Clinical, physiological and radiological features of asthma with incomplete reversibility of airflow obstruction compared with those of COPD

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OBJECTIVES: To compare clinical features, pulmonary function and high-resolution computed chest tomography (HRCT) findings of asthmatic patients with a component of incomplete reversibility of airflow obstruction (AIRAO) with those of patients with smoking-induced chronic obstructive pulmonary disease (COPD).

METHODS: Thirteen patients with COPD (six males and seven females, mean age 59 years, mean smoking 50.5 pack-years) and 14 patients with AIRAO (six males and eight females, mean age 52 years) despite optimal treatment, with no significant smoking history (mean 1.5 pack-years) and no significant environmental exposure or any other respiratory disease, were studied. Patients had respiratory questionnaires, pulmonary function tests, allergy skin-prick tests and an HRCT to evaluate possible parenchymal or bronchial abnormalities. Eight patients in each group also had exercise tests. All patients were stable at the time of the study.

RESULTS: As expected, atopy was more prevalent in AIRAO (n=13) than in COPD (n=1) patients. Mean forced expiratory volume in 1 s (FEV1) and forced vital capacity (percentage of predicted value) were 39% and 61%, respectively, in COPD patients and 49% and 71%, respectively, in AIRAO patients; FEV1 improved by 18% in COPD patients and by 22% in AIRAO patients after use of inhaled salbutamol. Mean functional residual capacity was greater in COPD patients than in AIRAO patients (178% versus 144% of the predicted value), while the mean carbon monoxide diffusing capacity of the lungs (DLCO) was lower in COPD patients than in AIRAO patients (62% versus 89% of the predicted value). Exercise tolerance was similar in both groups, as were postexercise changes in arterial oxygen pressure (Pao2). Emphysematous changes were observed in COPD patients and AIRAO patients who had evaluable HRCTs (10 versus two patients, although very mild in asthma), bronchial dilations (zero versus six patients), bronchial wall thickening (two versus eight patients) and an acinar pattern (one versus five patients). Mean thickness of the large airway wall to outer diameter (intermediary bronchus) ratio was 0.176 in COPD and 0.183 in AIRAO (P>0.05).

CONCLUSIONS: Asthma may lead to physiological features similar to COPD but may be distinguished by demonstrating a preserved DLCO and a higher ratio of airway to parenchymal abnormalities on HRCT scan.

Key Words: Asthma with incomplete reversibility of airflow obstruction, Chronic obstructive pulmonary disease, Exercise tolerance, High resolution chest tomography, Pulmonary function tests

Pour le résumé, voir page 271
Comparaison entre l’asthme avec réversibilité incomplète de l’obstruction respiratoire et la MPOC sur le plan de leurs caractéristiques cliniques, physiologiques et radiologiques

OBJECTIFS : Comparer les caractéristiques cliniques, les résultats aux tests de fonction respiratoire et à la tomodensitométrie thoracique de haute résolution (TDM-HR) de patients asthmatiques présentant une réversibilité incomplète de leur obstruction respiratoire (ARIOR) à ceux de patients atteints de maladie pulmonaire obstructive chronique (MPOC) provoquée par le tabagisme.

MÉTHODES : On a étudié treize patients atteints de MPOC (six hommes et sept femmes, âgés en moyenne de 59,1 ans et fumant en moyenne 50,5 paquets de cigarettes par année) et 14 patients souffrant d’ARIOR (six hommes et huit femmes, âgés en moyenne de 52,0 ans) malgré un traitement optimal et en l’absence d’antécédents significatifs de tabagisme (moyenne 1,5 paquet par année), d’exposition ambienne ou d’autres maladies respiratoires quelles qu’elles soient. On a administré aux patients des questionnaires sur leur fonction respiratoire, des tests de fonction pulmonaire, des tests d’intradermoréaction et des TDM-HR pour déceler de possibles anomalies du parenchyme ou des bronches. Huit patients de chaque groupe ont également subi des épéueuses d’effort. Tous les patients étaient stabilisés au moment de l’étude.

