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Perception of dyspnea in mild smoking asthmatics

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Summary

Background: Previous data from the literature reported blunted perception of airway obstruction in severe asthmatics with near fatal asthma. Approximately 25% of patients with asthma are current smokers.

Aim: To determine whether there is an alteration in perception of airway obstruction during a non specific provocative challenge with methacholine in mild controlled asthmatics who smoke.

Methods: Enrolled in this study were 50 subjects, including 26 mild asthmatics and 24 healthy subjects, all of them current smokers. The first objective was the sensitivity of airway obstruction calculated by the regression slope linking the change in the visual analogic scale (VAS) assessed by the patient and the fall in FEV_1 during a methacholine challenge.

Results: Asthmatics who smoke had a blunted perception of airway obstruction during the bronchial challenge significantly different from that seen in healthy smokers ($p = 0.03$). This impaired dyspnea perception was inversely related to baseline VAS ($r = -0.29$, $p<0.05$) and positively related to baseline FEV_1 ($r = 0.35$, $p<0.05$). Perception of airway obstruction was not correlated with age, sex, atopy or with airway inflammation features such as exhaled NO or sputum eosinophils.

Conclusion: Mild asthmatics who smoke display reduced dyspnea perception during a non-specific provocative challenge with methacholine. This altered perception of airway obstruction does not relate to airway inflammation.

Keywords

Dyspnea perception; Smoking; Asthma; Methacholine challenge

Introduction

The diagnosis and management of asthma is based on a combination of clinical symptoms and lung function measurement. However, altered perception of dyspnea, an important symptom of asthma, may well obscure the diagnosis[1] and lead to inappropriate asthma management thereby placing the patient at risk of severe exacerbations.

Evaluation of dyspnea is difficult because it is a subjective perception. Sensitivity of asthmatics towards symptoms like dyspnea is variable and patients can be classified in three different categories: the "poor perceivers", the "moderate perceivers" and the "high perceivers".[2,3] Dyspnea perception has been previously studied in asthma[4] and was reported to be associated to some degree with the presence of bronchial eosinophilic inflammation.[5,6] The links between near fatal asthma exacerbations and a blunted perception of symptoms were investigated and controversial findings have emerged.[2,7] In most studies, dyspnea perception was found to be higher in healthy subjects than in asthmatics but impaired dyspnea perception in asthma seems to be essentially limited to severe asthma.[4]

In developed countries, approximately 25% of asthmatic patients are current smokers.[8] Compelling evidence suggests that smoking makes asthma worse. In the USA, the rate of smokers among asthmatics is greater in adult asthmatics visiting emergency rooms for asthma attacks.[9] Inhalation of cigarette smoke at rates as low as CO_2 2ppm induces a significant fall of the FEV_1 in subjects with bronchial hyper reactivity.[10] Sippel et al.[11] reported a

worse quality of life and a poorer control of the disease in asthmatics who smoked. It was reported that severe asthmatics who smoke are at a higher risk of death from recurrent acute attacks than those who quit.[7] To date dyspnea perception in asthmatics who smoke has not been investigated well.

We hypothesized that altered dyspnea perception is a potential explanation of under treatment and poor control in asthmatics who smoke. We aimed in the present study to investigate dyspnea in mild smoking asthmatics during methacholine bronchial challenge. Furthermore, we sought any relationship between dyspnea perception and airway inflammation as assessed by sputum eosinophils and exhaled NO.

Subjects and Methods

Subjects

The asthmatic subjects included in this study were recruited among the patients attending our asthma clinic between October 2004 and April 2005, while healthy subjects were recruited among the hospital staff. Demographic and functional characteristics of both healthy subjects and asthmatics are given in Table 1. Both asthmatics and healthy subjects were current smokers as reflected by elevated urinary cotinine levels (Table 1). At the first contact, all patients were counselled and encouraged to try to give up smoking. Those who declined or failed were enrolled in the study. The asthmatics belonged to the category of intermittent or mild persistent controlled asthma according to the last GINA guidelines.[12] Asthma was diagnosed on the basis of a clinical history of recurrent symptoms of wheezing, coughing and breathlessness and the demonstration of a methacholine bronchial hyper reactivity with a PC20M<16mg/ml. None of the asthmatics had experienced severe asthma exacerbation in the past. The asthma was well controlled as revealed by a short asthma control questionnaire <1.5.[13,14] The healthy subjects all had a negative challenge with methacholine. Atopy was diagnosed on the basis of positive skin prick tests towards common aeroallergens of our area (mites, cat, dog, molds, grass and birch pollens). This study and its design were approved by the local ethic committee and all patients gave written, informed consent.

