

Risk factors associated with irreversible airway obstruction in nonsmoking adult patients with severe asthma

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ABSTRACT

Persistent airways obstruction (PAO) may affect some patients with severe asthma and may significantly worsen the prognosis. This study was designed to detect risk factors associated with persistent airflow limitation in nonsmoking adult patients with severe asthma. A total of 68 adults with severe asthma were recruited and followed prospectively for four to six weeks during the stable phase of disease. For all patients, at every visit spirometry with reversibility test was performed. Based on the results, patients were stratified into group 1 (reversible obstruction) or group 2 (PAO). In both cohorts, associations of postbronchodilator forced expiratory volume in one second/forced vital capacity ratio (FEV₁/FVC) with patients' age, gender, asthma duration, history of atopy and allergy, family history, medications, frequency of previous exacerbations, infections, hospitalizations, and artificial ventilation due to the asthma attack-related respiratory failure were investigated. Using a univariate logistic regression analysis, we have shown that older age, more than six exacerbations per year, artificial ventilation in the past, at least one hospitalization per year, the presence of atopic dermatitis, and exposure to domestic visible mold were all independent risk factors of PAO. Furthermore, multivariate regression analysis demonstrated that especially those with domestic exposure to visible molds, with very frequent exacerbations and with at least one hospitalization throughout the last year, were at risk for developing PAO. Domestic exposure to molds, hospitalization during the last year, and very frequent exacerbations were associated with PAO in patients with severe asthma. These factors may help in predicting fixed airflow limitation in nonsmoking patients with severe asthma.

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Asthma is a chronic inflammatory disorder of the airways characterized by bronchial hyperresponsiveness and recurrent symptoms caused by diffused airflow obstruction, which usually resolves either spontaneously or after treatment. Inhaled corticosteroids, in the majority of patients, efficiently suppress airway inflammation, reduce the frequency of exacerbations, normalize lung function, and improve patients' quality of life.¹ However, there is a group of asthmatics with uncontrolled disease and frequent exacerbations despite the best treatment carried out in accordance with our knowledge and recommendations.^{1–4} This subset of patients, whose disease is described as severe,¹ difficult to treat¹, or refractory,⁵ incurs a significant fraction of the cost and morbidity of the disease.^{2,3,6} Of those, especially patients with persistent airflow limitation, which is resistant to high doses of inhaled corticosteroids, supported some-

times with systemic corticosteroids and long-acting β_2 agonists, are at the highest risk for complications and fatal prognosis.^{1,5,6}

The exact cause of persistent airways obstruction (PAO) in this small subset of asthmatics is far from being understood.⁶ Although airway remodeling is regarded as the most important cause,^{2,7} other factors, like persistent airway inflammation leading to release of bronchoconstricting mediators,² resistance to therapy, or change in cellular phenotype, are also significant.^{2,6,7} In addition, active and passive cigarette smoking is the most important factor for the development of persistent airflow limitation.^{2,3,7,8} However, non-reversible airways obstruction (RAO) may also occur in never-smoking asthmatics.⁹ Under the present state of knowledge, the pathophysiology of PAO can only be precisely defined with histologic sampling.^{10,11}

Nevertheless, it is extremely important for clinicians to characterize the group of patients at particularly high risk of developing irreversible airway obstruction and significantly worse prognosis.

There were other studies focusing on persistent airflow limitation in patients with asthma. Factors such as longer duration of asthma,^{3,7} older age,⁶ environmental exposure to allergens,⁶ increased peripheral blood eosinophilia,⁷ hypersensitivity to nonsteroidal antiinflammatory drugs,¹² smoking cigarettes,^{3,6} and occupational exposure⁶ were considered for the development

