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Assessment of airway inflammation in asthmatic patients by visual endoscopic scoring systems

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ABSTRACT: Inflammation is a hallmark of bronchial asthma. Inflammatory cells both in bronchoalveolar lavage (BAL) and bronchial biopsies of asthmatic patients have been studied and correlated with functional or clinical parameters. We have recently attempted to assess airway inflammation by a visual endoscopic scoring system. The purpose of this study was to compare our own endoscopic scoring system with the bronchitis index previously described by Thompson and coworkers, and to determine whether these scores were correlated with clinical or functional parameters.

Sixty asthmatics of variable severity (forced expiratory volume in one second (FEV_1) 33–117% of predicted values) and 30 healthy volunteers were studied. The clinical severity of asthma was assessed by the clinical score as described by Aas in all of the patients, and in the last 15 patients by a daily symptom score. Beta$_2$-agonist consumption was recorded daily during a period of 7 days before the endoscopic procedure. During this period, circadian variation and day-to-day variation of peak expiratory flow rate (PEFR) were determined. During bronchoscopy, airway inflammation was assessed by two independent observers, prior to BAL, by visual inspection of each lobe and the lingula, and the results were quantitated using the bronchitis index and our endoscopic scoring system.

Both endoscopic scores were significantly higher in asthmatics than in controls. A significant correlation was observed between the two endoscopic scores both in asthmatics and in controls. In asthmatics, a weak but significant correlation was found between both endoscopic scores and the daily symptom score, as well as the β_2-agonist consumption. There was also a correlation between our endoscopic score and the clinical score of Aas. However, there was no correlation between the endoscopic scores and the BAL cell differentials.

We conclude that the macroscopic examination of the airways using a visual scoring system in asthmatic patients might represent a useful additional indicator of the activity of the disease.

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Inflammation is a hallmark of bronchial asthma. Many authors have studied inflammatory cells both in bronchoalveolar lavage (BAL) and in bronchial biopsies of asthmatic patients [1–7], and some have attempted to find correlations with functional or clinical parameters [8–14]. In one study, there was no correlation between cellular counts in bronchial biopsies and clinical parameters [12], whereas we found, in two other studies, a correlation between the clinical scoring system described by Aas [13] and the eosinophilic inflammation assessed in BAL or in bronchial biopsies [14, 15]. Visual inspection of the airways during fibreoptic bronchoscopy in asthmatics has been reported previously [16, 17] and we have recently attempted to assess and grade airway inflammation by a visual endoscopic scoring system [18, 19]. In two previous studies [20, 21], we have found that there was a weak but significant (Rho=0.39, $p<0.05$) correlation between the endoscopic score that we usually use and the clinical scoring system of severity described by Aas [13]. Since the clinical score of Aas is a chronic score, which takes into account the symptoms over a one year period [13], we hypothesized that the activity of asthma assessed by recent asthma symptoms, β_2-agonists consumption and peak expiratory flow rate (PEFR) variations (fig. 1) could be better correlated with the endoscopic score. On the other hand, it was recently proposed by Thompson *et al.* [22] that bronchial inflammation in chronic bronchitis be assessed by an endoscopic semi-quantitative scale, namely the bronchitis index. These authors found that the bronchitis index was significantly higher in chronic bronchitis than in control subjects.

Fig. 1. – Clinical assessment of bronchial asthma. Aas score: clinical severity score described by AAS [13]. PEFR: peak expiratory flow rate.

The aim of this prospective study was: 1) to compare our endoscopic score with the bronchitis index, in asthmatics of variable severity and in control subjects; and 2) to determine if these endoscopic scoring systems were correlated with the severity and activity of asthma, and with BAL differential cell counts. To evaluate the clinical severity and activity of asthma, we used the chronic clinical score as described by AAS [13], the modified form of a daily symptom score previously reported [23], and salbutamol consumption.

Materials and methods

Patient population

We prospectively studied 60 asthmatic patients aged 18–71 yrs (mean±SD, 37±16 yrs). Asthma was defined according to the criteria of the American Thoracic Society [24]. All patients had, at least once during the previous year, show a reversible airways obstruction, characterized by a 15% increase in forced expiratory volume in one second (FEV_1) after the inhalation of 200 μg of salbutamol. None of the patients were current smokers, and none had smoked within the previous 2 years. Patients were excluded from the study if they had taken systemic corticosteroids in any form during the previous two months, or if they had inhaled corticosteroids during the previous month, nedocromil sodium, cromolyn sodium, or ketotifen during the previous week, or theophylline during the 48 h before the test. Treatment with β_2-agonists was withheld for only 8 h. Allergy was defined, according to a previous paper [14], by the presence of positive skin prick tests to common environmental aeroallergens, and serum specific immunoglobulin E (IgE) was measured by radio allergosorbent test (RAST) (Pharmacia Diagnostics, Uppsala AB, Sweden).