Methods

Study design

The study began with the skin prick tests followed by measurement of exhaled NO. Then the challenge with methacholine was carried out associated to evaluation of the perception of dyspnea on a visual analogic scale (VAS). The induced sputum was carried out the same day or a few days later.

Exhaled NO

We used a Niox® machine, recommended by the ATS, with a flow of 50 ml/s. The average of three successive measurements was retained and expressed in part per billion (pbb).

Bronchial methacholine challenge

Before starting with the bronchial methacholine challenge, a measure of the forced expiratory volume in 1 s (FEV_1) and vital capacity (VC) was carried out. Then the subject was asked to inhale for 1 min from several aerosols containing a solution of methacholine of fourfold increasing concentrations (from 0.06 to 16mg/ml). The nebuliser used was an ultrasonic type (Devilbiss 2000, Sommerset, USA). One minute after each aerosol, the subject was asked to produce a forced expiration in a spirometer. This measure was repeated twice and the best value of FEV_1 was saved. The fall of the FEV_1 was compared to the baseline value. The test was interrupted and considered as positive when the FEV_1 value fell by 20% or more compared to the baseline value. The program then calculated by interpolation the concentration of methacholine responsible for a reduction of 20% of the FEV_1. This concentration represented the PC20M.

Dyspnea perception

The two most current tools validated for dyspnea evaluation are the Borg scale and the VAS.[15,16] In this study, we used the 100 mm VAS with the words minimum and maximum on the left and right ends, respectively. After explanation of the VAS, the patient was invited to indicate the intensity of the dyspnea felt by a point (or a

vertical line) on the VAS. Dyspnea intensity was assessed before the test as 30 s after each inhaled methacholine concentration. At the end of the test, a linear regression was then applied between the variations of the VAS compared to the starting value and the fall of the FEV_1 expressed as a percentage of the initial value. A straight regression line was obtained. The slope represents the sensitivity to dyspnea of the patient. A strong sensitivity corresponds to a high value.

Sputum induction and processing

In order to obtain induced expectoration, the subject was invited to inhale a 5% hypertonic saline solution with ultrasonic nebulization for 3 × 5 min (Devilbiss, 2000, Som-merset, USA). An attempt at expectoration was carried out after each 5 min series after the subject had rinsed his mouth. The administration of 400 µg salbutamol before the test and during the saline inhalation (saline solution coupled to salbutamol) made it possible to avoid excessive bronch-oconstriction.[17] FEV_1 was measured every 5 min. A fall of more than 20% of the FEV_1 led to stopping the test. The sputa were treated by dilution in PBS for homogenisation and the cells treated the second time by a mucolytic agent (dithiothreitol or DTT.0.01M) before performing of cytos-pins. Cell differential was calculated after counting 400 non-squamous cells.

Statistical analysis

The results were expressed as mean (SEM) or median (IQR) following the distribution of the variables. For the continuous variables, a Mann-Whitney test was carried out to compare the two groups. For the nominal variables, we used the chi square test or the Fischer test. The correlations were sought by the coefficients of Pearson or Spearman according to the normal distribution or not of the variables. The threshold of significance was fixed at $p<0.05$. The statistical program used was Statistica 6.0.©

Results

There was no significant difference between groups with regard to age, sex, tobacco, urinary cotinin, atopy, and eNO ($p>0.05$ for each variable) (Table 1). By contrast smoking asthmatics had a raised sputum eosinophil count as compared with healthy smokers ($p<0.05$). No difference was noticed regarding the other sputum cell types. Baseline FEV_1, whilst in the clinically normal range in all subjects, was statistically lower in the asthmatic groups than in the healthy subjects ($p<0.05$). None had a ratio $FEV_1/FVC < 70\%$.

Maximal fall in FEV_1 at the end of the methacholine challenge was on average 27% (21.4-32.4%) in asthmatics vs. 8% (4-11.8%) in healthy subjects (Table 1).

