ORIGINAL ARTICLE

Lung hyperinflation, perception of bronchoconstriction and airway hyperresponsiveness

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Abstract

Purpose: To compare the influence of underlying airway inflammation and lung hyperinflation on dyspnea during induced bronchoconstriction in subjects with mild asthma (or asymptomatic airway hyperresponsiveness (AAHR).
Methods: Fourteen mild asthmatic and 14 AAHR subjects had methacholine and 5'-adenosine monophosphate (AMP) challenges, and induced sputum analysis. Changes in inspiratory capacity (IC) and respiratory symptom scores were measured after challenges. Perception of respiratory symptoms was recorded on a modified Borg scale.
Results: The mean baseline FEV_1, IC, mean provocative concentration of methacholine inducing a 20% decrease in FEV_1 (PC_{20}), the mean PC_{20} AMP and median inflammatory cell counts were similar in both groups. After methacholine, mean (±SD) reductions in FEV_1 were 24.7±10.3% in mild asthma and 35.6±19.1% in AAHR (P>0.05); reductions in IC were, respectively, 10±12% and 24±20% (P>0.05); mean breathlessness scores at PC_{20} were 1.1 in mild asthma and 0 in AAHR P=0.003), and mean chest tightness scores were 1.2 in mild asthma and 0.8 in AAHR (P>0.05). Maximum chest tightness scores following MC correlated with the maximum decrease in IC in mild asthma (r_s=0.75,P=0.009) and with the maximum decrease in FEV_1 in AAHR (r_s=0.60,P=0.04). After AMP, symptom scores were not significantly correlated with decreases in FEV_1 or IC. The number of inflammatory cells was not correlated with decreases in IC after methacholine, AMP or with their PC_{20s}, although inflammation was minimal in both groups.
Conclusion: Lower breathlessness scores in AAHR compared to mild asthma were not explained by differences in lung hyperinflation nor in airway inflammation.
Keywords: Asthma, airway hyperinflation, inspiratory capacity, induced sputum

List of Abbreviations

AAHR	Asymptomatic airway hyperresponsiveness
AHR	Airway hyperresponsiveness
AMP	Adenosine 5'-monophosphate
ATS	American Thoracic Society
B	Breathlessness
CT	Chest tightness
BD	Bronchodilator
COPD	Chronic obstructive pulmonary disease
ECRHS	European Community Respiratory Health Survey
$FEF_{25-75\%}$	Forced expiratory flows 25-75%
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
IC	Inspiratory capacity
IS	Induced sputum
MC	Methacholine challenge
PC_{20}	Provocative concentration inducing a 20%

	decrease in FEV_1
RV	Residual volume
SD	Standard deviation
TLC	Total lung capacity
VO_{2max}	Maximal oxygen consumption

Although the degree of airway hyperresponsiveness (AHR) does not always correlate with clinical features, AHR is universally observed in symptomatic asthma.[1,2] A proportion of individuals with no history of asthma or other respiratory diseases, who have no current symptoms and are not taking any respiratory medication have an increased airway response to agents such as histamine or methacholine.[3-5] However, we do not know why these patients are asymptomatic in the presence of AHR.[6-8] One mechanism that could influence the perception of respiratory symptoms is dynamic lung hyperinflation. This is considered to be an important determinant of the sensation of dyspnea in obstructive airway diseases, as is airway inflammation.[9,10] The intensity of dyspnea during induced bronchoconstriction in asthma has indeed been associated with the reduction in inspiratory capacity (IC), as a result of lung hyperinflation.[10-12]

Another potential contributor to the absence of symptoms in asymptomatic AHR (AAHR) could be a lower grade of airway inflammation than in asthma.[13,14] Both airway inflammation and structural changes can contribute to AHR.[15,16] The degree of airway inflammation has previously been associated with the severity of clinical features of asthma, including the frequency of exacerbations.[17] We have suggested that AAHR is associated with airway remodeling and inflammation, but that these processes are less active in AAHR than in asthma and other diseases.[18] Moreover, airway challenges such as with methacholine cause airflow limitation principally by acting directly on airway smooth muscle, while indirect challenges, such as with adenosine 5'-monophosphate (AMP), act by increasing mediator release from mast cells. The latter have been shown to reflect better the overall degree of airway inflammation.[19] Comparative responses to AMP challenge and to methacholine challenge (MC) remain to be documented in AAHR.

