhagen (Rigshospitalet), Denmark, were re-examined ~10 yrs after the first examination. Informed written consent was obtained from all participating subjects, and the study was approved by the ethics committee of Copenhagen.

The diagnosis of asthma was made at the first examination on the basis of typical history, including attacks of breathlessness with wheezing, and results of laboratory tests, including significant reversibility in FEV1 with salbutamol. At both examinations, all patients were interviewed about respiratory symptoms, duration of symptoms, use of anti-asthma medication (drug and mean daily dose during last 12 months), and smoking habits. Furthermore, the questions concerning previous and current smoking habits were repeated prior to the pulmonary function tests. Only patients (n=92) who, at both examinations, stated that they were life-long nonsmokers are included in the present analysis.

On both occasions subjects were asked not to take theophylline or an antihistamine for at least 24 h, astemizole for 6 weeks, or an oral β_2-agonist for 18 h, and not to use an inhaled bronchodilator for 6 h before the tests; long-acting β_2-agonists and leukotriene modifiers were not available in Denmark at the time of this study.

Skin-prick tests

Skin-prick tests were performed with standard dilutions of allergens in 50% glycerol. The standard allergens for the region used were: birch, grass, mugwort, animal hair and dander (cat, horse, and dog), house dust mite (*Dermatophagoides pteronyssinus* and *D. farinae*) and mould (*Alternaria iridis* and *Cladosporium herbarum*). Histamine HC1, 1 mg·mL^{-1} in 50% glycerol, was used as a positive reference; a negative reference (50% glycerol) was also included. The wheal was read after 15–20 min. The area of the wheal produced by each antigen was compared with the area of the histamine wheal and regarded as positive if it was at least the same size as the histamine wheal [15].

Radioallergosorbent test

Tests for allergen specific immunoglobulin (Ig)E were performed with the aluminium radioallergosorbent test (RAST) kit (ALK, Tørsholm, Denmark) according to the method of WEEKE [16]. The patients were screened by a modification of this, in which a mixture of allergen extracts (a "pool") was used. The following pools were used: pollens (birch, grass, mugwort and oxeye daisy), moulds (*A. iridis*, *Aspergillus fumigatus*, *C. herbarum* and *Mucor racemosus*), animals (horse, dog, cat, cow, and guinea pig), and "other" (house dust, *D. farinae*, *D. pteronyssinus* and duck feathers). When the reaction to a pool was 10 sorbent units (SU) or above, each separate allergen within the pool was used for further RASTs; a reaction to one allergen of 20 SU or more was regarded as a positive response [15].

Histamine release from basophil leucocytes

The percentage of histamine released (out of the total histamine that could be released from the cells) was recorded. A characteristic curve was obtained by expressing the released histamine as a percentage of the total histamine (ordinate) with four dilutions of the allergen extract (abscissa). A positive result was defined as release of ≥30% of the total cell content [15].

Specific bronchial provocation

One millilitre aqueous extract of allergen in phenol saline was nebulized to dryness with a Pari atomizer (Beyer, Munich, Germany) and a compressor (Inhaler Boy (Beyer)). Allergen extracts in concentrations that increased by a factor of 10 were used. A positive reaction was defined as a fall in FEV1 of ≥20% [15].

Pulmonary function tests

FEV1 (Bell spirometer (P.K. Morgan, Birmingham, UK) and vital capacity (VC) (Bernstein spirometer (P.K. Morgan) were measured, using the same equipment and technique at both examinations, and the best of three technically acceptable readings was used for analysis. The tests were repeated 15 min after inhalation of 5 mg of salbutamol. Reversibility of FEV1 was calculated as: FEV1% pred after - FEV1% pred before.

The helium dilution rebreathing technique was used for measuring the total lung capacity (TLC) (Godard spirometer (P.K. Morgan)). The end-concentration of helium was recorded when it (after 5–10 min) had been constant for ≥2 min. The diffusion capacity for carbon monoxide (total diffusion capacity (TL,CO) and diffusion constant (KCO) (TL,CO·L alveolar volume^{-1})) was measured using the single breath technique in accordance with the recommendations of the American Thoracic Society [17] (type 101; P.K. Morgan).

Definitions and data analysis

Patients were defined as having nonatopic asthma if they had normal concentrations of serum IgE and no evidence of atopic asthma from history, skin tests, RASTs, and, when the results of these were doubtful, histamine release from basophilic leukocytes and specific bronchial provocation tests.

The presence or absence of NRAO was determined at the time of follow-up, and NRAO was defined as a post-bronchodilator FEV1 <80% pred and change in (Δ)FEV1 after salbutamol (5 mg) <9% pred [9].