***Table 1** : Demographic characteristics, functional and inflammatory characteristics of patients.*

Group variable	Asthmatics smokers *N* = 26	Non-asthmatics smokers *N* = 24
Sex ratio (M/F)	14/12	11/13
Age	38.5 (25-45)	24.5 (22-40.5)
Smoking history (pack-year)	7.9 (4-25)	5.1 (3-14)
Urinary cotinin (µg/l)	971 (776-1680)	1478 (671-1522)
Atopy	9	7
Inhaled steroids	7	0
Exhaled NO (ppb)	18.4 (9.8-28.5)	14.4 (10.7-24.8)
Baeline FEV_1 (% pred)	96.4 (89.3-106.5)	106.8 (100.9-116.1)
Maximal fall in FEV_1 (% of baseline)	26.95 (21.4-32.4)	7.7 (4-11.8)
PC20M (mg/ml)	3.49 (0.05-11)	>16
Sputum eosinophils (%)	1.0 (0.0-5.0)	0.0 (0.0-0.0)

The values are expressed in medians and IQ 25-75 for continuous variables without normal distribution. Median values for NO and FEV_1, values of the geometric mean for the PC20M and values of the median for the sputum eosinophils. IQ 25-75.

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Perception of dyspnea

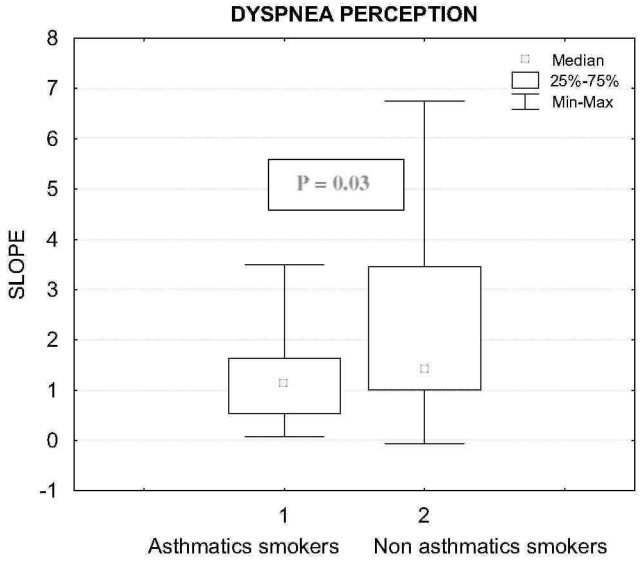
There was no significant difference between the groups with regard to baseline dyspnea assessed by baseline VAS. Smoking asthmatics displayed a lower perception of metha-choline-induced airway obstruction than healthy smokers as reflected by a lower slope value $\Delta VAS/\Delta FEV_1$ ($p = 0.03$) (Fig. 1). Neither the age, the sex nor atopy influenced the perception of dyspnea ($p>0.05$). Bronchial hyper responsiveness, as defined by PC20M, failed to correlate with the slope. Likewise, there was no correlation between dyspnea perception and exhaled NO and sputum eosinophils ($p > 0.05$). However, we found a weak, but significant correlation between the slope and baseline FEV_1 value ($r = 0.35$, $p<0.05$), and an inverse significant correlation between the slope and the baseline value on the VAS ($r = -0.29$, $p<0.05$).

Discussion

Blunted perception of dyspnea in asthmatics has often been described in severe asthmatics.[5] Our study shows that current smoking may alter the perception of airway obstruction induced by methacholine in a population of mild asthmatics. We did not include in this study nonsmoking asthmatics; however, we found significant results with altered dyspnea perception in smoking mild asthmatics compared with smoking non-asthmatics. Our data indicate that, in this population, the blunted perception appears to be independent of the extent of eosinophilic airway inflammation and bronchial hyperresponsiveness itself. This is an original finding that may cast light on some clinical observations.