We hypothesized that, for a given decrease in expiratory flows, subjects with AAHR have less dynamic hyperinflation following airway challenges than do mild symptomatic asthmatic subjects, as well as less airway inflammation as assessed by induced sputum (IS) analysis and AMP challenge. Such reduced change in lung volume would correlate with a reduced perception of respiratory symptoms after induced bronchoconstriction.

Methods

The study was approved by the institutional Ethics Committee and all subjects gave written informed consent.

Patients

Twenty-eight subjects (19 female, 9 male) participated in this study (Table 1). They were non-smokers or ex-smokers (n=6, <6 pack-year) for ≥1 year and had no respiratory infections in the previous 4 weeks.

AAHR was defined as a positive response to a provocative concentration (PC_{20}) of methacholine ≤16 mg/ml inducing a 20% decrease in forced expiratory volume in one second (FEV_1), and no past or present history of asthma symptoms or of asthma medication use. AHR was detected but subjects had no symptoms compatible with asthma. Subjects with AAHR were identified among volunteers recruited from the community by radio and newspapers advertising to act as normal controls for studies on asthma.

Subjects with mild asthma had current symptoms compatible with asthma, such as chest tightness, breathlessnness, cough, phlegm production and/or wheeze, and a positive MC. Baseline FEV_1 was ≥70% of the predicted value and asthma was stable, requiring only inhaled short-acting β_2-agonist on demand to control symptoms. None had received an anti-inflammatory agent for at least 3 months nor had used nasal or inhaled corticosteroids in the previous month or during the study. They were recruited from the outpatient and asthma clinics of Laval Hospital, Quebec, Canada.

TABLE 1. Subject characteristics

	Asthma (n=14)	AAHR (n=14)	P
Age (yr) (range)	27 (20-41)	28 (20-46)	0.87
Baseline FEV_1*	101.7 ± 10.3	95.9 ± 13.2	0.20
Baseline FVC*	110.6 ± 8.8	99.0 ± 13.6	0.01
Baseline $FEF_{25-75\%}$*	98.4 ± 24.3	99.5 ± 20.2	0.90
Baseline IC*	104.1 ± 18.9	101.0 ± 18.4	0.67
PC_{20} on screening methacholine(mg/ml) (Mean and range)	2.19 (0.30-16)	4.15 (1.78,9.68)	0.13

AAHR = asymptomatic airway hyperresponsiveness; FEV_1 = forced expiratory volume in one second; $FEF_{25-75\%}$ = forced expiratory flows between 25-75% of FVC; FVC = forced vital capacity; IC = inspiratory capacity; PC_{20} on screening methacholine = provocative concentration of methacholine inducing a 20% decrease in FEV_1.

*Data are presented as mean % of predicted values ± SD

Order of Testing

Each subject made 4 visits to the laboratory within a 15-day period. The visits were done at the same time of day at intervals of at least 24 hr. Visit 1 was a screening visit while Visits 2 to 4 were conducted in random order.

During Visit #1 all subjects underwent an evaluation, including the administration of a respiratory questionnaire to confirm the asymptomatic or asthmatic status. Expiratory flows, including FEV_1, forced vital capacity (FVC), IC and a standard tidal breathing MC were conducted, with quantification and qualitative evaluation of induced-symptom scores. Following MC, an IS was obtained for analysis of differential cell counts. The European Community Respiratory Health Survey (ECRHS) respiratory symptom questionnaire was administered.[20]

Visit #2 included an AMP inhalation test with measurements of FEV_1, FVC, IC and induced symptom scores.

On Visit #3, body plethysmography was conducted to assess total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) and IC. FEV_1 and FVC were measured pre- and post-bronchodilator (bd). The $\Delta FEV_1/\Delta FVC$ bronchodilator response (post- minus pre-bd) was recorded to evaluate flow-dominant responders (ratio >1) and volume-responders (ratio <1).[21]

During Visit #4 a standard tidal breathing MC was conducted with measurement of FEV_1, FVC, IC and symptom scores.