Predicted values for FEV1, VC, TLC, TL,CO and KCO were calculated by using the regressions of QUANJER *et al.* [18]. Data are reported, unless stated otherwise, as arithmetic means and standard deviations (SD). Various groups of interest were compared using the Chi-squared test for noncontinuous variables and the two-sample t-test, paired or unpaired, as appropriate, for continuous variables.

Decline in FEV1 over time was calculated as the difference in measured FEV1 at the two examinations divided by the number of years of follow-up. Logistic regression

analyses were used to assess possible predictors, *e.g.* treatment requirements, for outcome at the follow-up examination, *i.e.* the presence or absence of NRAO. It is debated whether the initial FEV1 should be considered as a confounder of the relationship between exposure and subsequent change in FEV1 [19–21]. It may be argued that adjustment for the initial level of FEV1 would remove some of the effects under study, if the exposure of interest (*e.g.* asthma) has been present for several years. Furthermore, as suggested by VOLLMER [20], adjusting for initial FEV1 may lead to biased results, when initial values differ substantially between the groups of interest (in the present study, patients with and without NRAO at the time of follow-up). Finally, it was therefore decided not to adjust for the initial FEV1 because most of the exposure of interest took place prior to the initial measurement of lung function. Thus, in the present study the initial FEV1 was considered to reflect the same exposure as that studied during the observation period.

Results

Of the 92 life-long nonsmokers with asthma, who participated in the two examinations with an interval of ~10 yrs, 58 had nonatopic (17 males) and 34 atopic (14 males) asthma. At the time of enrolment, the mean age was 37 yrs (range 18–64 yrs) and the mean duration of asthma 16 yrs (range 2–60 yrs); further details of the enrolled patients are given in tables 1 and 2.

At the time of re-examination, 72% of the patients were treated with inhaled corticosteroids, and 52% of the patients were treated with >2 anti-asthma drugs (table 3); none of the patients (n=13) on monotherapy (*i.e.* inhaled β_2-agonist) had a postbronchodilator FEV1 <80% pred.

Of the 92 patients enrolled in the study, 21 (23%) (15 nonatopics and 6 atopics; 9 males) fulfilled the criteria for NRAO at the time of follow-up. All 21 of these patients were treated with relatively high doses of inhaled corticosteroid (mean daily dose 1,500 μg, range 500–2000 μg; lowest daily dose in patients not treated with oral corticosteroid 1,500 μg) and two-thirds were also on long-term oral corticosteroid; 16 of the patients were treated with ≥3 anti-asthma drugs.

Compared with the patients who were found to have RAO (n=71) at the re-examination, NRAO patients had higher degree of FEV1 reversibility at enrolment (table 4) and a steeper decline of FEV1 (53 mL·yr^{-1} (SD 23) *versus* 36 mL·yr^{-1} (SD 21) in RAO patients; p<0.003) (fig. 1). The comparison of data from the re-examination for NRAO and RAO patients revealed no significant differences in mean values for $T_{L,CO}$, K_{CO}, or TLC (table 4).

Logistic regression analysis of the data showed increased risk of NRAO at the second examination associated with long-term treatment with oral corticosteroids (odds ratio (OR) 3.7, 95% confidence interval (95% CI) 1.4–9.8; p=0.009) and increasing bronchodilator reversibility (ΔFEV1% pred) at enrolment (OR 2.7, CI 1.4–5.0; p=0.002). Age (OR 1.0, p=0.99), sex (OR 1.1, p=0.90), type of asthma (*i.e.* atopic *versus* nonatopic) (OR 1.4, p=0.60), duration of asthma (OR 1.2, p=0.52), age at debut of asthma (OR 1.1, p=0.58), or therapy with anti-asthma drugs including inhaled corticosteroids other than oral corticosteroids (OR 1.2, p=0.81) were not significant markers for an increased risk for the presence of NRAO.

Table 1. – Characteristics of the 92 life-long nonsmoking patients, of whom 58 (17 males) had nonatopic and 34 (14 males) atopic asthma, at the time of enrolment

	Males	Females
Patients n	31	61
Age yrs	39±11	37±13
Duration of asthma yrs	16.2±13.9	15.4±12.4
FEV1		
Prebronchodilator L	2.4±0.7	2.2±0.8
Postbronchodilator L	3.0±0.8	2.7±0.5
% pred	77.6±19.9	91.0±16.8#
FEV1/VC	0.61±0.15	0.71±13.8#
FEV1 reversibility Δ% pred	13.7±4.2	13.9±4.1

Data are presented as mean±SD. #: p<0.003. FEV1: forced expiratory volume in one second; VC: vital capacity; Δ: change.