RÉSULTATS : Comme prévu, l’atopie s’est révélée plus prévalente chez les patients présentant un ARIOR (n = 13) que chez les patients atteints de MPOC (n = 1). Le volume expiratoire forcé en une seconde (VEMS) et le volume forcé (pourcentage de la valeur prévue) ont été respectivement de 39 % et de 61 % chez les patients atteints de MPOC et de 49 % et 71 % chez les patients souffrant d’ARIOR ; le VEMS s’est amélioré de 18 % et de 22 % chez les patients atteints de MPOC et d’ARIOR, respectivement, après l’administration de salbutamol. La capacité fonctionnelle résiduelle a été plus grande chez les patients atteints de MPOC que chez les patients souffrant d’ARIOR (178 %, contre 144 % de la valeur prévue), alors que la capacité de diffusion pulmonaire pour le monoxide de carbone (DLCO) a été plus basse chez les patients atteints de MPOC que chez les patients souffrant d’ARIOR (62 %, contre 89 % de la valeur prévue). La tolérance à l’effort a été semblable dans les deux groupes, tout comme les changements de la PaO₂. Des anomalies associées à l’emphysème ont été notées chez les patients atteints de MPOC (n = 10) et chez les patients souffrant d’ARIOR (n = 13) qui présentaient une TDM-HR évaluable (10 patients, contre deux, quoique très léger dans l’asthme), les dilatations bronchiques (zéro patient, contre six), l’épaississement de la paroi bronchique (deux patients, contre huit) et un mode de présentation acéne (un patient contre cinq). Le ratio entre l’épaissseur moyenne de la paroi des voies respiratoires épaissie et le diamètre extérieur (bronche moyenne) a été de 0,176 dans la MPOC et de 0,183 dans l’ARIOR (P > 0,05).

CONCLUSIONS : L’asthme peut éventuellement s’accompagner de caractéristiques similaires à celles de la MPOC, mais on le distingue en confirmant une DLCO préservée et un ratio anomalies des voies respiratoires/anomalies du parenchyme plus élevé à la TDM-HR.

Respiratory diseases that induce airway obstruction can be subdivided into two main categories: asthma and chronic obstructive pulmonary disease (COPD). The latter disease includes primarily chronic bronchitis and emphysema (1,2). These conditions are the most frequent chronic respiratory ailments in North America and are responsible for considerable morbidity (3). In asthma, airflow obstruction is usually completely reversible, either spontaneously or following treatment (1). This feature helps to distinguish asthma from COPD, although both diseases may occur concomitantly. On the other hand, in COPD, airflow obstruction related to prolonged smoking is mostly fixed (4). Although expiratory flows normalize completely in most asthmatic patients with appropriate treatment, an irreversible component of airflow obstruction (AIRAO) may be observed in some patients, even after optimal therapy and without any evidence of other pulmonary disease or significant smoking history (5-7). This subtype of asthma has previously been demonstrated to be associated with atopy, a prolonged duration of asthma, airway wall thickening and intense bronchial subepithelial collagen deposition, suggesting irreversible airway damage in this condition (8,9). In clinical practice, AIRAO and COPD are difficult to differentiate, and the two conditions are often confounded.

Both asthma and COPD are associated with a complex bronchial inflammatory process (10,11). They share numerous pathological similarities, such as epithelial desquamation, goblet cell metaplasia, mucous gland hyperplasia and smooth muscle hypertrophy (11,12). Although many comparisons have been made between asthma with reversible air-flow obstruction and COPD, little is known of the comparative features of AIRAO and COPD.

The aim of this study was to compare the clinical, physiological and radiological features of patients with COPD with those of AIRAO not attributable to smoking or a condition other than asthma in order to identify features that may help differentiate these two conditions.

PATIENTS AND METHODS

Patients: Twenty-seven patients participated in this study: 13 patients (six males and seven females), aged 50 to 67 years, with smoking-induced COPD, and 14 asthmatic patients (six males and eight females), aged 40 to 64 years, with AIRAO (Table 1). COPD and asthma were defined according to the criteria of the American Thoracic Society (ATS), and AIRAO was defined as an optimal forced expiratory volume in 1 s (FEV₁) 75% of the predicted value or less despite inhaled and systemic corticosteroid treatment (8,13). Criteria for the AIRAO group were the typical symptoms of asthma, a less than 15% increase in FEV₁ either spontaneously or following treatment, no significant history of smoking (less than six pack-years) and no environmental exposure or other condition, such as bronchiectasis, that could induce AIRAO.