We also studied 30 normal nonsmoking subjects (aged 18–76 yrs; mean±SD, 44±16 yrs) as a control group. Their pulmonary function was in the normal range, and they had no allergic diseases and had never had asthma. This study fulfilled the criteria of the Ethics Committee of our Institution, and the subjects gave informed consent.

Asthma score

The clinical severity of asthma was assessed in all patients according to the scoring system described by AAS [13]. Very mild forms received a score of 1, and incapacitating disease requiring medication received a score of 5. The grading was based on events that took place over a one year period, and takes into account both the symptoms (the number and duration of asthma episodes, total duration of symptom, and presence or absence of symptom free intervals between attacks) and the requirement for medication. It does not take into account the patient's pulmonary function. A score of 5 was given to patients who were receiving oral or parenteral corticosteroids.

The last 15 patients were also studied prospectively. The clinical severity of asthma was assessed by a previously reported daily symptom score [23], which was modified and recorded daily during a period of 7 days before the endoscopic procedure. The patient's daily symptoms of wheezing, shortness of breath and cough were monitored, and the severity of symptoms quantitated with a graded scale that reflects their intensity during day and night. The index used for symptoms score was as follows: 1) for day: 0=none; 1=mild, clearly present, but not causing marked discomfort; 2=moderately severe, causing marked discomfort; 3=severe, some interference with activities but not incapacitating; 4=incapacitating; and 2) for night: 0=slept well, no symptoms; 1=slept well but mild symptoms; 2=awake one time; 3=awake several times; 4=awake most of the night because of asthma. The results were expressed as the daily mean of the six scores.

Patients took salbutamol from a metered dose inhaler (100 $\mu g \cdot puff^{-1}$) as required to relieve their asthma symptoms, and were invited to record the number of inhalations. The results were expressed as the daily mean number of inhalations.

Pulmonary function

Pulmonary function was assessed by measuring FEV_1% just before bronchoscopy with a spirometer Fukuda ST 250 (Emo International, Dompierre-sur-Mer, France), and normal values were defined according to the standards of KNUDSON *et al.* [25]. The spirometer provided expiratory flow-volume loops from which FEV_1 was obtained. At least three flow-volume loops were obtained, and the values associated with the best FEV_1 were recorded.

In the last 15 asthmatics, peak expiratory flow rate (PEFR) was recorded by means of a peak flow meter, twice a day during the 7 days before fibreoptic bronchoscopy. Results were expressed as the amplitude percentage mean PEFR (morning PEFR-evening PEFR/mean PEFR), and the day-to-day variation in PEFR (coefficient of variation of morning daily PEFR values), according to DJUKANOVIC *et al.* [26], and National Heart, Lung and Blood Institute (NHLBI) guidelines [27].

Fibreoptic bronchoscopy

Fibreoptic bronchoscopy was performed as described previously [28]. Briefly, after premedication with 0.5 mg atropine and 5 mg diazepam, and local anaesthesia with 2% lidocaine applied to the upper respiratory tract, a BFTR Olympus fibreoptic bronchoscope was inserted into

the trachea and the airways were systematically examined. Prior to BAL airway inflammation was assessed by two independent observers, who were unaware of the severity of the patients, by visual inspection of each lobe and the lingula. The results were quantitated using the endoscopic score that we have described previously [18–21], and the bronchitis index previously described by THOMPSON *et al.* [22]. According to our experience, the endoscopic score was graded from 0 (absence) to 1 (presence) for hypersecretion, hyperaemia, oedema, and friability. It was a score taking into account the whole appearance of the bronchi, grading from 0 to 4. The score described by THOMPSON *et al.* [22], namely the bronchitis index, is a scale that takes into account each lobe and the lingula. It is graded from 0 to 3 for hyperaemia, oedema, friability, and secretions as follow: 0=normal, 3=severely abnormal. The index is determined by summing all the scores from six sites, and, thus, grading ranges from 0 to 72. Comparison of scores independently, as assessed by the two different bronchoscopists, showed excellent correlation (Rho=0.95, data not shown). The BAL was carried out in one subsegmental bronchi of the middle lobe, using the injection of five aliquots of 50 ml of saline at room temperature, and reaspiration by gentle syringe suction. During bronchoscopy, oxygen and epinephrine were readily available, and the patient had an intravenous infusion to provide venous access. Nebulization with 1 mg of salbutamol was performed after the procedure, if bronchospasm was noted. All subjects were observed for 3 h, and were given a contact telephone number.