Table 2. – Characteristics of the 92 life-long nonsmoking adult asthmatics at the time of re-examination (interval ~10 yrs)

	Males	Females
Patients n	31	61
Age yrs	49±11	47±13
FEV1		
Prebronchodilator L	2.1±0.8	1.9±0.6
% pred	57.5±21.5	68.6±21.2#
Postbronchodilator L	2.6±0.8	2.3±0.6
% pred	69.2±22.5	81.8±19.3#
FEV1 reversibility Δ% pred	10.0±5.1	11.0±5.9
TLC L	6.8±1.3	5.0±0.8
% pred	102.3±16.7	98.5±13.9
$T_{L,CO}$ mmol·min^{-1}·kPa^{-1}	9.6±1.4	7.7±1.2
% pred	83.6±15.6	92.1±13.9#
K_{CO} mmol·min^{-1}·kPa^{-1}·L^{-1}	1.7±0.3	1.7±0.4

Data are presented as mean values±SD. #: p≤0.02. FEV1: forced expiratory volume in one second; Δ: change in; TLC: total lung capacity; $T_{L,CO}$: total diffusion capacity; K_{CO}: diffusion constant.

Discussion

This study showed an excess overall annual decline of lung function in life-long nonsmokers with long-standing moderate to severe asthma compared with the decline in nonasthmatics, but more importantly, the findings also suggest that a subgroup of asthmatics may experience very steep rates of decline of lung function leading to severe,

Table 3. – Current therapy (mean daily dose during last 12 months) at the time or re-examination in 92 adult asthmatics

	Males	Females
Patients n	31	61
Inhaled β_2-agonist	31	61
Oral β_2-agonist	6	9
Theophyline	18	34
Inhaled corticosteroids	24 (77%)	42 (69%)
mean daily dose	740 μg	1135 μg
Oral corticosteroids	14 (45%)	14 (23%)

Data are presented as number of patients, unless indicated otherwise.

Table 4. – Comparison of pulmonary function in life-long nonsmoking adult asthmatics with nonreversible airflow obstruction (NRAO; n=21) and reversible airflow obstruction (RAO; n=71) examined on two occasions (interval approximately 10 yrs)

	NRAO	RAO
Age yrs	32	38
At enrolment	12	12
Postbronchodilator FEV_1		
At enrolment L	2.6±0.7	2.8±0.6
% pred	77.6±19.7	89.1±18.0
At follow-up L	2.0±0.6	2.5±0.7
% pred	57.8±16.9	83.4±18.7
Reversibility FEV_1		
At enrolment Δ% pred	17.2±3.1	12.8±3.8#
At follow-up Δ% pred	4.6±2.4	12.4±5.2
VC L		
At follow-up	3.3±0.8	3.6±0.8
TLC		
At follow-up L	5.6±1.3	5.7±1.3
% pred	95.6±13.8	101.0±15.1
K_{CO} mmol·min^{-1}·kPa^{-1}·L^{-1}		
At follow-up	1.84±0.32	1.68±0.40
$T_{L,CO}$		
At follow-up mmol·min^{-1}·kPa^{-1}	8.7±1.1	8.3±1.7
% pred	86.2±11.4	90.0±15.9
ΔFEV_1	53	36
mL·yr^{-1}	23	21#

Data are presented as absolute numbers and mean±SD. #: $p<0.003$. FEV_1: forced expiratory volume in one second; Δ: change in; VC: vital capacity; TLC: total lung capacity; K_{CO}: diffusion constant; $T_{L,CO}$: total diffusion capacity.

potentially life-threatening, NRAO. Furthermore, the risk for disease progression to NRAO seems to be highest in patients who initially had very variable airflow obstruction, which might reflect the long-term consequences of poorly controlled airway inflammation. The findings do not support the notion that long-standing asthma leads to the development of emphysema.

Asthma is a chronic inflammatory disease of the airways, and evidence from a number of recent studies suggest that persistent airway inflammation may cause irreversible remodelling of the airways, including thickening of the reticular basement membrane and the bronchial smooth muscle [22]. Disease progression to NRAO might therefore be anticipated not least in asthmatics with persistent severe airways inflammation. However, the observed presence of NRAO in some of the patients included in the present study does not necessarily imply that all of these patients have structural irreversibility. It is a possibility that even more intensive treatment with especially corticosteroids could have improved the lung function in some of the patients. But, as all of the patients with NRAO were treated with high dose inhaled corticosteroids (*i.e.* mean daily dose 1.5 mg) and two-thirds were also treated with long-term oral corticosteroids, it seems unlikely that currently available treatment options would have normalized the lung function in these patients.

