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Assessment of asthma control: clinical, functional and inflammatory aspects

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Key words

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Summary

Background: *Asthma is a complex disease with numerous markers of severity/activity. Clinical assessment, functional parameters and inflammation biomarkers are the most used. A correlation between them is difficult, as each one evaluates a particular aspect of the disease.* ***Objective and Methods:*** *To explore the possible association between asthma control, pulmonary function and inflammation in patients with asthma, consecutive asthmatics underwent simultaneous spirometry (measurement of FEV1), exhaled nitric oxide (eNO) evaluation and Asthma Control Test (ACTTM) questionnaire.* ***Results:*** *The study included 232 asthmatics (mean age: 37.48 years; 78.4% female): 43% had uncontrolled asthma (ACTTM≤19) with FEV1 mean values of 83.3%±21.8; 48% partially controlled (ACTTM:20-24) with FEV1 of 87.6%±17; 9% complete control (ACTTM=25) with FEV1 of 93.1±20.6. The relation ACTTM/FEV1 and ACTTM/FEF25-75% was statistically significant (p=0.001 and p=0.034, respectively). Among patients with eNO<35 ppb, 66% had FEV1>80% and 52% had ACTTM>19. No association was found combining ACTTM/eNO or FEV1/eNO. A subgroup of 66 patients was evaluated twice.* ***Conclusion:*** *An association was found between ACTTM and spirometry, with higher ACTTM scores reflecting less bronchial obstruction. The authors advise a combined approach in asthma follow-up, involving clinical aspects, functional parameters and inflammation biomarkers, although in some circumstances ACT could be a valid instrument to be used alone to assess control.*

Introduction

Asthma is a chronic, complex and multifaceted disease. According to the new Global Initiative for Asthma (GINA) and to the National Asthma Education and Prevention Program (NAEPP) guidelines, the goal of treatment is asthma control (1, 2).

Among the several available and validated markers and measurements of asthma's severity, functional parameters (peak expiratory flow measurement and spirometry values), clinical assessment (symptoms and quality of life) and biomarkers of inflammation are the most widely used (1-11). However, there is no gold standard for asthma control assessment (6, 7, 12).

Evaluation of lung function provides an assessment of airflow obstruction severity, its reversibility and variability, and can confirm the diagnosis of asthma. Spirometry is reproducible, but is an effort-dependent method (1).

During the past few years new tools for asthma evaluation have been developed. One is the measurement of exhaled nitric oxide (eNO) that has attracted a growing interest since it is a non-invasive, easy and rapid technique to per-

form. It seems to be a reproducible marker of eosinophilic airway inflammation in asthma. Increase in eNO levels may be an early marker of loss of control (4, 8, 10, 13-16). Monitoring this parameter (eNO) may be useful in the evaluation of asthma control (15).
Although the level of asthma control has an impact on quality of life of asthmatic patients, these two are different parameters (17). Specific and validated questionnaires exist to assess asthma control, like the ACT™ (1, 11). This questionnaire is a short and simple tool, consists of scores attributed to five questions that the patients themselves have to answer, enquiring about the frequency of symptoms in the last 4 weeks (daytime symptoms and sleep interference), use of rescue medication and activity limitations (3, 6, 7, 11, 12, 18). Each question has five possible answers scored from 1 (worst) to 5 (best). The higher the ACT™ score, the better the asthma control is (4, 6). The ACT™ allows a quick self-assessment of the degree of that control. The NAEPP uses the ACT™ scores to categorize degrees of asthma control: an ACT™ score of 20 or more indicates that asthma is well controlled; 16 to 19 is not well controlled; 15 or lower is poorly controlled (2). The cut-off score of 19 or less has also been used to identify patients with poorly controlled asthma, as defined by GINA (6).
Although several tools are available to evaluate asthma control, none of them can be used alone to define and determine how well the disease is controlled. Therefore, the purpose of this study was to explore the possible association, in asthmatic patients, between pulmonary function, asthma control and airway inflammation.