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of fixed airways obstruction. However, most of these studies included ex or active smokers^{2,3,13} with a history of more than 10 pack-years of smoking,^{2,3,13} which could be a confounding factor. Tobacco smoke is the main cause of chronic obstructive pulmonary disease (COPD).⁸ Therefore, some studies, which initially included asthmatics, in fact partly consisted of COPD patients or patients with overlap syndrome rather than asthmatics with PAO.^{2,3} In addition, forced expiratory volume in one second/forced vital capacity ratio (FEV_1/FVC) is not stable, because it was used for diagnosis in previous studies^{1,2,3} but decreases with age.^{4,8} Therefore, the application of a fixed ratio of less than 0.7, instead of a lower limit of normal (LLN) may result in overdiagnosis of PAO.^{4,8}

Therefore, we decided to carry out the study in non-smoking asthmatics whose fixed obstruction of airways was diagnosed using the LLN for FEV_1/FVC ratio. We aimed to present the characteristic of those patients, and we wanted to compare the patients with severe asthma with PAO and the patients with RAO in relation to demographic data, disease history, family history, treatment, social factors, exhaled nitric oxide (ENO), and spirometric parameters. Additionally, using qualitative and quantitative variables, we wanted to find the risk factors that were associated with fixed airways obstruction in adult, nonsmoking patients with severe asthma.

METHODS

We conducted a prospective, observational study of patients with severe asthma referred to the hospital and outpatient clinics. The patients were treated with their usual asthma treatment during the study, which was indicated by specialist.

The study cohort comprised adults, aged more than 18 years, with severe asthma diagnosed according to recommendations.¹ The diagnosis of asthma had to be made at least five years before the study, and patients had to be treated with a stable dose of medications for at least four weeks before the screening visit. Patients were excluded if they had more than five pack-years or they were current smokers, if they had restrictive respiratory pattern in lung function tests, if they suffered from COPD, emphysema, tuberculosis, neoplastic disease, cystic fibrosis, bronchiectasis, severe heart failure, or autoimmune disease. All patients signed written informed consent, and the medical Ethics Committee of Medical University in Lodz approved the study protocol.

At baseline demographic and clinical data were collected on asthma, allergy, medications, the necessity of treatment with systemic corticosteroids, comorbid conditions, family history, sensitization, as well as asthma-related healthcare use (hospitalizations, artificial ven-

tilation due to the asthma attack-related respiratory failure from the time of asthma diagnosis). All participants filled in asthma control questionnaire (ACQ)¹ and asthma control test (ACT).¹ Next, concentration of NO was measured in exhaled breath, and skin-prick tests as well as spirometry before and after short-acting β_2 agonist (400 μ g of salbutamol) and blood sampling were performed in all participants. After a six-week interval, the patients were asked to fill in ACQ and ACT, and measurement of NO, spirometry with reversibility test, and blood sampling were repeated. At each visit the patients had to be in a stable condition, without asthma exacerbation. According to the results of spirometry at two consecutive visits, patients were divided into groups with PAO or with RAO.

Spirometry

Spirometry was performed according to American Thoracic Society guideline¹⁴ at each study visit with daily calibrated, certified spirometer Lungtest 1000 (Mes, Dymek, Krakow). PAO was defined as a post-bronchodilator (400 μ g of salbutamol) FEV_1/FVC ratio below the LLN at two consecutive visits in four- to six-week intervals.

ACQ and ACT

All participants completed the validated, self-administered ACQ¹ and ACT¹ at both study visits. The ACQ questionnaire contains 7 items (each scored 0–6), five of which concern night time and daytime symptoms and activity limitation, one concerns the use of rescue bronchodilator, and one is related to value of $FEV_1\%$ predicted. The ACQ result was calculated as a mean, with score more or equal to 1.5 reflecting uncontrolled asthma. The ACT comprises five questions (each scored 1–5) concerning activity at school or work, asthma symptoms, the use of rescue medication, and own assessment of asthma control. The calculated ACT score of 19 or less indicated that asthma is uncontrolled.

Concentration of ENO

The concentration of ENO was measured according to the ATS/ERS guidelines¹⁵ with a single-breath method at the expiratory flow rate of 50 mL/s (Hyp'Air FeNO, Medisoftware, Belgium). The measurement was repeated 3 times, and the mean value was collected for statistical analysis. The results were presented as a number of parts of NO per billion.

