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A comparison of airway responsiveness in smokers with chronic bronchitis and in asthmatic subjects

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A comparison of airway responsiveness in smokers with chronic bronchitis and in asthmatic subjects. T. Engel, J.H. Heinig, O. Madsen, M. Hansen, E.R. Weeke.

ABSTRACT: Fifty two of 95 smokers with a forced expiratory volume in one second (FEV_1) above 70% predicted and with chronic bronchitis were found to have increased bronchial responsiveness, expressed as $PC_{20}FEV_1$, upon challenge with inhaled histamine. The degree of responsiveness was significantly below that found in matched asthmatics, but substantially higher than that reported in normals. The degree of responsiveness was significantly correlated to prechallenge ventilatory capacity, age and tobacco consumption but not to sex. $PC_{40}MEF_{50}$ showed the same distribution as $PC_{20}FEV_1$, but did not add further information. The slope of the dose response curve expressing the maximum expiratory flow at 50% of vital capacity expired (MEF_{50}) did not correlate with any of the parameters measured. The slope of the FEV_1 dose-response curves showed significant correlation with tobacco consumption. The degree of bronchial responsiveness as an indication for future disability needs to be investigated.

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Airway hyperresponsiveness is a characteristic feature of asthma [1], but occurs in other diseases, *e.g.* allergic rhinitis [2], and is seen in normals after respiratory tract infections [3]. Subjects with chronic bronchitis with reduced forced expiratory volume in one second (FEV_1) often have increased bronchial responsiveness [4–6], which may, at least in part, be due to the narrowed airways [7]. There is, however, no general acceptance concerning the existence and degree of responsiveness in subjects with chronic bronchitis and normal ventilatory capacity, and only limited data comparing bronchial responsiveness in asthmatics and subjects with chronic bronchitis are available [8]. The present study was, therefore, undertaken to characterize the responsiveness in smokers with chronic bronchitis with FEV_1 above 70% predicted, compared to that obtained in matched asthmatics.

Material and methods

Bronchitic subjects

Advertising in the local newspapers for "smokers with cough" resulted in applications from 207 persons, 127 of whom had a history of chronic bronchitis, defined as cough and expectoration for at least three months a year for at least the last two years [9]. None of the 127 subjects had a history of asthma or allergic rhinitis, airway infection during the last 6 weeks, or treatment with glucocorticoids during the last year. We excluded 13 atopic subjects due to elevated serum IgE or blood- eosinophilia, or positive skin prick tests, 15 due to an FEV_1 less than 70% predicted [10], and three due to both. One patient was excluded due to cardiac failure. The material therefore consists of 95 subjects with chronic bronchitis (table 1).

All subjects smoked at least 5 cigarettes each day or a corresponding amount of pipe tobacco, cigarillos or cigars. The total consumption of tobacco was expressed as pack-years, *i.e.* the average number of cigarette packs (20 cigarettes each) a day, multiplied by the duration in years [11]. The men were significantly heavier smokers than the women ($p<0.0001$, Mann-Whitney test).

None of the bronchitic subjects had symptoms of farmers' lung or other pulmonary diseases, apart from bronchitis. Chest X-rays were normal in all 95 subjects.

Asthmatic patients

For comparison we selected patients with chronic asthma followed at the Allergy Clinic [12]. Seventy nine such patients were selected regarding sex, age±10 yrs, and FEV_1 % predicted±3% (table 1). In spite of the selection procedure, the asthmatics were significantly younger ($p<0.01$, Mann-Whitney test). No proper controls were available for the remaining sixteen bronchitic subjects.

Table 1. – Descriptive data of bronchitic and asthmatic subjects

	Bronchitics	Asthmatics
Number of subjects	95	79
Age yrs	46.9 (30–60)	42.7 (21–65)
Sex M/F	55/40	38/41
Smokers/nonsmokers	95/0	41/38
Pack-years (smokers only)	31.4 (6–78)	12.2 (1–60)
Atopy +/-	0/95	36/43
FEV_1 *l*	3.00 (1.57–5.25)	2.96 (1.37–5.56)
FEV_1 % predicted	104.3 (74–153)	101.3 (70–152)
FEV_1/FVC	78 (55–95)	78 (58–94)
Concurrent medication:		
Inhaled β_2-agonists	4	79
Inhaled anticholinergics	0	0
Oral theophyllines	0	6
Oral β_2-agonists	0	1
Inhaled steroids	0	29
Oral steroids	0	1

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; M: male; F: female; median (and range in parentheses).