Material and Methods

During March 2007, the asthmatic patients observed in our Allergy Division, by five different doctors, were evaluated.
The study evaluation consisted in spirometry (only FEV1 and FEF25-75% values were analysed), score registration of the Asthma Control Test™ and exhaled nitric oxide (eNO) measurement in two different visits.
ENO was determined by chemiluminescence analysis, using NIOX instrument (Aerocrine; Sweden). Spirometry values, FEV1 and FEF25-75%, were expressed as 3-level variables: percent predicted less than 60%, between 60 and 80% and greater than 80%. Only spirometry measures that met the American Thoracic Society (19) criteria were included.
The ACT™ score was divided into 3 different groups: less or equal to 19 (uncontrolled asthma), 20 to 24 (partially controlled) and equal to 25 (well controlled asthma). A second analysis was performed dividing ACT™ score in 2 groups (score ≤19 and >19).
For eNO evaluation a cut-off value of 35 ppb was used (15) with higher levels reflecting a greater probability of airway eosinophilic inflammation.

Statistical methods

Comparison between more than two groups was carried out using ANOVA.
Qui-square test was used to compare categorical variables and to verify the independency between them. When there was dependency, V Cramer Index evaluated association between variables.
The analysis was performed with software SPSS 13.0 (SPSS Inc, Chicago, IL) and Statistica7.
The effects with a p value less than or equal to 0.05 were considered statistically significant.

Results

During March 2007, 232 consecutive asthmatic patients were observed. The mean age of the participants was 37.48 ± 14.88 years. Fifty patients were male (21.6%) and 182 female (78.4%). The male patients had a significantly higher mean age than the females (41.34 ± 15.62 versus 36.42 ± 14.53, $p=0.038$).
Due to technical problems during the study, only 185 patients could perform the ENO evaluation.

FEV1

Table I presents the FEV1 and FEF25-75% results. The mean value of FEV1 was 83.34%. Most patients (66%) had FEV1 values above 80% (controlled asthma) and only a minority (11.6%) with FEV1 below 60% (uncontrolled asthma).
With regards to the distribution of FEV1 by gender, the most frequent FEV1 value for females and males was above 80%: 72% and 44%, respectively. In the group of FEV1 below 60% seven patients were male and 20 female. This analysis showed that the severity of the disease was dependent on gender ($p<0.001$; V Cramer coefficient: 0.262).
The patients mean age was 34.80 years for those with FEV1>80%, 39.73 for FEV1 between 60 and 80% and 48.30 years for FEV1<60%. The ages differed significantly for all 3 types of severity; younger patients had less severe disease (figure 1-A).

Table 1 - Distribution of FEV1 and FEF25-75%

(%Pred)		Total of the patients (n=232)		Gender			
				Male (n=50)		Female (n=182)	
		n (%)	Mean±sd	n (%)	Mean±sd	n (%)	Mean±sd
FEV1	<60 %	27 (11.6)	48.3±9.4	7 (14.0)	53.7±5.5	20 (11.0)	46.4±9.9
	60 – 80 %	52 (22.4)	72.1±5.8	21 (42.0)	74.1±5.4	31 (17.0)	71.8±5.8
	>80 %	153 (66.0)	97.1±11.1	22 (44.0)	96.3±13.2	131 (72.0)	97.3±10.7
FEF25-75	<60 %	121 (52.2)	36.7±16.7	31 (62.0)	36.6±15.2	90 (49.4)	36.8±17.2
	60 – 80 %	46 (19.8)	69.5±4.7	12 (24.0)	69.2±5.8	34 (18.7)	69.5±4.4
	>80 %	65 (28.0)	99.8±15.7	7 (14.0)	91.1±8.0	58 (31.9)	99.8±16.1

FEF25-75%

One hundred and twenty one participants (52.2%) had FEF25-75<60%; 28% had FEF25-75>80%; a minority had FEF25-75 between 60 and 80% (table I).
Regarding gender, the results were similar in both genders: the class with the highest percentage of patients was <60%, however there was a greater percentage of males in this class [62.0% and 49.4% for males and females, respectively]. Almost 32% of females and 14% of males had FEF25-75>80%. The percentage of patients in the 60%-80% class was 24.0% for males and 18.7% for females. FEF25-75% was dependent on gender (*p=0.045*). According to multiple comparison of means, age differed significantly for the three types of severity, and the older individuals were those with more severe disease (figure 1-B).

FEV1 and FEF25-75

Higher values of FEV1 (mean: 102.1%) were observed in the group also with higher FEF25-75% and lower values of FEV1 (75.0±19.6%) in the series with lower FEF25-75% (figure 2). The same occurred with FEF25-75%.

ACT™

According to the ACT™ scores, 42.7% of patients had poorly controlled asthma (ACT≤19), 48.3% partially controlled (ACT: 20-24) and only 9.1% had controlled asthma (ACT=25).