Skin-Prick Tests and IgE

Skin-prick tests were performed as previously described¹⁶ with the standard set of allergens (Allergopharma, Reinbek, Germany).

Total serum IgE levels were quantitatively determined using IgE kit (UniCap, Pharmacia & Upjohn, Diagnostics AB). The sensitivity for detection was 0.15 kU/L.

Evaluated Variables

Variables evaluated in the study were: patients' age, sex, duration of asthma (years), coexistence of allergic rhinitis diagnosed according to recommendations,¹⁷ sensitization to seasonal and perennial allergens, the history of: atopic dermatitis, exposure to allergens (including pet and molds allergens), childhood infections, infections in adults, asthma exacerbations (defined as a more acute and severe loss of control requiring urgent treatment, an increase or addition of systemic corticosteroids with or without hospitalization¹ or treatment with antibiotics), and frequency of asthma exacerbations (during the year), antibiotic treatment, hospitalizations, and artificial ventilation due to the asthma attack-related respiratory failure (the presence of any hospitalization or artificial ventilation in the past, frequency of hospitalization during the year), and also smoking status, family history of allergy and asthma, patients income (stratified as low, medium, or high), and place of residence.

In addition, we have evaluated the treatment of asthma with short- and long-acting β_2 agonists, ipratropium bromide, inhaled corticosteroids, systemic corticosteroids (the need to use and the dose of systemic corticosteroids), antieukotrienes, methylxanthines, concentration of total IgE, FEV₁, FEV₁%, and FEV₁/FVC ratio.

Statistical Methods

First, frequencies and percentages were calculated to enable comparison of characteristics between asthmatics with PAO and those with RAO. For continuous variables, the Student's *t* test was used for normally distributed data, whereas for not normally distributed data, Mann-Whitney *U* test was done. In addition, χ^2 test was used to compare proportions.

Selection of the risk variables for regression analysis was based on the results of previous studies and other potential causes of PAO. However, FEV₁ and asthma medications were not included, as a potential confounder because of the significant correlation of these variables with FEV₁/FVC ratio. Variables including the frequency of hospitalizations and exacerbations were categorized as follows: without exacerbation or hospitalization (0), one to three exacerbations or hospitalizations for one year (1), four to six exacerbations or hospitalizations (2), and more than seven exacerbations or hospitalizations (3).

The data were analyzed with logistic regression to produce odds ratios and 95% confidence intervals

(CIs). Univariate logistic regression analysis was initially performed to examine the unadjusted association of all variables with PAO. Next, significant variables with $p < .05$ in univariate analyses were tested by multivariate analyses with the forward stepwise approach. Significance was defined as a value of $p < .05$. Statistica 10.0 (StatSoft, Poland, Krakow) was used for analysis. The study protocol was approved by the Ethics Committee of Medical University in Lodz.

RESULTS

Out of patients with asthma included initially, 15 patients discontinued the trial due to asthma exacerbation ($n = 10$), consent withdrawal ($n = 2$), and low compliance ($n = 3$). Finally, there were 68 adult patients with severe asthma (Table 1). The patients with PAO ($n = 38$, 56%) were older and suffered from atopic dermatitis more frequently but did not differ from those with RAO ($n = 30$, 44%) in relation to: gender, duration of asthma, history of allergic rhinitis, history of smoking, sensitization to seasonal and perennial allergens, total serum IgE levels, family history of asthma and allergy, place of residence, and patients' income (Tables 1 and 2). Females dominated in both groups.

Asthmatics with persistent airflow limitation had significantly lower values of FEV₁, FEV₁%, and lower FEV₁/FVC ratio. They were treated with higher dose of inhaled corticosteroids and have taken antileukotrienes more frequently (Table 2). The number of patients with at least one asthma-related exacerbation or hospitalization and/or emergency interventions during the last year was higher in the cohort with PAO. The frequency of these events was higher in the PAO group too. Furthermore, the patients with PAO were more frequently intubated due to the complication of asthma and were more frequently affected by infections. Finally, more patients with PAO were exposed to visible molds at home (Table 2). ENO levels were not significantly higher in PAO group.