Measurement of Expiratory Flows

Spirometry was performed with an ATS-approved spirometer (Medisoft, Dinant, Belgium). according to standard recommendations[22] and using Knudson's predicted values.[23]

Evaluation of Symptoms

Respiratory symptoms were evaluated during the tests using a modified Borg scale ranging from 0 (no symptoms) to 10 (maximum bearable symptoms).[24] At baseline and after each inhalation of methacholine and AMP.[25], a list of five symptoms: breathlessness (B), chest tightness (CT), phlegm production, wheeze and cough was shown to the subjects. They were asked if they presently experienced any symptoms on the list and had to evaluate separately each symptom in the order of their choice.

Methacholine Challenges

Methacholine challenges with concentrations up to 16 mg/ml were conducted according to standardized methods, with measures of symptom scores.[26]

Induced Sputum Analysis

Sputum was obtained with hypertonic saline as previously described.[27,28] Subjects inhaled increasing concentrations of saline (3 to 5%) for 7 minutes each through a mouthpiece without a valve or nose clip, after which differential cell counts were obtained.

AMP Inhalation Test

Airway responsiveness to doubling concentrations of AMP, up to 320 mg/ml, was measured using the 2-minute tidal breathing method for histamine applied to AMP.[1,29]

Statistical Analysis and Sample Size Calculation

Based on previous studies reporting changes in dynamic lung hyperinflation in asthma, it was estimated that 14 subjects per group would be sufficient to observe significant differences between groups.[10] The PC_{20} values (methacholine, AMP) were log-transformed before analysis. Subjects with PC_{20} >320 for AMP were considered equal to 320 to calculate the mean PC_{20}; the mean PC_{20} is thus underestimated in both groups. Results are expressed as mean ± SD for expiratory flows and volumes and as median and range for cell differentials. Borg scores for symptoms at PC_{20} were calculated by interpolation of the scores at nearest decreases of FEV_1 below and above 20%.[30] Baseline values of FEV_1 for the tests were compared by ANOVA and an unpaired-t test was used for comparisons between groups. Symptom scores were compared by Mann-Whitney U two-sample test. Relationships between pulmonary function parameters, symptom scores and airway inflammation (sputum eosinophilia) were estimated by linear regression analysis or Spearman rank correlation.[30] *P* values <0.05 were considered significant. For multiple comparisons, the Bonferroni correction was applied.

Results

Subject Characteristics at Baseline

All subjects had a PC_{20} methacholine ≤16 mg/ml. There were no differences between asthma and AAHR subjects with respect to baseline FEV_1, $FEF_{25-75\%}$ and IC (*P*>0.05, Table 1). FVC was lower in AAHR than in asthma subjects (*P*=0.01).

Airway Inflammation

Airway inflammation was generally minimal in all subjects, as assessed by cell-count analysis of induced sputum, and there was no difference in airway inflammation between those with asthma and with AAHR. Median cell counts for asthma and AAHR subjects, respectively, were: eosinophils — 0.25% (range 0-4) and 0.25% (0-27); neutrophils — 27% (3-69) and 30% (7-67); macrophages — 66% (28-94) and 69% (29-79); lymphocytes — 1.75% (<1-4) and 3.3% (0-47); and bronchial cells — 0.5% (0-8) and 0.5% (0-4). Numbers of inflammatory cells were not significantly correlated with maximum decreases in FEV_1 or with IC on MC or AMP challenge, nor with PC_{20} methacholine or PC_{20} AMP.

Pulmonary Function

The only difference found between subjects with AAHR and those with asthma with respect to baseline lung volumes was the FVC that was slightly lower in subjects with AAHR (*P*=0.04) (Table 2).

The mean $\Delta FEV_1/\Delta FVC$ was 2.2 ± 1.7 in subjects with asthma and 0.4 ± 2.2 in those with AAHR (*P*=0.019). The 13 asthma and 7 AAHR subjects were flow-dominant responders, while the others were volume responders.[21] The mean increase in FEV_1 post-minus pre-bd was 243 ± 78 ml for the asthma subjects and 151 ± 143 ml for the AAHR subjects (*P*=0.04), while the mean change in FVC was, respectively, 142 ± 69 ml and 14 ± 216 ml (*P*=0.04).