Tolerance of the bronchoscopic procedure was excellent, as there was no severe attack during endoscopy, and only two mild exacerbations were noticed, which did not require the cessation of the procedure and resolved easily after nebulization with 1 mg of salbutamol.

Examination of BAL cells

After recovery, BAL fluid was strained through a monolayer of surgical gauze to remove mucus. After mixing, an aliquot of 5 ml of each sample was used to obtain total cell count using a haemacytometer. Cells were examined by an investigator who was unaware of the subject group. Cell differential counts were performed after cytocentrifugation (Cytospin, Shandon, UK), and staining by May-Grünwald Giemsa by counting 200 cells on each slide. Macrophages, lymphocytes, eosinophils, neutrophils and epithelial cells (including ciliated and goblet cells) were enumerated, and results were given in percentages.

Statistical analyses

Statistical analyses were performed with a Macintosh Computer (Apple Co., New York, USA) using the Statview II Software (Statview, Inc., USA). We used Mann-Whitney U test for comparison of unpaired data. Correlation coefficients were calculated by the Spearman-Rank test (Rho). Results were expressed as mean±SD (or SEM) for FEV_1 and age, and as range and median for other data.

Results

Severity and activity of asthma

Characteristics of the 60 patients are shown in tables 1. Six patients had an Aas score of 1 (mild asthma), 28 had a score of 2 (moderate asthma), 16 a score of 3 (moderately severe asthma), 10 a score of 4 (severe asthma). No patient had a score of 5, since this implies an anti-inflammatory treatment, and the patients received no medications except inhaled β_2-agonists.

Table 1. – Characteristics of asthmatic patients

Aas Score	n	Age* yrs	Sex M/F	FEV_1* % pred
1	6	45±14	3/3	101±6.4
2	28	33±15	20/8	96±16.2
3	16	35±13	10/6	76±15.3
4	10	40±17	3/7	54±15.4

*: data are expressed in mean±SD. FEV_1: forced expiratory volume in one second.

Characteristics of the last 15 asthmatic patients are shown in table 2. Mean daily symptom scores recorded during the last 7 days ranged 0.4–5.7 (median, 2.7), and the mean daily number of inhalations of salbutamol ranged 0–4 (median 0.9). Diurnal variations of PEFR ranged -34.7–9.1% (median -4.65%), and day-to-day variations ranged 2.9–16.9 (median 7.65). FEV_1 ranged 33–117% of predicted values (mean±SD, 84.3±22.5%). A significant correlation was found between the daily symptom score and the PEFR day-to-day variation (Rho=0.67, p=0.016).

Thirty four patients were allergic and were polysensitized to various allergens, including perennial allergens (house dust mites and/or moulds) and, in some patients, pollens.

Cellular BALF content

The percentage of fluid recovered from the bronchoalveolar lavage, the number of cells per volume of recovered BAL fluid and the differential cell counts in asthmatics and normal subjects are shown in table 3. As expected the former had larger numbers of eosinophils.

Endoscopic score in asthmatics

In asthmatics, our endoscopic scoring system ranged 1–3 (median 2), and the bronchitis index ranged 0–18 (median 6). A significant correlation was found between these two endoscopic scoring systems (Rho=0.82, p=0.0001, by Spearman Rank test).

Table 2. – Characteristics of the last 15 asthmatic patients

Age yrs	FEV_1 % pred	Diurnal PEFR variation %	Day-to-day PEFR variation*	Salbutamol usage**	E1	E2	Symptom score***
44	98	2.5	2.9	0	1	2	1.4
39	76	-2.8	7.5	0.15	2	9	0.4
53	78	2.5	7.2	0	1	2	1.9
51	93	-7.0	7.8	0	2	12	4.3
29	110	-4.1	13.6	2.4	2	12	3.9
50	87	-0.4	6.9	0.9	1	6	1.7
21	50	-8.1	16.9	1.8	2	6	5.7
22	69	-14.7	8.4	0	0	0	1.4
40	51	9.1	5.7	3	1	2	0.4
19	101	-27.1	12.7	2	2	12	3.8
29	88	-9.9	3.4	0.15	1	2	1.9
22	97	1.4	10.3	0	0	0	2.7
43	114	ND	ND	4	2	12	4.4
56	85	-5.2	5.8	2	3	17	3.0
29	74	-34.7	9.9	1.15	3	10	3.4

*: coefficient of variation of morning expiratory flow rate; **: mean daily number of inhalations; ***: mean daily score of three symptoms; E1: our endoscopic scoring system; E2: bronchitis index; FEV_1: forced expiratory volume in one second; PEFR: peak expiratory flow rate; ND: not determined.