Further analysis revealed significant correlations between some of the monitored parameters both in PAO and RAO groups (Tables 3 and 4 and Fig. 1). Briefly, in both cohorts, FEV₁ and FEV₁/FVC ratio correlated negatively with asthma duration, the number of exacerbations, hospitalizations, and infections. In both groups, mean dose of systemic corticosteroids correlated positively with the frequency of infections, and in PAO group, mean dose of inhaled corticosteroids correlated positively with the number of infections. Both low lung function parameters and complications of asthma had negative impact on ACT score.

Univariate logistic regression analysis revealed the following factors associated with persistent airflow limitation: patients' age odds ratio [OR] 1.056; 95%CI: 1.005–1.110, $p = .032$), more than six exacerbations

Table 1 Patients' baseline characteristics

	PAO Group	RAO Group	<i>p</i> Value
Number of patients (<i>N</i> = 68)	38 (56%)	30 (34%)	
Age (years)	53.5 ± 10.55	45.63 ± 10.41	.039
Gender			
Female	26 (68%)	25 (83%)	NS
Male	12 (32%)	5 (17%)	NS
Race	Caucasian 100%	Caucasian 100%	–
Duration of asthma (years)	23.13 ± 12.3	19.73 ± 10.98	NS
Number of patients with early onset of asthma (n)	26 (68%)	22 (73%)	NS
History of allergic rhinitis (n)	24 (63.2%)	24 (80%)	NS
History of atopic dermatitis (n)	15 (39%)	6 (20%)	.02
ACT score	14.0 ± 3.58	15.23 ± 3.46	NS
ACQ score	3.01 ± 0.9	2.92 ± 0.91	NS
FEV ₁ (L)	1.5 ± 0.53	2.25 ± 0.54	.00001
FEV ₁ (% of predicted value)	52.76 ± 12.72	79.00 ± 11.91	.00001
FVC (L)	2.59 ± 0.79	3.07 ± 0.78	.01
FEV ₁ /FVC	0.57 ± 0.07	0.74 ± 0.06	.00001
Serum concentration of IgE kU/L	220.8 ± 203	198 ± 196	NS
Mean concentration of NO in exhaled air (ppb)	33.3 ± 23.51	24.69 ± 14.7	NS
Smoking history (n) (with <5 pack-years)	10 (26%)	6 (20%)	NS
Mean number of pack-years	4.12 ± 1.24	3.6 ± 1.5	NS
Number of patients with positive SPT (n)	26 (68.4%)	19 (63.33%)	NS
Positive SPT to seasonal allergens (n)	18 (47.36%)	13 (43.33%)	NS
Positive SPT to perennial allergens (n)	23 (60.5%)	17 (56.67%)	NS
Number of patients with family history of allergy (n)	24 (63.16%)	18 (60%)	NS
Number of patients with family history of asthma (n)	17 (44.7)	13 (43.33%)	NS

p value represents results of χ^2 , *t* test, or U Mann-Whitney test, respectively.

ACT = asthma control test; ACQ = asthma control questionnaire; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; ppb = parts per billion; NS = not significant; PAO = persistent airways obstruction; RAO = reversible airways obstruction; SPT = skin prick test.

during the year (OR 3.271; 95%CI: 1.136–9.421, *p* = .028), the presence of at least one hospitalization during the year (OR 3.41; 95%CI: 1.714–6.807, *p* = .001), a history of intubation with artificial ventilation due to an asthma attack-related respiratory failure in the past OR 1.720; 95%CI: 1.013–2.92, *p* = .045), and presence of atopic dermatitis (OR 1.907; 95%CI: 1.07–3.39, *p* = .029) and exposure to domestic visible mold (OR 2.038; CI: 1.025–4.053, *p* = .042). Multivariate regression analysis revealed that patients were more likely to have a FEV₁/FVC ratio below LLN if they had: more than six exacerbations during the year (OR 4.455; 95% CI: 1.416–14.01, *p* = .01), at least one hospitalization per year due to the asthma complications (OR 3.607; 95% CI: 1.726–7.538, *p* = .001), or exposure to molds (OR 2.247; 95% CI: 1.00–5.046, *p* = .047).