Direct and Indirect Challenges

Mean PC_{20} methacholine was 3.83 (-1SD = 1.15, +1SD = 12.7) mg/ml in subjects with asthma and 4.22 (1.16, 15.4) mg/ml in subjects with AAHR (*P*>0.05). Maximum decreases in FEV_1, $FEF_{25-75\%}$ and FVC were not different between the two groups (Table 3)

Mean PC_{20} on AMP test was 24.8 (range 2-294) mg/ml in subjects with asthma and 87.5 (15->320)

TABLE 2. Expiratory flows and lung volumes (body plethysmography)

	Asthma (n = 14)	AAHR (n = 14)	P
FEV_1*	101.4 ± 10.1	96.7 ± 10.8	0.24
FVC*	106.6 ± 8.6	99.1 ± 10.1	0.04
$FEF_{25-75\%}$*	89.2 ± 16.1	93.9 ± 22.8	0.54
IC*	108.5 ± 13.8	101.4 ± 19.1	0.28
Total lung capacity* (TLC)	104.5 ± 12.2	97.4 ± 12.6	0.14
Functional residual capacity (FRC)	103.1 ± 20.2	100.3 ± 15.6	0.69
FEV_1 improvement post-bd (%)	6.0 ± 3.2	3.2 ± 6.3	0.18

AAHR = asymptomatic airway hyperresponsiveness; FEV_1= forced expiratory volume in one second; $FEF_{25-75\%}$ = forced expiratory flows 25-75%; FVC = forced vital capacity; IC = inspiratory capacity; and bd = bronchodilator
* Data are presented as mean % of predicted values ± SD

TABLE 3. Maximum decreases in FEV_1, IC, $FEF_{25-75\%}$ and FVC following MC and AMP challenge *

		Asthma (n = 14)	AAHR (n = 14)	*P*
FEV_1	MC	24.7 ± 10.3	35.6 ± 19.1	0.07
	AMP	20.8 ± 9.3	11.1 ± 20.7	0.12
IC	MC	10.2 ± 12.1	24.0 ± 20.0	0.04
	AMP	10.1 ± 12.6	0.6 ± 23.5	0.14
$FEF_{25-75\%}$	MC	35.2 ± 19.3	37.9 ± 18.6	0.71
	AMP	14.5 ± 33.3	15.1 ± 23.9	0.96
FVC	MC	14.4 ± 10.0	26.0 ± 18.4	0.05
	AMP	11.8 ± 8.6	9.8 ± 9.8	0.57

AAHR = asymptomatic airway hyperresponsiveness; MC = methacholine challenge; AMP = adenosine 5'-monophosphate test; FEV_1 = forced expiratory volume in one second; $FEF_{25-75\%}$ = forced expiratory flows 25-75%; FVC= forced vital capacity; and IC = inspiratory capacity.
*Data are presented as mean % decreases ± SD

mg/ml in those with AAHR (*P*=0.08). Eleven subjects with asthma and 7 with AAHR had a decrease in FEV_1 of ≥20%. At baseline, no respiratory symptoms were reported in either group. Maximum decreases in FEV_1, $FEF_{25-75\%}$, IC and FVC were not different between the two groups. PC_{20} AMP was not correlated with baseline IC in either study group.

Correlations between Tests

PC_{20} MC and PC_{20} AMP were correlated in AAHR (r=0.67, *P*=0.008) but not in asthma (r=0.22, *P*=0.46). There were no correlations between the responses to MC and AMP for the maximum decrease in FEV_1, IC, $FEF_{25-75\%}$, and FVC induced by each of these tests (*P*>0.05).