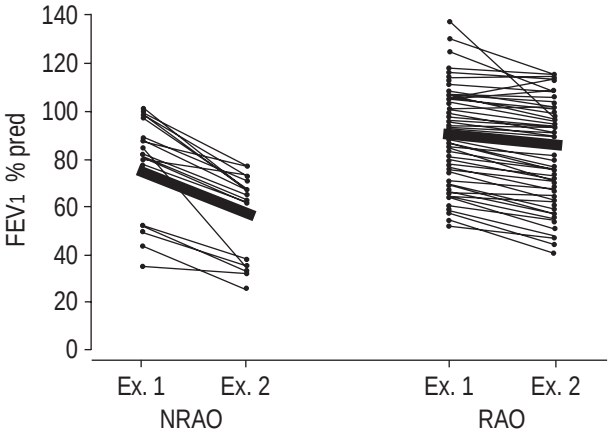

Fig. 1. – Forced expiratory volume in one second (FEV_1) % predicted at the first (Ex. 1) and the second (Ex. 2) examination (interval 10 yrs) in nonsmoking adult asthmatics with nonreversible airflow obstruction (NRAO; n=21) and reversible airflow obstruction (RAO; n=71). ——: mean values.

High degree of bronchodilator reversibility in apparently stable patients with asthma may indicate that more intensive anti-asthma therapy is needed in order to improve airway function and obtain control of the airway inflammation. The observed association between the degree of bronchodilator reversibility at enrolment, when the patients already had been asthmatic for a mean duration of 16 yrs, and the presence of NRAO at the follow-up examination ~10 yrs later, therefore, raises the possibility that improved control of asthma early in the course of the disease, *i.e.* improved control of the airway inflammation, might have reduced the excess decline of lung function and prevented the development of NRAO. Although most of the patients were treated with inhaled corticosteroids at the time of enrolment, they were at that time treated with doses much lower than those currently recommended by the various asthma guidelines. Furthermore, as already mentioned, at the time of referral to the University Hospital in Copenhagen, Denmark, most of the patients had had asthma for a number of years. Taken together, this might imply that delay in institution of sufficient anti-inflammatory therapy early in the course of the disease may increase the risk for a poor long-term outcome. In keeping with this, PANHUYSEN *et al.* [9] have previously reported that asthmatics, who were found to have NRAO, had a longer delay from onset of respiratory symptoms until referral for specialist treatment than patients who continued to have RAO.

Evidence from cross-sectional studies of adult asthmatics suggest that the degree of pulmonary function deficit is a function of the duration of previous asthma [4, 5, 7, 8], which appears to be in line with observations concerning an inverse association between duration of respiratory symptoms and response to anti-inflammatory therapy [23–25]. However, the present longitudinal study did not reveal an association between duration of previous asthma and the presence of NRAO, probably because most of the patients in the study had had asthma for a number of years already at the time of enrolment. The latter suggestion is further supported by evidence from longitudinal population studies reporting that adult asthmatics may have an excess annual decline of lung function both prior to the time of diagnosis and in the first years following the onset of asthma [3, 26, 27].

From a study of life-long nonsmokers with nonatopic asthma, BIERNACKI *et al.* [11] have previously reported that the asthmatics had lower lung computed tomographic (CT) density than the normal controls, whereas no significant correlation was found between CT lung density,

and FEV_1, K_{CO}, or residual volume (RV)/TLC ratio. PANHUYSEN *et al.* [9] reported from their 25-yr follow-up of asthmatics that 22% of the patients had a postbronchodilator diffusion constant <80% pred, which might suggest disease progression to emphysema, although these patients had higher lifetime tobacco exposure (pack-yrs) than patients with a diffusion constant within the reference range. In contrast to the findings in the present study, these findings might therefore suggest that patients with long-standing asthma may develop clinically important emphysema. However, correlations between pathological changes, and CT lung density and diffusion capacity have not been demonstrated in patients with asthma, and low CT lung density in asthmatics may be due to air trapping. So although emphysema-like changes have been observed in a small subset of patients with asthma, it seems premature to draw conclusions concerning the possible disease progression to emphysema in patients suffering from asthma.

In conclusion, this study showed that some life-long nonsmokers with moderate to severe asthma have very steep rates of decline of lung function leading to severe, potentially life-threatening, nonreversible airflow obstruction, whereas the present findings did not suggest that long-standing asthma may lead to the development of emphysema.

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