ACT™ and FEV1

Among patients with ACT™ scores≤19, 18.2% had values of FEV1<60%, 23.2% had FEV1 between 60-80% and 58.6% had FEV1>80%. The majority (71.4%) of patients with partially controlled asthma (ACT™ 20-24) had FEV1 values above 80%, 21.4% between 60 and 80% and 7.1% under 60%. For patients with totally controlled asthma (ACT™ score = 25), 71.4% were in the FEV1> 80% group, 5 (23.8%) between 60-80% and just one patient (4.8%) had FEV1 <60%.
Table III shows that the patients with uncontrolled asthma had a mean value of FEV1 of 83.3% and those with partially controlled asthma had a mean value of FEV1 of 87.6%. Patients with totally controlled asthma were those with the highest mean FEV1 value (93.1%). Comparing

Figure 1 - Mean age of patients distributed by: A. FEV1 (%Pred); B. FEF25-75 (%Pred)

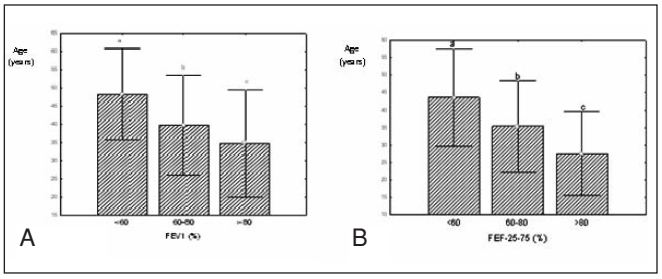
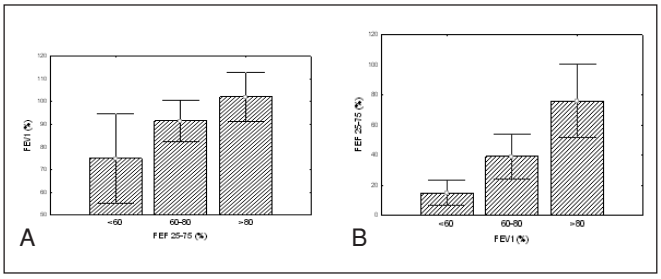


Figure 2 - FEV1 by degrees of disease severity defined with FEF25-75. B. FEF25-75 by degrees of disease severity defined with FEV1. (Values presented as mean±sd)



the relationship between these two variables through the qui-square test, we found they are dependent (*p = 0.001*). One hundred and fifty seven patients (67.7%) had an ACT™ score ≤19 or FEV1≤80%.

ACT™ and FEF25-75%

Among patients with uncontrolled asthma (ACT™ score ≤19), 59.6% had a value of FEF25-75% below 60%, 16.2% between 60-80% and 24.2% had a value above 80%. Approximately 30% of patients with partially controlled asthma (ACT™ 20-24) had FEF25-75>80%, 23.2% between 60%-80% and 46.4% had FEF25-75<60%. In the group of patients with totally controlled asthma (ACT™ score = 25) 33.3% had FEF25-75>80%, 4 (19.1%) between 60-80% and 10 (47.6%) below 60%.
Patients with uncontrolled asthma had a mean value of FEF25-75 of 55.7% while patients with partially controlled asthma 64.4% and patients with totally controlled asthma 63.4% (Table III).
Regarding the relationship between these two variables (ACT™ and FEF25-75%) we also found, using qui-square test, they are dependent (*p=0.034*).

Exhaled Nitric Oxide

One hundred and ten participants (59.5%) had eNO<35 (low probability of bronchial inflammation) and 75 (40.5%) had high probability of airway inflammation (eNO≥35).

Among patients with ACT™>19 (partially and controlled asthma), 60% had eNO less than 35 (Table IV). ACT™ and eNO are independent variables (*p=0.473 using qui-square test*).
In the group of patients with low probability of inflammation (eNO<35), 65.5% had a FEV1>80%, 19.1% between 60 and 80% and 15.4% FEV1<60%. Regarding patients with high probability of inflammation, 62.7% had FEV1>80%, 30.7% between 60 and 80% and just 6.7% had FEV1<60%.
The mean values of FEV1 were 85.5% (SD of 21.6%) for patients with low probability of inflammation (eNO<35) and 84.8% (SD of 16.0%) for those with eNO≥35. Statistical analysis (qui-square test) showed that FEV1 and eNO are independent variables, with *p=0.065*.
Among patients with eNO<35, 24.5% had a value of FEF25-75> 80%, 18.2% between 60 and 80% and 57.3% had less than 60%. Regarding patients with probability of bronchial inflammation, 25.3% had FEF25-75>80%, 22.7% had 60≥FEF25-75≤80% and 52% had FEF25-75<60% (Table IV). FEF25-75% and eNO, are statistically independent variables (qui-square test: *p=0.710*).