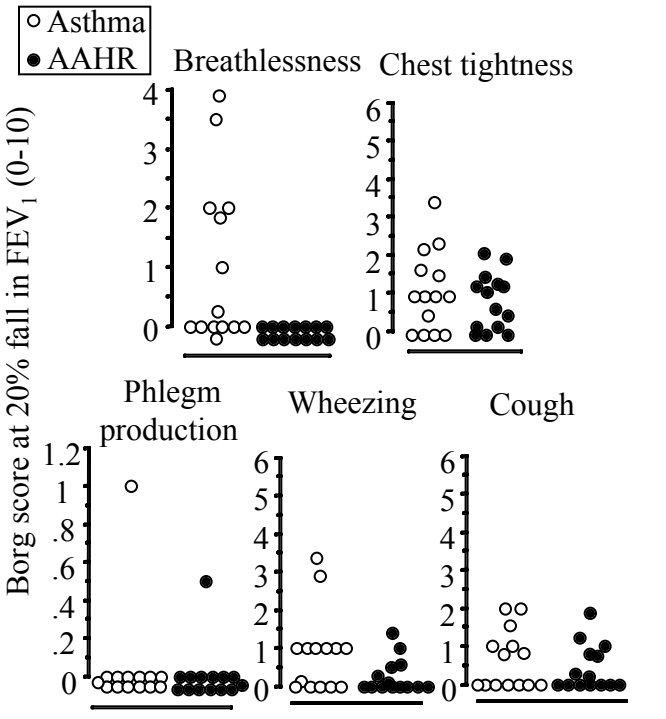

FIGURE 1. Comparison of symptom scores at PC_{20} MC between subjects with asthma and those with asymptomatic AHR. Although subjects with AAHR did not perceive breathlessness, their perception of other asthma symptoms was similar to that perceived by subjects with asthma.

Perception of Induced Bronchoconstriction

Before MC, there were no differences in the perception scores for symptoms at baseline (no symptoms in both groups, $P>0.05$). Furthermore, mean perception scores at 20% decrease in FEV_1 were greater in subjects with asthma than in those with AAHR for breathlessness with scores of, respectively, 1.1 (range 0-4) and 0 ($P=0.003$), while symptoms of chest tightness, with respective mean scores of 1.2 (0-4) and 0.8 (0-5); phlegm production: 0.07 (0-1) and 0.04 (0-0.5); wheeze: 0.9 (0-5) and 0.3 (0-3), and cough:0.7 (0-2), and 0.4 (0-5) were similarly perceived in both groups (Fig. 1, $P>0.05$).

The asthma group had higher maximum symptom scores for breathlessness than the group with AAHR (respectively, mean:1.0, range 0-3.5 and 0 ; $P=0.007$); other maximum symptom scores were similar in both groups. Maximum respiratory symptom score for chest tightness (mean:1.5, range 0-4, in asthma subjects and mean: 2.3, 0-7 in AAHR subjects; $P>0.05$).