Ventilatory capacity

Measurements of the ventilatory capacity included FEV_1, peak expiratory flow (PEF), maximum expiratory flow, 50% of vital capacity expired (MEF_{50}), and forced vital capacity (FVC). The measurements were made on a recently calibrated dry wedge spirometer (Vitalograph Ltd, Buckingham, UK). MEF_{50} was calculated from flow-volume curves obtained on a recently calibrated Monaghan M403 flow monitor (Monaghan Co., Littleton, Colorado, USA) interfaced to a Nicolet 3091 oscilloscope and a XY-plotter. All manoeuvres were repeated until 3 consecutive measurements showed a variation of 5% or less, or a maximum of 8 attempts was reached.

Bronchial histamine challenge

Bronchodilating drugs were withheld for 6 h, tobacco for 4 h, and other medication, if any, was withheld prior to the challenge [13], which was performed with a jet nebulizer (Pari Inhalier boy, airflow 11 $l \cdot min^{-1}$, output 0.27±0.03 $ml \cdot min^{-1}$ (mean±SD) (measured at the Allergy Clinic), particle size 0.5–5.5 μm (manufacturer's declaration). Inhalations were performed for 2 min with 5 min interval. After inhaling isotonic saline, the subjects inhaled increasing doses of unbuffered histamine dihydrochloride, alternating with measurement of ventilatory capacity 60 s after termination of inhalation. The starting histamine concentration was 0.125 $mg \cdot ml^{-1}$ in the bronchitics and 0.03 $mg \cdot ml^{-1}$ in the asthmatics. If a 20% decrease in FEV_1 had not yet been obtained, the test was discontinued after inhalation of histamine dihydrochloride 8 $mg \cdot ml^{-1}$ [14]. The result was expressed as the concentration of histamine causing a 20% decrease in FEV_1 compared to the FEV_1 value after inhaling isotonic saline ($PC_{20}FEV_1$) using interpolation on the log dose response curve. Values above 8.0 $mg \cdot ml^{-1}$ were reported as '>8' $mg \cdot ml^{-1}$. The results were graded as high ($PC_{20}FEV_1$ ≤0.125 $mg \cdot ml^{-1}$), moderate ($PC_{20}FEV_1$ ≤1 $mg \cdot ml^{-1}$), light ($PC_{20}FEV_1$ ≤4 $mg \cdot ml^{-1}$), or no responsiveness ($PC_{20}FEV_1$ >4 $mg \cdot ml^{-1}$) [1]. Since our nebulizer had twice the output of the Wright nebulizer, our results can be compared with those obtained with a Wright nebulizer by multiplying our histamine concentration by 2, *e.g.* results obtained from 4 $mg \cdot ml^{-1}$ of histamine dihydrochloride with the Pari Inhalier boy correspond to approximately 8 $mg \cdot ml^{-1}$ with the Wright nebulizer. $PC_{40}MEF_{50}$ was calculated and graded in the same way as $PC_{20}FEV_1$. $PC_{40}MEF_{50}$ was not available for the asthmatic patients.

The slopes were available only when a definite PC-value was obtained, and were calculated where the corresponding PC-value was read.

The reproducibility of the inhalation procedure was measured in 17 subjects by repeated bronchial histamine challenges with two weeks' interval, $r=0.76$, $p<0.001$ (Wilcoxon test). All bronchial histamine challenges were carried out during the period November–April.