Gender, duration of asthma, age at debut of asthma, type of asthma (atopic vs nonatopic), the presence of allergic rhinitis, smoking history, family history of allergy and asthma, frequent infections in the childhood, less than six asthma exacerbations during the year,

frequency of infections or antibiotic therapy during the year, exposure to pet allergens, living in the city, or patients' income were not significant markers for an increased risk for the presence of PAO.

DISCUSSION

Based on multivariate analysis, we have presented that nonsmoking adult patients, suffering from severe asthma, with seven or more exacerbations during the year, with environmental exposure to molds, and especially those with the history of severe exacerbation requiring hospitalization in the past 12 months, were at significantly increased risk of having persistent airflow limitation. In addition, older age, history of intubation with artificial ventilation due to the asthma attack-related respiratory failure, and the presence of atopic dermatitis together with aforementioned factors independently increased risk of PAO.

According to the definition of the disease, asthma is caused by chronic allergic inflammation, is accompa-

Table 2 Contributing factors such as treatment, exacerbations of asthma, infections, patients' income in patients with severe asthma with persistent airways obstruction, and reversible airways obstruction

	PAO Group	RAO Group	<i>p</i> Value
Mean daily dose of ICS (equivalent to beclomethasone, in μg)	2172.63 $\pm$ 1286.2	1622.00 $\pm$ 1038.56	0.041
Number of patients treated with SC (n)	20 (52.6)	19 (63%)	NS
Mean daily dose of SC (equivalent to prednisone, in mg)	17.38 $\pm$ 16.24	12.37 $\pm$ 9.03	NS
Mean daily dose of LABA (μg)	56.74 $\pm$ 41.83	53.67 $\pm$ 37.2	NS
Number of patients treated <i>ad hoc</i> with SABA (n)	30 (79%)	24 (80%)	NS
Number of patients treated with ipratropium bromide (n)	21 (55%)	13 (43%)	NS
Number of patients treated with antileukotriene (montelukast, daily dose 10 mg)	28 (74%)	14 (47%)	0.022
Number of patients treated with methylxanthines	14 (37%)	12 (40%)	NS
Number of patients with at least one exacerbation in the last year	36 (95%)	20 (67%)	0.02
Number of exacerbations of asthma during the last year	7.66 $\pm$ 4.07	4.7 $\pm$ 4.63	0.006
Number of patients with at least one asthma related hospitalization and/or emergency interventions in the last year	35 (92%)	15 (50%)	0.0001
Number of asthma-related hospitalizations and/or emergency interventions during the last year	5.0 $\pm$ 3.31	2.83 $\pm$ 3.95	0.016
History of intubation due to asthma-related exacerbation (n)	18 (47%)	7 (30%)	0.038
Number of patients with frequent infections in childhood	32 (84%)	22 (73%)	NS
Number of adult asthmatics with frequent infections	35 (92%)	22 (73%)	0.035
Number of infection during the last year (n)	3.92 $\pm$ 2.34	3.7 $\pm$ 3.12	NS
Number of patients treated with antibiotics during the last year	34 (89%)	24 (80%)	NS
Mean frequency of antibiotic therapy during the last year	3.39 $\pm$ 1.92	3.23 $\pm$ 2.19	NS
Number of patients exposed to allergens to which they are sensitized (n)	19 (50%)	18 (60%)	NS
Number of patients exposed to pet allergens (n)	11 (28%)	15 (50%)	NS
Number of patients exposed to molds (n)	12 (32%)	3 (10%)	0.03
Number of city inhabitants (n)	29 (76%)	23 (76%)	NS
Patients income (n)			NS
Low	8 (21%)	3 (10%)	
Medium	22 (58%)	19 (63%)	
High	8 (21%)	8 (27%)	

p value represents results of χ^2 , *t* test, or U Mann-Whitney test, respectively.