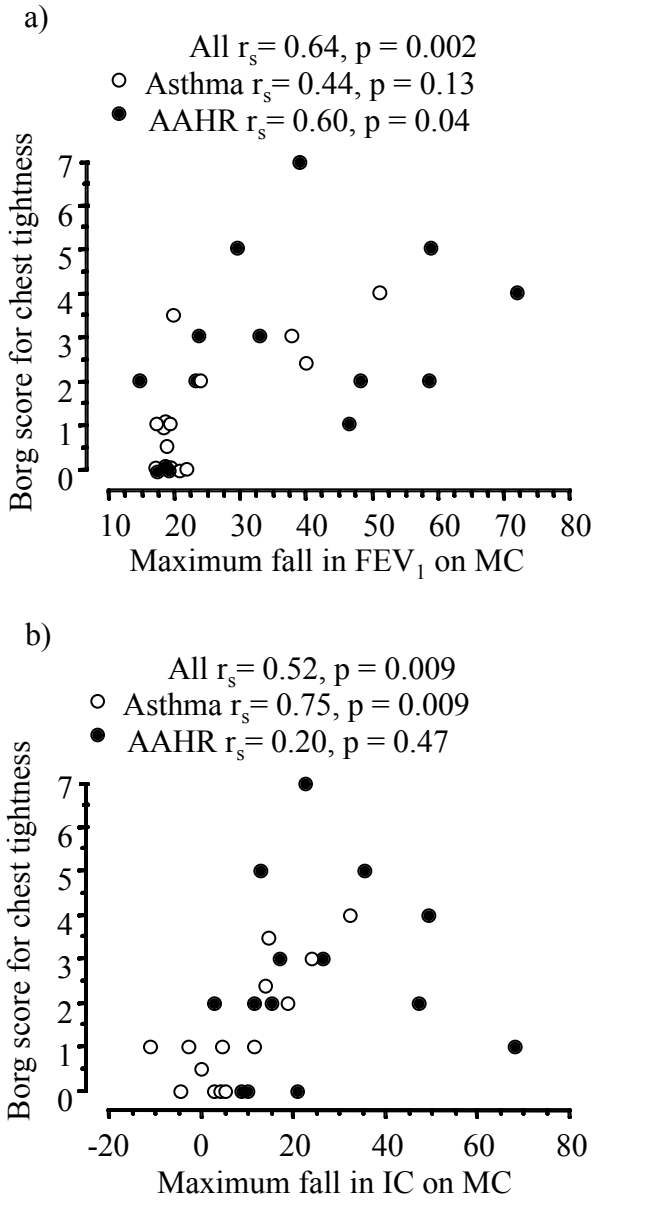

FIGURE 2. (a) Maximum scores for chest tightness following MC were correlated with the maximum decrease in FEV1 in subjects with AAHR but not in those with asthma. (b) Maximum scores for chest tightness following MC were correlated with the maximum decrease in IC in subjects with asthma but not in those with AAHR.

was correlated with the maximum decrease in FEV_1 in subjects with AAHR (r_s=0.60, *P*=0.04) (Fig. 2a) and with the maximum decrease in IC in asthma subjects (r_s=0.75, *P*=0.009) (Fig. 2b). The maximum perception score for cough in AAHR subjects correlated with maximum decrease in FEV_1 (r_s=0.97, *P*=0.005). Other symptom scores were not significantly correlated with the maximum decreases in FEV_1 or in IC on MC in either group.

AMP challenge

Mean perception scores for breathlessness at PC_{20} were greater in subjects with asthma than in those with AAHR: 2.6 (range 0-9.0, n=11) and 0 (0, n=7) (*P*=0.002); while symptoms of chest tightness: 1.7 (range 0-6.4) and 1.3 (0-4.9), phlegm production: 1.4 (0-9.0) and 0.7 (0-3.0), wheeze: 1.9 (0-9.0) and 0.7 (0-3.8), and cough:1.9 (0-6.0) and 1.2 (0-3.2) were similarly perceived in both groups (*P*>0.05). In both groups maximum respiratory symptom scores were not significantly correlated with the maximum decrease in FEV_1 or in IC following AMP challenge.

Comparisons of symptom scores on MC and AMP challenge

Symptom scores for breathlessness, chest tightness, phlegm production and wheeze at PC_{20} were not different following MC or AMP challenge in subjects with asthma or in those with AAHR. Cough was perceived more intensely after AMP than after MC in subjects with asthma (*P* = 0.007) but not in those with AAHR (*P* = 0.08). Symptom scores for chest tightness at PC_{20} after MC were slightly correlated with those obtained at PC_{20} after AMP challenge in the whole but not in subjects with asthma or AAHR separately (all subjects: r_s= 0.49, *P* = 0.04; Asthma: r_s= 0.51, *P* = 0.11 (n=11); AAHR: r_s= 0.49, *P* = 0.19 (n=7)). No correlations were observed for the other symptoms between MC and AMP challenge.

Discussion

We found a lower perception score for breathlessness following methacholine and AMP- induced bronchoconstriction in subjects with AAHR than in those with asthma. However, those scores were not correlated with the changes in IC or with the degree of airway inflammation. We also observed that, in subjects with asthma, at maximum decrease in IC following MC, but not in those with AAHR, symptoms of chest tightness correlated with the change in IC although no difference was observed in the perception of chest tightness between both groups. Besides, in subjects with AAHR, symptoms of chest tightness and of cough correlated with the maximum decrease in FEV_1.