Follow-up

In a subgroup of 66 patients (28%) it was possible to perform two evaluations, with an interval of 4 months.
In the second evaluation, the mean values of FEV1 and ACT™ improved (from 86.35 to 87.68% and from 18.70

Table 2 - FEV1 (%Pred) versus FEF25-75 (%Pred)

FEV1	FEF25-75			Total
	<60 (%)	60 – 80 (%)	>80 (%)	
<60 (%)	27 (100%)	0 (0%)	0 (0%)	27 (100%)
60 – 80 (%)	48 (92.3%)	4 (7.7%)	0 (0%)	52 (100%)
>80 (%)	46 (30.1%)	42 (27.4%)	65 (42.5%)	153 (100%)

Table 3 - Distribution of FEV1 and FEF25-75%

ACT score		FEV1				FEF25-75			
		<60 %	60 – 80 %	>80 %	Mean ± sd (%)	<60 %	60 – 80 %	>80 %	Mean ± sd (%)
3 groups	≤19	18 (18.2%)	23 (23.2%)	58 (58.6%)	83.3±21.8	59 (59.6%)	16 (16.2%)	16 (16.2%)	55.7±31.8
	20-24	8 (7.1%)	24 (21.4%)	80 (71.4%)	87.6±17.0	52 (46.4%)	26 (23.2%)	26 (23.2%)	64.4±30.1
	25	1 (4.8%)	5 (23.8%)	15 (71.4%)	93.1±20.6	10 (47.6%)	4 (19.1%)	4 (19.1%)	63.4±26.4
2 groups	≤19	18 (18.2%)	23 (23.2%)	58 (58.6%)		59 (59.6%)	16 (16.2%)	24 (24.2%)	
	>19	9 (6.8%)	29 (21.8%)	95(71.4%)	P = 0.001	62 (46.6%)	30 (22.6%)	41 (30.8%)	P = 0.034

to 20.11, respectively) and eNO decreased (from 42.46 to 39.28 ppb) reflecting patient improvement (although without statistical significance, with *a p* value above *0.05* for all the variables).

Discussion

Asthma control is very important to assess in clinical practice, as it is the goal of asthma treatment. Control can be difficult to assess since it is multidimensional in nature and characterized by symptoms, changes in pulmonary function and effects on quality of life and respiratory parameters. Quantitative composite measures should be used to asses, monitor and improve disease control (6).
Establishing a clear correlation among parameters available to evaluate asthma control is extremely difficult, as each of them measures a particular aspect of the disease and seems to be partially independent from the others.
A study by Lopes et al to analyse the contribution of eNO in the variability of asthma control, concluded that clinical questions using ACQ questionnaire, airway inflammation and lung function are complementary for the evaluation of asthma status in adults (20).
The present study aimed to search an eventual association between functional parameters, clinical assessment of asthma control through the ACT™ score and biomarkers of inflammation.
Statistical analysis showed that most of our patients had values of FEV1>80%, ACT™ score between 20 and 24 and eNO below 35. So, according to spirometry, the patients had good pulmonary function, without bronchial obstruction, with a clinical assessment (using ACT™) showing, in the patient's opinion, that their asthma was partially controlled and, according to the objective measure eNO, they did not have bronchial inflammation in most cases. All the parameters were in agreement.
The analysis by gender showed that most of both male and female patients had normal pulmonary function (with FEV1>80%). Apart from this fact, male gender was significantly associated with poor pulmonary function, probably related to a higher mean age in this group of patients.
Also the patient's age was significantly related with spirometry values, with younger patients presenting less severe disease. There was a correlation between values of FEV1 and FEF25-75% (*p < 0.001*), reinforcing that these two variables are dependent.
Although spirometry and the ACT™ questionnaire analyse different time periods (the first one provides a point-in-time evaluation, while the second assesses a clinical status over a given time period (6)), we found dependency with statistically significance between FEV1 or FEF25-75% and ACT™ scores, according to the GINA classification (*p = 0.001* and *0.034*, respectively). Nathan et al also had found that ACT and FEV1 have a good correlation (3).
The measurement of exhaled nitric oxide, considered one of the markers of airway inflammation, did not correlate with FEV1 or ACT™ score (*p* value *0.065* and *0.491*, respectively). Inflammation appears to be independent from airway obstruction and does not affect the patient's perception of asthma control. This could be explained, partially, because the effect of inflammation is not only caused by asthma but also by rhinitis and other factors. The other variables are only related to asthma.
Despite the lack of correlation between eNO and the other variables, changes in levels of this parameter may be an early marker of loss of control and it also could be useful to evaluate patient adhesion to therapy. Although that and the fact that eNO is a simple and non-invasive tool, if used alone, it could be not sufficient to recognize the level of control in asthmatic patients.
The ACT™ proved to be an important tool in the assessment of asthma control. It takes into account the asthma symptoms, the impact on daily life and the patient's perception of control. It was easy to apply and showed a good correlation between the patient's opinion about control and the measurable and objective values of bronchial obstruction.