PAO = persistent airways obstruction; RAO = reversible airways obstruction; LABA = long-acting β_2 agonists; SABA = short-acting β_2 agonists; ICS = inhaled corticosteroid; SC = systemic corticosteroid; NS = not significant.

nied by episodes of RAO, and is generally associated with good prognosis. However, in some patients, irreversible airflow limitation may develop, which worsens the prognosis significantly.^{1,6,7} Up until today, the natural course of persistent airflow limitation in asthma is poorly understood. There is growing evidence that various external (smoking cigarettes, infections, exacerbations, occupational exposure)^{1,6,7} and internal (patients age, adult onset of asthma, eosinophilic inflammation)⁶ factors are responsible for structural changes and progressive remodeling in the airways, which may lead to irreversible airflow limitation despite the optimal therapy.¹⁸ The structural changes are

not known, and the role of remodeling in the development of persistent airflow limitation is not precisely described. However, the theory that airway remodeling participates in the evolution of irreversible airflow limitation has important clinical implications. It is accepted that remodeling of the airways results from chronic inflammation, which is driven by damage to the epithelium.^{19,20} As it was postulated, the environmental stimuli together with impaired ability of epithelium to repair activate signals, which propagate and stimulate inflammation within epithelium, subepithelial compartment, smooth muscles, and vessels. Many irritants or specific factors, including allergens, air pol-

Table 3 Correlations of continuous variables in patients with reversible airways obstruction

	Mean Dose of ICS	Mean Dose of SC	FEV ₁ %	Number of Hospitalizations	Number of Infections	ACT Score	Number of Antibiotics/ Year	Number of Exacerbations	FEV ₁ /FVC
Duration of asthma	R = 0.51 p = .004	R = 0.5 p = .004	R = -0.49 p = .006	R = 0.45 p = .014	R = 0.38 p = .038	R = -0.42 p = .019			
Mean dose of SC		—	R = -0.48 p = .007	R = 0.71 p = .0001	R = 0.51 p = .004	R = -0.51 p = .004	R = 0.53 p = .003	R = 0.6 p = .0001	
FEV ₁ %			—	R = -0.51 p = .004	R = -0.49 p = .006		R = -0.36 p = .046	R = -0.56 p = .001	
Number of hospitalizations				—	R = 0.79 p = .0001	R = -0.55 p = .022	R = 0.63 p = .0001	R = 0.84 p = .0001	
Number of infections					—			R = 0.81 p = .0001	
ACT score						—	R = -0.59 p = .001	R = -0.62 p = .001	R = 0.39 p = .03
Number of antibiotics per year							—	R = 0.72 p = .001	

ACT = asthma control test; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; SC = systemic corticosteroid.

Table 4 Correlations of continuous variables in patients with persistent airways obstruction

	FEV ₁ %	Number of Hospitalizations	Number of Infections	ACT Score	Number of Antibiotics/Year	Number of Exacerbations	FEV ₁ /FVC
Duration of asthma	R = -0.45 p = .004			R = -0.38 p = .02			R = -0.34 p = .03
Mean dose of ICS			R = 0.38 p = .02				
Mean dose of SC			R = 0.52 p = .0001	R = -0.36 p = .03	R = 0.6 p = .0001		
FEV ₁ %	—	R = -0.57 p = .0001		R = 0.39 p = .02	R = -0.4 p = .01	R = -0.55 p = .0001	
Number of hospitalizations		—	R = 0.4 p = .01	R = -0.54 p = .0001			R = -0.47 p = .02
Number of infections			—		R = 0.79 p = .0001	R = 0.51 p = .001	R = -0.37 p = .02
ACT score				—	R = -0.37 p = .02	R = -0.33 p = .03	R = 0.39 p = .02
Number of antibiotics per year					—		R = -0.35 p = .03
Number of exacerbations						—	R = -0.48 p = .002