Table 3. – Comparison of BALF differential cell counts between asthmatics and control subjects

	Asthmatic patients	Control subjects
BALF recovery %	48±1.5*	60±1.2
Cells n $10^3 \cdot ml^{-1}$	170±15.7	184±16.5
Macrophages %	72±2.3	79±2.2
Lymphocytes %	13±1.5	12±1.5
Eosinophils %	3.6±1.0*	0.8±0.5
Neutrophils %	5.2±1.2	3.1±0.6
Epithelial cells %	6.9±1.5	4.8±1.4

Results are expressed as mean±SEM. *: significant ($p<0.05$, Mann-Whitney U-test) difference between asthmatics and control subjects. BALF: bronchoalveolar lavage fluid.

Endoscopic score in control subjects and comparison with asthmatics

In control subjects, our endoscopic scoring system ranged 0–2 (median 0), and the bronchitis index ranged 0–18 (median, 0). A significant correlation was found between these two endoscopic scoring systems (Rho=0.90, p=0.0008). These two endoscopic scoring systems were significantly higher in asthmatics than in control subjects (Z=4.061, p=0.0001 and Z=4.02, p=0.0001, respectively, by Mann-Whitney U-test).

Correlations between endoscopic scores and the severity of asthma

We found a weak correlation between our endoscopic scoring system and the chronic clinical severity of asthma assessed by the Aas score (Rho=0.38, p=0.036 by Spearman Rank test), whereas a significant correlation was not found for the bronchitis index (Rho=0.25, p=0.054 by Spearman Rank test). When the activity of asthma was assessed by the symptom score or β_2-agonist consumption, a significant correlation was observed between the symptom score and both our endoscopic score and the bronchitis index (Rho=0.55, p=0.039 and Rho=0.59, p=0.027, respectively), and between β_2-agonist consumption and both our endoscopic score (fig. 2) and the bronchitis index (Rho=0.53, p=0.047 and Rho=0.58, p=0.031, respectively).

Correlations between endoscopic scores, functional parameters or differential BAL cell counts in asthmatic patients

There was no significant correlation between both endoscopic scoring systems and FEV_1, diurnal peak expiratory flow rate variation or day-to-day peak expiratory flow rate variation. There was no correlation between the endoscopic scores and differential BAL cells counts.

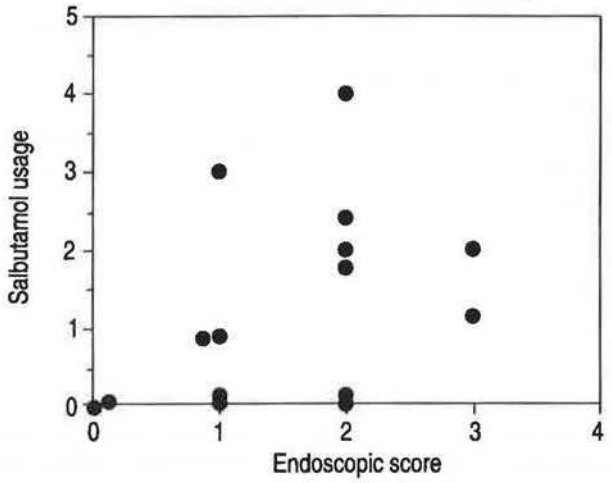

Fig. 2. – Correlation between our endoscopic score and the mean daily salbutamol usage (number of inhalations). Rho=0.53, p=0.047, by Spearman Rank test.

Discussion

In the present study, we found that the bronchial inflammation assessed by our endoscopic scoring system or the bronchitis index described by THOMPSON *et al.* [22] was significantly more marked in asthmatics than in control subjects. Furthermore we confirmed the weak but significant correlation previously reported between the clinical scoring system of AAS [13] and our endoscopic score [20, 21], and showed that there was a better correlation between the activity of asthma assessed by a daily symptom scoring system or β_2-agonist consumption and both our endoscopic scoring system or the bronchitis index.