Patients with contraindications to the proposed evaluation or with previous or current history of significant systemic or pulmonary disease other than asthma or COPD were excluded from the study, as were women of childbearing potential without adequate contraception and patients with unstable respiratory conditions because of a recent (less than one month) respiratory infection or allergen exposure. The...
study was approved by Laval University’s Ethics Committee, and all patients signed informed consent forms.

**Study design:** Patients came to the laboratory on two to three different occasions. On a first visit, they completed a standardized questionnaire on the characteristics and duration of their disease, medication requirements, duration and severity of symptoms, disease-related global discomfort on a scale of 0 (no discomfort) to 5 (unbearable), smoking habits and environment. Patients were asked to evaluate their discomfort while under current medication.

Pre- and postbronchodilator expiratory flows, lung volumes, carbon monoxide diffusion (DLCO), airway resistance (Raw), specific conductance (SGaw), lung compliance (Cstat) and expiratory flows were measured. Allergy skin-prick tests were also done at the first visit.

Patients were asked to measure their peak expiratory flows (PEF) with a mini-Wright peak flow meter four times daily, for a period of two weeks before the second visit. At that visit, high resolution chest tomography (HRCT) was done to measure bronchial wall thickness at the level of the large airways by the follow-up technique. For comparison between groups, the ratio of bronchial wall thickness was calculated as follows: internal diameter was the smallest internal diameter measured; wall thickness was measured in the same axis as that of adjacent internal bronchial diameter; and the total bronchial diameter was the sum of the internal diameter and twice the wall thickness. Airway narrowing was defined as an airway with a diameter less than one-half the diameter of an adjacent vessel. All measurements were taken with electronic calipers.

**Exercise tests:** An arterial cannula was placed in a radial artery. Subjects were then seated on an electrically braked ergocycle and connected to the exercise circuit through a mouthpiece. Five-breath averages of minute ventilation (VE) oxygen uptake (VO2) and carbon dioxide excretion (VCO2) were measured with the exercise circuit equipped with a pneumotachograph, oxygen and carbon dioxide analyzers, and a mixing chamber (Quinton Qplex, A-H Robins Company, Washington). After 5 mins at rest, a progressive stepwise exercise test was performed up to the individual’s maximum capacity (26). Each exercise step lasted 1 min, and increments of 10 or 15 W were used. During exercise, arterial blood samples were drawn at rest and at maximum exercise capacity to determine lactate concentration and blood gases.
**Statistical Analysis:** Patient's dead space volume (V_D) to V_E ratio was calculated as follows.

\[
V_D/V_E = \frac{V_E - V_A - V_{DE}^V}{V_E - V_{DE}^V}
\]

where \( V_E \) is the minute ventilation in litres; \( V_A \) is the alveolar ventilation:

\[
V_A = \frac{VCO_2 \times 0.0863}{PaCO_2}
\]

\( V_{DE}^V \) is the dead space of the apparatus, \( VCO_2 \) is expressed in mL/min, \( PaCO_2 \) is the arterial carbon dioxide pressure in mmHg and \( V_{DE}^V \) is 0.085 L multiplied by the respiratory rate.

Results are expressed as medians and ranges; median and range values were preferred because they reflect more accurately the tendencies of the two groups (one subject with AIRAO had outstanding performances on exercise test, modifying considerably the means for several measurements). Because variance and normality assumption were not met, unpaired \( t \) tests on transformed values in their ranks were used to compare duration of asthma, expiratory flows, bronchodilator response, lung volumes, DLCO, Cstat, Raw, median 0 pack-years).

Patients with COPD and AIRAO had significantly higher FEV1/FVC ratios (19% to 63%) and 59% (34% to 95%), respectively, in COPD patients and 53% (42% to 63%, \( P=0.058 \)) and 71% (49% to 98%, \( P=0.085 \)) respectively, in AIRAO patients (Figure 1). Postbronchodilator FEV1 and FVC were improved by 22.7% (~13% to 52%) and 15.6% (~20% to 48%), respectively, in COPD patients and by 18.5% (10% to 50%) and 14% (1% to 41%), respectively, in AIRAO patients (both \( P<0.05 \)). The FEV1 to FVC ratio was similar in COPD (0.51, 10% to 75% of predicted) and AIRAO patients (0.54, 37% to 63% of predicted).