Table 4 - Distribution of FEV1 and FEF25-75%

		eNO	
		< 35	¤35
n (%)		110 (59.5%)	75 (40.5%)
ACTTM score	≤19	45 (40.9%)	32 (42.7%)
	20-24	57 (51.8%)	34 (45.3%)
	25	8 (7.3%)	9 (12.0%)
	Mean±sd	19.2±4.7	19.3±4.8
FEV1 (Pred%)	<60 %	17 (15.4%)	5 (6.7%)
	60 – 80 %	21 (19.1%)	23 (30.7%)
	>80 %	72 (65.5%)	47 (62.7%)
	Mean±sd	85.5±21.6	84.8±16.0
FEF25-75 (Pred%)	<60 %	63 (57.3%)	39 (52.0%)
	60 – 80 %	20 (18.2%)	17 (22.7%)
	>80 %	27 (24.5%)	19 (25.3%)
	Mean±sd	57.7±32.2	60.6±28.4

The relation between ACT™/FEV1 and ACT™/FEF25-75% was statistically significant (*p=0.001* and *P=0.034, respectively*). The ACT™, as a simple questionnaire, can be a useful tool in clinical practice, enabling periodic evaluation of disease control and closely involving the patient in this process. The ACT™ questionnaire and exhaled nitric oxide should both complement medical history and the conventional approach of airway function evaluation, through spirometry, a recognized important method. Also in the clinical practice, but in settings where spirometry is not available, ACT™ questionnaire could be a useful instrument to rapidly provide information about asthma control and could guide the physician to improve disease control.

Because it is expected that control changes over time, a periodic re-evaluation is essential (8).

Two evaluations, with a 4 months interval, were performed in a subgroup of 66 patients. In the second evaluation, the mean values of FEV1 and ACT™ improved and eNO decreased, reflecting patient improvement (although without statistic significance). The number of patients re-evaluated was limited, hampering the analysis.

Another limitation of this study was that only 185 of the 232 patients involved had eNO measures because of a technical problem. We can speculate that this fact could contribute to the absence of a statistically significant correlation of this parameter with the others.

The fact that some patient characteristics haven't been included, such as atopy, smoking, current medication, or exacerbations, and the lack of information about the physician observation, can also be mentioned as limitations.

In spite of limitations, our data reinforce that all these parameters are important in the evaluation of an asthmatic patient and contribute to the assessment of control. Objective measures, like pulmonary function, complemented with the patient's point of view of disease control and daily life implications, and with the measurement of airway inflammation, which is also influenced by comorbidities, like rhinitis (frequently associated to asthma), can help the physician in achieving the goal of asthma treatment, the control. These study data, recognizing the association between ACT™ and spirometry, allow us to conclude that the ACT™ questionnaire can be used to simply and quickly assess asthma control.

Conclusion

An association was found between ACT™ and spirometry values, with higher scores of ACT™ reflecting less bronchial obstruction. Exhaled NO values had no association with ACT™ or FEV1.

The authors advise that the follow-up of asthma in order to achieve control should be based, ideally, on a combined approach that involves clinical aspects, functional parameters and biomarkers of inflammation. If not possible, the data allow us to conclude that the ACT™ questionnaire is a valid instrument to assess asthma control.

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