Fibreoptic bronchoscopy is a widely-used method of investigation and diagnosis in chest diseases, and mainly in lung carcinoma [29, 30]. However, its major purpose in asthma is to be a research tool to obtain cells and bronchial tissue [2–12, 14, 15]. The macroscopic aspect of the airways might represent an additional method of assessing the severity and activity of bronchial asthma. In obstructive lung diseases, THOMPSON *et al.* [22] have used an endoscopic scoring system, namely the bronchitis index, and showed that this score was significantly greater in bronchitics than in control subjects. This scoring system was more complex than the one that we used, which might explain some differences in the results. In the present study, mean bronchitis index was 6 and ranged 0–18, whereas our mean endoscopic scoring system was 2 and ranged from 0–3. Macroscopic abnormalities evaluated by the bronchitis index, hyperaemia, oedema, friability and secretions were mild (graded 1) in most of the patients, and rarely graded 2 (data not shown). Therefore, only the lower part of the scale of THOMPSON *et al.* [22] was used in the present study. Nevertheless, we found a very good correlation between these endoscopic scoring systems validating our score. In the present study, our endoscopic score was significantly higher in asthmatics than in control subjects, and BAL eosinophilia was also significantly higher in asthmatics. In the present study, BAL first sample was not separated from the others, and we were, therefore, unable to correlate bronchial sample cell counts with the endoscopic score.

Bronchial inflammation at the cellular level is a hallmark of bronchial asthma, and many authors have studied inflammatory cells both in BAL and in bronchial biopsies of asthmatics [2–7]. These findings have been compared with clinical and functional parameters [8–12, 14, 15]. There is considerable discrepancy between these studies; some authors found a correlation between the cell counts and the bronchial reactivity [8–11], others failed to find a correlation with a clinical scoring system assessing the recent severity of asthma [12]. These authors concluded that it reflects the complexity of mechanisms responsible for the symptoms.

Recently, we have found a correlation between both eosinophil counts in BAL fluid [14, 15], number of eosinophils in the epithelium of bronchial biopsies and the clinical severity of asthma assessed by the chronic clinical scoring system of AAS [13]. Studying the inflammatory cells in BAL and bronchial biopsies, represents only the accessible part of the airways, and it seems obvious that it does not accurately reflect the complexity and the severity of bronchial asthma. Furthermore, the time of the procedure represents only a time-point in the year of symptoms assessed by the chronic clinical score.

The precise site of the bronchial obstruction is not known. Functional data have indicated that in some patients it predominates in the proximal airways, whereas in others it appears to be more distal [31]. Obstruction of the proximal airways occurs after allergen or pharmacological challenges [32, 33], and distal obstruction is found mainly in chronic and unstable asthma [34]. Thus, the changes found at the macroscopic level assessing the proximal airways, might better reflect recent asthma exacerbation. Previous authors [12] have shown the lack of correlation between bronchial inflammation assessed by BAL differential cell counts and a daily symptom score. By contrast, in the present study bronchial inflammation assessed by macroscopic findings was correlated with a daily symptom score. These findings suggest that in unstable asthma, plasmatic leakage leading to mucosal oedema might play an important role, and could be investigated by fibreoptic bronchoscopy examination. The purpose of this study was not to point out the specificity of the macroscopic findings in asthma, but rather to argue that this observation can provide additional criteria in the assessment of the stability of the disease. It is very interesting to notice the correlation, of the endoscopic scores with the symptom scores and the β_2-agonist consumption, indicating the usefulness of this marker.

By contrast, the scoring system described by AAS [13] was poorly correlated with our endoscopic scoring system and was not correlated with the bronchitis index reported by THOMPSON *et al.* [22]. This confirms that a daily symptom scoring system better assesses the recent activity of asthma than a chronic system.

Finally, there was no significant correlation between functional data assessed by FEV_1, PEFR daily variation, or PEFR day-to-day variation and the endoscopic scoring systems.

In conclusion, we have shown in the present study that bronchial inflammation assessed by an endoscopic scoring system is significantly different in asthmatics and control subjects. In addition, we found a correlation between the two endoscopic scoring systems and the activity of asthma as assessed by a symptom score and by β_2-agonist consumption. Thus, the macroscopic examination of the airways might represent a useful additional indicator of the activity of the disease.

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