TLC was slightly greater in COPD than in AIRAO patients (Figure 2). Residual volume (RV) (\( P=0.015 \)) and functional residual capacity (FRC) (\( P=0.042 \)) were significantly increased in COPD compared with AIRAO patients. DLCO was significantly lower in COPD patients, with a median baseline value of 58% of the predicted value compared with 90.5% of the predicted value in AIRAO patients (\( P=0.0024 \)). 10 COPD and four AIRAO patients had a baseline DLCO of less than 80% of predicted values. Median baseline Raw, \( s\)Gaw and Cstat were 4.1 (range 2.5 to 5.9) cm H2O/L/s, 0.05 (range 0.02 to 0.20) L/s/cm H2O, 0.169 (range 0.078 to 0.350) L/cm H2O, respectively, in the COPD group and 4.0 (range 3.0 to 6.9) cm H2O/L/s, 0.050 (range 0.04 to 0.08) L/s/cm H2O, 0.169 (range 0.078 to 0.350) L/cm H2O, respectively, in the AIRAO group (all \( P<0.05 \)).

**PEF:** Median daily changes in PEF were similar in patients with COPD and AIRAO, with respective changes of 22.6% and 13.0% (\( P=0.05 \); Figure 3). Maximum daily change in PEF observed over the two-week period was 35.0% in COPD and 21.9% in AIRAO patients (\( P=0.05 \)).

**HRCT findings:** Twelve patients with COPD and 13 with AIRAO agreed to have an HRCT; results were evaluable in 10 COPD and 12 AIRAO patients (T:D ratio only was measured in the other AIRAO patient; computed tomography scans were not evaluable because of the presence of linear artefacts [Table 2]). Bronchial dilations were found exclusively in AIRAO patients (n=6, \( P=0.011 \)). Bronchial wall thickening was found in both groups but was more frequent in AIRAO (n=8) than in COPD patients (n=2, \( P=0.023 \)); bronchial wall narrowing was observed only in four AIRAO patients (\( P>0.05 \)). Emphysematous changes occurred in all COPD patients, being discrete in two patients, moderate in five and important in two, while in patients with AIRAO,
Figure 1) Individual data and medians of expiratory flows in the two groups studied at baseline evaluation and after administration of 200 µg of inhaled salbutamol. BD Bronchodilator; COPD Chronic obstructive pulmonary disease; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; IRAO Incomplete reversibility of airflow obstruction; NS Not significant

Figure 2) Individual data and medians for total lung capacity (TLC), functional residual capacity (FRC), carbon monoxide diffusion (DLCO) and residual volume (RV). COPD Chronic obstructive pulmonary disease; IRAO Incomplete reversibility of airflow obstruction; NS Not significant
only two showed discrete manifestations of emphysema \((P=0.0007)\). Only five AIRAO patients presented focal areas of acinar pattern; this alteration was present and focal in one COPD patient \((P>0.05)\). T:D was similar in COPD \((0.18; \text{range } 0.11 \text{ to } 0.29)\) and AIRAO \((0.18, \text{range } 0.13 \text{ to } 0.21, \text{ } P=0.05)\) patients. No significant correlations were found between T:D and either DLCO or VO\(_{2}\text{max}\) or \(V_{\text{Emax}}\) (in percentage of predicted values).

**Exercise tests:** Eight COPD (four males and four females; mean age 59.4±2.2 years) and eight AIRAO patients (four males and four females; mean age 49.9±3.2 years, \(P=0.04)\) had an exercise test. Baseline and end of exercise parameters are given in Table 3. Median peak-minute ventilations were 47.8 and 57.4 L/min (102.7% and 89.5% predicted) in COPD and AIRAO patients, respectively, representing 117.5% and 91.5% of maximum voluntary ventilation (MVV), where \(\text{MVV}=\text{FEV}_1 \times 35\) \((27)\).

Maximum heart rate was slightly greater in AIRAO patients, but this difference did not reach statistical significance when expressed as percentage predicted. Although the median arterial oxygen saturation was lower at rest in COPD patients, this value was similar for both groups at end of exercise. In contrast, exercise hypercapnia was frequently observed in COPD patients with a median end of exercise \(PaCO_2\) value of 45.0 mmHg, which was significantly greater than the \(PaCO_2\) of 38.5 mmHg found in AIRAO patients \((P<0.05)\). The \(V_D\) to \(V_E\) ratio was significantly greater in COPD than in AIRAO patients, both at rest and at the end of exercise: respective median ratios were 0.56 (range 0.381 to 0.67) and 0.44 (range 0.31 to 0.53) at rest \((P=0.011)\) and 0.47 (range 0.31 to 0.59) and 0.35 (0.22 to 0.50) at the end of exercise \((P=0.049)\).