ACT = asthma control test; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; SC = systemic corticosteroid.

lutants, cigarette smoke, and pathogens, may activate the production of mediators by the epithelium and thus may feed the remodeling.^{19,20} If chronic inflammation is responsible for airway progressive and non-reversible remodeling, adequate and early decisions concerning treatment can be made, especially in patients with mild and moderate asthma.^{1,7}

If persistent airflow limitation occurs, it cannot usually be reversed with medications, and it is associated with poor or even fatal prognosis.^{6,8}

Therefore, it is extremely important to select, as early as possible, those asthmatics who are particularly prone to develop fixed airway obstruction. There were several retrospective as well as long-term and short-term prospective studies that aimed to identify the risk factors of PAO in patients with mild to moderate asthma^{21–23} but only a few studies that focused on the development of PAO in severe asthma.^{3,4} Although asthma may have a severe and uncontrolled course, it still can be characterized by RAO. Risk factors respon-

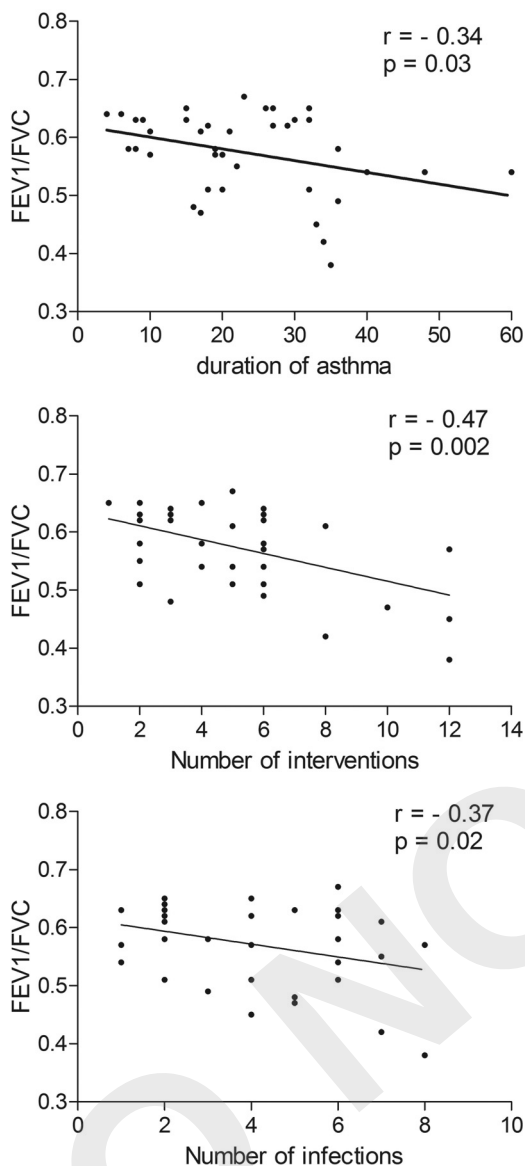


Figure 1. Relationships between FEV₁/FVC ratio and duration of asthma, number of emergency interventions, and hospitalizations due to severe exacerbation of asthma, and number of infections in patients with severe asthma and persistent airflow limitation.