Concurrent allergies

All subjects underwent skin prick testing [15] with a panel of the most common inhalant allergens in Denmark: pollen (birch, timothy, mugwort), animal dander (horse, dog, cat), house dust mite (*Dermatophagoides pteronyssinus*), and fungi (*Cladosporium herbarum* and *Alternaria alternata*) (SoluPrick®, ALK, Copenhagen, Denmark). A positive skin prick test was defined as one or more reactions ≥ 3 mm in diameter. Blood eosinophils were counted in a chamber, the normal value was less than 400×10^6 eosinophils per litre of whole blood. Total serum IgE was measured by the paper radioimmunosorbent test (PRIST) method, the normal value was less than 100 $kU \cdot l^{-1}$

Statistics

The Mann-Whitney rank-sum test was used for unpaired comparisons, and the Wilcoxon matched-pairs rank-sum test for paired data. Correlation analyses were performed by the Spearman rank correlation analyses. All $PC_{20}FEV_1$ and $PC_{40}MEF_{50}$ values were logarithmically transformed (log_{10}) prior to statistical analysis.

Table 2. – Correlation coefficients (r) and level of significance (p) for bronchitic (normal letters) and asthmatic (italics) subjects. $PC_{20}FEV_1$ values were logarithmically transformed prior to analysis

		Bronchitic subjects				
Asthmatic patients		$PC_{20}FEV_1$	FEV_1 % predicted	FEV_1/FVC	Age	Tobacco pack-years
$PC_{20}FEV_1$	r=		0.27	0.22	-0.32	-0.21
	p=		0.006	0.020	0.001	0.033
FEV_1 % predicted	r=	*0.38*		0.48	-0.32	-0.11
	p=	*0.000*		0.000	0.001	0.170
FEV_1/FVC	r=	*0.51*	*0.56*		-0.23	-0.02
	p=	*0.000*	*0.000*		0.013	0.424
Age	r=	*0.04*	*-0.27*	*-0.22*		0.48
	p=	*0.366*	*0.007*	*0.041*		0.000
Tobacco pack-years	r=	*0.15*	*-0.21*	*0.14*	*0.18*	
	p=	*0.100*	*0.030*	*0.144*	*0.060*	

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; $PC_{20}FEV_1$: concentration of histamine producing a 20% fall in FEV_1.

Results

Six subjects with chronic bronchitis were unable to accomplish the entire bronchial histamine challenge due to cough and discomfort. Eighty nine completed bronchial histamine challenges showed that none had highly, 19 (21%) had moderately, 33 (37%) had lightly responsive airways, and 37 (42%) had non-responsive airways (fig. 1) [1].

Even though FEV_1 was above 70% predicted in all 95 subjects with chronic bronchitis, FEV_1/FVC was less than 0.70 prior to histamine challenge in 28. No significant differences in $PC_{20}FEV_1$, sex, or tobacco consumption (p=0.08, 0.33 and 0.63, respectively, Mann-Whitney test) could be demonstrated when subjects with an FEV_1/FVC above 70% were compared to those with an FEV_1/FVC less than 70%. However, subjects with an FEV_1/FVC less than 70% were significantly older (p<0.01, Mann-Whitney test). Since the results for subjects with FEV_1/FVC above and below 70% showed no major differences, all data were analysed together.

$PC_{20}FEV_1$ in the 79 asthmatics was found to be significantly lower as compared to the subjects with chronic bronchitis (geometric mean 0.75 mg·ml^{-1} and 2.88 mg·ml^{-1}, respectively) (p<0.001, Mann-Whitney test) (fig. 1).

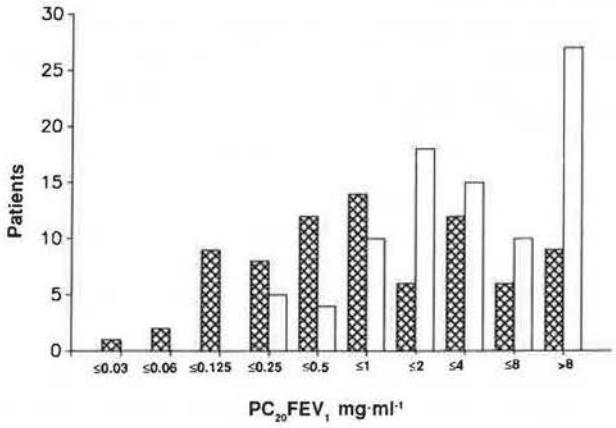

Fig. 1. – Bronchial responsiveness ($PC_{20}FEV_1$) in 89 smokers with chronic bronchitis (not determined in 6 subjects - see text) and asthmatics. ▭: bronchitics; ⊠: asthmatics.