The fact that smoking asthmatics poorly perceive acute airway obstruction is likely to lead to underreport of symptoms and thereby to a lack of recognition of asthma among smokers. Thus it is conceivable that, in daily practice, real asthma may be misdiagnosed as a tobacco related chronic airway disease. Obviously, the misdiagnosis could lead to poor management, placing the patient at risk of severe asthma exacerbation, which might even occur in very mild asthma.[18] Another risk is represented by the potential occurrence of a silent permanent airflow obstruction in those patients left without anti-inflammatory treatment for a variable period of time.[19]

Figure 1: *Dyspnea perception expressed as the slope of the regression line linking the change in VAS in mm from baseline to the change in FEV_1 in % fall from baseline.*



Altered corticosteroid sensitivity has been extensively reported in smoking asthmatics.[20] Most of the scheduled or unscheduled visits for asthma are symptoms, and more specifically, dyspnea driven. Thus, the blunted dyspnea perception found in the present study will prevent smoking asthmatics from seeking an early and appropriate antiinflammatory treatment. Furthermore, it can contribute to their lack of adherence to this therapy, which is a major concern in mild asthma.

Our results could also provide an explanation as to why the proportion of smokers remains surprisingly high in asthma as compared to that seen in the general population. The tolerance to the harmful effect of tobacco among mild asthmatic smokers could be partially explained by the reduced perception of bronchial obstruction. However, long duration smoking habits in asthmatics make them evolve later towards a non-reversible bronchial obstruction with an accelerated decline of respiratory function.[21] Indeed, asthma and tobacco are independent and additive factors contributing to the decline of the respiratory function.[22]

Smoking may contribute to the development and manifestations of severe asthma; asthmatic smokers are more symptomatic, have more severe and frequent exacerbations and emergency care needs; have a reduced response to corticosteroids; and a more rapid decline in pulmonary function. However, a recent wide study did not find a relationship of smoking to severity or an accelerated decline in FEV_1.[23] Therefore, strategies to encourage smoking cessation are an important aspect of mild and severe asthma management.

Massasso et al.[24] showed that the COPD smokers did not perceive the obstruction induced by methacholine as well as asthmatic non-smokers. They postulated that poor dyspnea perception in COPD smokers could be related to the effect of tobacco smoke on the bronchial sensory nerves neurotransmitters. Indeed, a chronic depletion of these neurotransmitters such as substance P would induce a dysfunction of these related sensory nerves.[25] Later Chanez et al.[26] did not find the same results in asthmatics and COPD patients. The results of Massasso could consequently reflect the effect of the COPD itself rather than that of smoking. The team of Ottanelli et al.[27] showed, moreover, that among moderate COPD smokers the perception of dyspnea during a test with methacholine was variable and independent of the smoking history of the patient.

In our study, the baseline FEV_1 was slightly correlated with the perception of dyspnea. So patients with a lower FEV_1 value, but nevertheless considered as clinically normal, had a blunted perception of dyspnea. Our results are in keeping with those reported by Bijl-Hoffland et al.[4] However, contrary to the previous authors, we did not find that severe bronchial hyper responsiveness was a risk factor for limited dyspnea perception. This suggests that smoking alters the relationship between bronchial hyper responsiveness and perception of airway obstruction. We also found an inverse relationship between the dyspnea perception induced by methacholine inhalation and baseline dyspnea. The more breathless the patient felt before starting the methacholine challenge, the less the methacholine induced airway obstruction was perceived.

In our study, the perception of dyspnea was not correlated to the eosinophils level in the induced sputum as opposed to what In't Veen et al.[5] found. But our study population in asthma included mild patients, whereas In't Veen studied severe asthmatics. Although slightly increased as compared with healthy subjects, the eosinophil count in our smoking asthmatics was rather low. Therefore, the range was narrower than in a group of severe asthmatics making a significant correlation unlikely. Similarly, no correlation was found between exhaled NO, a marker of airway inflammation, and dyspnea perception. But it is well established that exhaled NO is of little value in smoking asthmatics.[28] In line with this, our data show that smoking asthmatics had rather similar exhaled NO levels to healthy smokers.

We recognize that our study has some limitations in that we have assessed the bronchial hyper responsiveness towards a direct constricting agent, i.e. methacholine. It would also be of interest to investigate the relationship between dyspnea and airway obstruction caused by indirect agents such as adenosine or hypertonic saline.[29] Another limitation is the absence of comparison with non-smoking asthmatics, however, this study has shown some significant results without relation to inflammatory parameters. Blunted dyspnea perception during methacholine challenge in non-smoking mild asthma is already known.[30]

We conclude that mild asthmatics who smoke have an impaired perception of bronchial obstruction caused by methacholine inhalation compared to smoking non-asthmatics. This finding may explain, in part, the tolerance asthmatics may show to smoking.

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