sible for irreversible obstruction in patients not exposed to cigarette smoke have been poorly investigated.^{3,4} One of the reasons for PAO in severe asthma could be recurrent and frequent exacerbations.³ As we have demonstrated in this study, seven or more exacerbations during the year constitute the “borderline” for the development of nonreversible obstruction. As it was demonstrated before, at least one asthma exacerbation is an important risk factor for recurrent exacerbations,⁷ and recurrent exacerbations strongly promote further exacerbations, thus activating a vicious circle. Patients presenting with very frequent exacerbations are especially prone to develop fixed airways obstruction. In addition, studies demonstrate that asthmatics

with multiple exacerbations (called as “exacerbations prone asthmatics”)¹² when compared with those with single exacerbation are at increased risk for future, severe exacerbation requiring more intense antiinflammatory treatment with systemic corticosteroids.¹² The reason why very frequent exacerbations may cause PAO is not well explained. It is promoted that recurrent exacerbations produce and accelerate the loss of lung function^{7,12,24} associated with decrease of FEV₁, which, in turn, has been shown to be a risk factor for multiple asthma exacerbations.¹² In addition, according to remodeling hypothesis,^{19,20} stimuli, which causes exacerbation of asthma, stimulate and maintain inflammation within the airways escalating structural changes and remodeling. This phenomenon may result from the activation of different inflammatory pathways (including metalloproteinases) during asthma exacerbations. These may have a sustained effect on airways remodeling and may promote further exacerbations in a self-escalating fashion.⁷ It is worth stressing that in our study, less than six exacerbations during the year were not enough to develop fixed airflow limitation (OR1.2, $p = .23$). Therefore, it is very important to prevent exacerbations in patients with severe asthma and to intensify treatment after the first exacerbation to prevent another. In this respect, especially females were susceptible to exacerbations of asthma and asthma-related hospitalizations.⁷ Similarly in our study, females predominated in both groups of asthmatics.

Furthermore, frequent hospitalizations are associated with asthma exacerbations.^{1,3,7} As we have demonstrated in this study, besides very frequent exacerbations, at least one exacerbation in the past 12 months severe enough to warrant treatment in the emergency department or in the hospital was enough to promote the persistent airflow limitation in patients with severe asthma. It agrees with previous studies, which demonstrated that even one severe exacerbation per year reduced the value of FEV₁ more than in patients with severe asthma without exacerbation and was associated with more severe obstruction after 11 years of observation.⁷

Furthermore, there were more intubations for respiratory failure associated with acute severe asthma exacerbations in PAO group. Intubation and artificial ventilation is the consequence of a severe disease course. However, artificial ventilation can also occur in those with RAO. As we have demonstrated retrospectively, especially those who were artificially ventilated are at higher risk for PAO.

Although mean concentration of ENO did not differ significantly between those with RAO and PAO, it was clearly greater in the latter group. The lack of significance may result from the low number of participants. However, other studies have shown significantly

higher concentrations of ENO in patients with fixed airway obstruction. Because the levels of ENO correlate with sputum eosinophilia,^{7,21} measurement of NO in exhaled air may serve as a biomarker of allergic inflammation in asthmatics.^{1,7} Therefore, higher levels of ENO in PAO group could reflect persistent inflammation within airways stimulated by recurrent exacerbations, which is resistant to treatment with inhaled and systemic corticosteroids.^{19,20} Exposure to visible molds at home in sensitized patients could be one of the causes of persistent stimulation of epithelial cells within the airway. As we have demonstrated in this study, such chronic exposure constitutes a strong, independent factor for the development of PAO in patients with severe asthma.

One of the drawbacks of this study is the exclusion of patients with intense exposure to tobacco smoke. However, smoking as a strong risk factor of permanent obstruction can interfere with the analysis of other variables here. Several prospective studies have confirmed the role of smoking in the development of RAO in patients with asthma and COPD.^{1-3,8} However, there were studies, which included smokers, with the median duration of smoking of 30 pack-years³ for the evaluation of risk factors for PAO.³ The diagnosis of PAO in those patients with a fixed postbronchodilator FEV₁/FVC ratio could be categorized with COPD or with an overlapping syndrome rather than asthma with PAO.

CONCLUSIONS

The results of this study confirm that prevention of asthma exacerbations and hospitalizations, especially in nonsmoking patients with severe asthma, could reduce the risk of irreversible airflow limitation, thus improving their prognosis. In addition, it is possible that environmental intervention to reduce exposure to molds will help to reduce risk of persistent airflow limitation in those patients.

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