Baseline and MC induced dynamic hyperinflation, and the degree of airway inflammation assessed by induced sputum and AMP challenge, were similar in the two groups of subjects. Therefore, our hypothesis that a smaller degree of dynamic hyperinflation resulting from a milder inflammatory process in subjects with AAHR than in patients with asthma could explain the absence of symptoms in AAHR subjects cannot be retained. Although the mean decrease in IC after MC in AAHR subjects was more than twice what was observed in subjects with asthma, AAHR subjects did not perceive breathlessness while those with asthma did.

The lack of an association between the breathlessness score and the change in IC during methacholine challenge in asthma is not in keeping with previous observations and may be due to the milder type of asthma in the study subjects: changes in FRC, assessed by the changes in IC, may have not occurred in our subjects because of insufficiently severe airflow obstruction, the subjects having sufficient time to exhale completely.[10]

In acute asthma, persistent inspiratory muscle activity during exhalation may also increase FRC and be a source or a consequence of breathing discomfort. The low degree of bronchoconstriction in the present study may account for the differences observed with previous studies. However, it was likely sufficient to reflect current day-to-day changes in airway calibre, at least in asthma.

Chest tightness has been considered specific to asthma, and in this regard we found that perception scores for this symptom following methacholine challenges were correlated with the maximum decrease in

IC in asthma subjects only.[31] Our observation that the degree of inflammation evaluated by IS analysis did not correlate with PC_{20} AMP, as previously reported, could be explained by the mild degree of inflammation in our subjects.[32,33] Furthermore, since IS primarily evaluates inflammation in medium-sized and large airways[34], peripheral airway inflammation — which could not be detected by IS — could have contributed to the observed IC changes in this study.

Chest tightness and dynamic hyperinflation are not always correlated. Moy et al demonstrated that symptoms of chest tightness, when subjects undergo methacholine challenge, could occur at very mild degrees of bronchoconstriction.[35] Binks et al showed that chest tightness may occur in association with bronchoconstriction, in subjects ventilated passively on a mechanical ventilator and that production of an elevated FRC with ventilator generated positive end expiratory pressure did not result in chest tightness.[36] Furthermore, Taguchi et al suggested that dyspnea sensation may result from stimulation of airway receptors when they observed a reduced sensation of dyspnea during histamine-induced bronchoconstriction under airway anesthesia by lidocaine aerosol inhalation.[37]

We observed a correlation between maximum decreases in FEV_1 and IC following MC, but again, breathlessness scores were not correlated with the decrease in IC. This could be due to the limited number of patients or to the presence of mechanisms other than volume changes. Subjects with asthma were mostly flow-dominant responders, suggesting an improvement post-bronchodilation primarily in large airway resistance.

PC_{20} methacholine and PC_{20} AMP were not correlated in asthma and respiratory symptoms at PC_{20} for these two stimuli were not correlated in asthma nor in AAHR, suggesting, as previously described, that both challenges do not reflect the same airway features.[38,39]

Previous studies had shown an increased perception of symptoms during indirect challenges such as AMP in comparison with methacholine challenge, possibly due to release of mast cell mediators and activation of airway sensory nerves.[39-41] In our study, only cough was increased in subjects with asthma after AMP. However, although they were not significantly different, mean symptom scores were slightly higher at PC_{20} AMP than at PC_{20} methacholine. The absence of differences between the perception of respiratory symptoms at PC_{20} methacholine and PC_{20} AMP in our study could be explained by the low degree of airway inflammation in our subjects.

In summary, no differences were found between asthma and AAHR groups in baseline or dynamic lung hyperinflation, airway inflammation from induced-sputum analysis, and lung volumes. Breathlessness scores were lower in subjects with AAHR than in those with asthma after MC and AMP challenge but changes in IC did not explain this feature. Symptoms of chest tightness correlated with the degree of hyperinflation in subjects with asthma following MC suggesting, at least in these subjects, an influence of the degree of hyperinflation on the perception of this symptom while perception of chest tightness and of cough in subjects with AAHR was related to changes in FEV_1 but not to those in inspiratory capacity. This, added to the fact that subjects with asthma but not those with AAHR perceived breathlessness at PC_{20} methacholine and PC_{20} AMP, may suggest a different sensitory threshold in both groups of subjects in detecting variations in these respiratory parameters.

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