**DISCUSSION**

Little attention has been paid to the potential clinical and functional consequences of an irreversible component of airflow obstruction associated with long standing asthma. This condition is also difficult to differentiate from COPD and is confusing for the clinician. Therefore, a need exists to characterize the clinical, functional and radiological status of these patients and to compare these features with those of patients with smoking-induced COPD in order to determine whether different types of inflammatory damage to the airways have the same consequences \((11,12)\).

We found that for a similar degree of airflow obstruction, AIRAO differs from COPD in showing no reduction in DLCO, less hyperinflation and fewer parenchymal abnormalities. Exercise tolerance was similar in the two groups. Large airway wall thickness, as reported by the T:D of the intermediary bronchi, was similar in the two groups, although many patients with AIRAO showed evidence of small and medium airway wall thickening.

In the present study, we did not compare AIRAO with a control group of normal or asthmatic subjects with reversible airflow obstruction because this had been done previously \((9)\). Studies that compared histopathological airway changes in asthma and COPD have previously shown that apart from the associated air-space destruction, the main difference between the two conditions was the increased subepithelial collagen deposition and the increased number of lymphocytes, mast cells and eosinophils in asthma \((11,28)\).

The physiopathology of AIRAO without associated smoking-related COPD is still uncertain \((29)\), but some physiological and radiological features may help to distinguish the two conditions. In COPD, in contrast to AIRAO, DLCO capacity is reduced, possibly in relation to the frequent and severe parenchymal damage observed \((30)\). On the other hand, AIRAO is characterized by bronchial defects, including airway wall thickening, mostly at the level of small and intermediary bronchi. As indicated by similar T:D ratios, the large airways’ wall thicknesses were similar in the two groups. This can be explained by the type of inflammatory insult and the respective physiopathology of these diseases, involving the protease-inhibitor system and a neutrophilic inflammation in COPD, and an eosinophilic bronchitis with a more intense airway repair process \((\text{eg, collagen deposition})\) in asthma \((12,28,31)\).

Despite significant airflow obstruction, exercise capacity was relatively preserved in both groups. This illustrates the weak relationship between indexes of airflow obstruction and exercise capacity \((32)\). However, as in COPD, our data show that in asthma with fixed airflow obstruction, marked reduction in exercise tolerance may occur, although it is quite variable from one subject to another. In addition, the response to exercise was abnormal in both groups. As indicated
Radiological techniques have been used to investigate airway wall and parenchymal abnormalities in obstructive diseases. Previous studies of airway structural changes using HRCT have shown that patients with more severe asthma tended to have more irreversible abnormalities such as bronchiectasis, bronchial wall thickening and emphysema (37,38,39). Paganin et al (38) also showed that patients with nonallergic asthma seem to have more extensive remodelling of airways than allergic patients. Finally, observations of Okazawa et al (39) suggest that in asthma, small and medium calibre airways show an increased wall thickness that may contribute to the physiological abnormalities observed in these patients (39). With regard to COPD, previous publications have described different parenchymal alterations, but to our knowledge, these studies have not compared COPD with asthma, particularly with regard to airway and parenchymal changes (23,40).

Because there is a relationship between the severity of asthma and the HRCT abnormalities, and because patients with AIRAO included in the present investigation had moderate to severe disease, our results should not be extended to the entire asthmatic population. Nevertheless, our observations should help to better characterize this subpopulation of asthmatic subjects, indicating that asthma may sometimes lead to significant functional and airway structural changes of similar magnitude to those found in COPD. This suggests that airway inflammation, whether intense, of long duration or insufficiently treated, may be responsible for irreversible changes that lead to significant disability. Further studies of the long term outcomes of these asthmatic subjects would help to determine whether the rate of decline of pulmonary function is similar to that found in COPD patients who stopped smoking, as well as examine the influence of different treatment modalities on these outcomes (42).

In conclusion, although our two study groups had different types of anatomical and physiological impairment, the functional consequences of these two types of obstructive diseases were broadly similar.

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