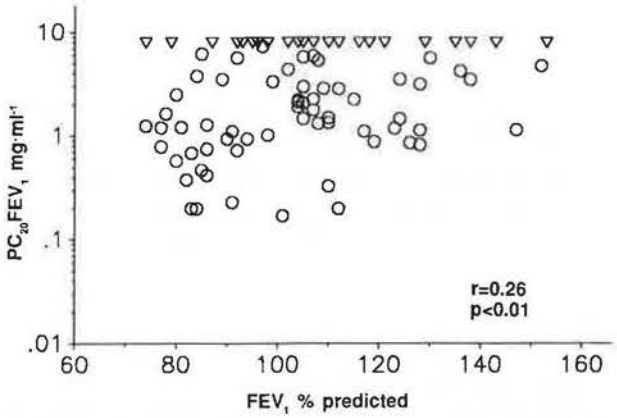

Fig. 2. – FEV_1 % predicted and bronchial responsiveness, $PC_{20}FEV_1$, in 89 smokers with chronic bronchitis. $PC_{20}FEV_1$ not determined in 6 subjects (see text). O: subjects with $PC_{20}FEV_1$ <8 mg·ml^{-1}; ∇: subjects exhibiting less than 20% decrease in FEV_1 after histamine 8 mg·ml^{-1} (see text).

A weak but statistically significant correlation between $PC_{20}FEV_1$ and prechallenge FEV_1 % predicted in both the subjects with chronic bronchitis (fig. 2) and the asthmatics (fig. 3) was found, the responsiveness increasing with decreased FEV_1 (table 2).

In the subjects with chronic bronchitis, $PC_{20}FEV_1$ correlated significantly with ventilatory capacity, age and tobacco consumption. In the asthmatics, $PC_{20}FEV_1$ correlated only with the ventilatory capacity (table 2). No significant difference in bronchial responsiveness between the sexes could be demonstrated ($p>0.05$, Mann-Whitney).

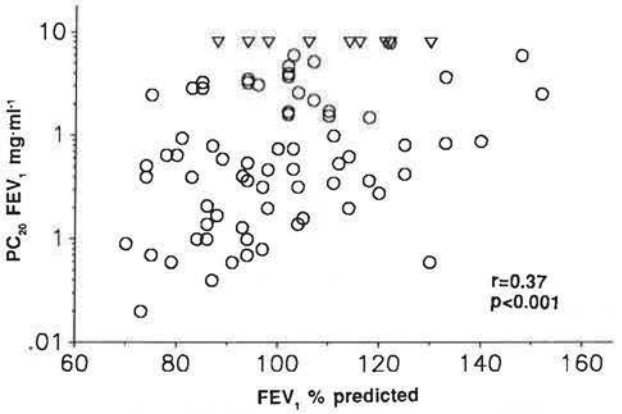

Fig. 3. – FEV_1 % predicted and bronchial responsiveness, $PC_{20}FEV_1$, in 79 asthmatics. O: Patients with $PC_{20}FEV_1$ <8 mg·ml^{-1}; ∇: patients exhibiting less than 20% decrease in FEV_1 after histamine 8 mg·ml^{-1} (see text).

$PC_{40}MEF_{50}$ could be determined in only 65 of the subjects with chronic bronchitis, since the critical value discontinuing the test was a 20% decrease in FEV_1. Using $PC_{40}MEF_{50}$ as a measurement of bronchial responsiveness, 2% had highly reactive airways, 31% had moderately, 23% had lightly, and 42% did not have reactive airways. There was a significant correlation between $PC_{20}FEV_1$ and $PC_{40}MEF_{50}$ ($p<0.001$, $r=0.65$). The small differences in responsiveness when using the two parameters could not be explained by differences in prechallenge ventilatory capacity, age, sex, or smoking habits.

Discussion

Even though some of our bronchitic subjects were only in their early thirties, they all fulfilled the criteria for chronic bronchitis, with cough and expectoration for 3 months a year during 2 consecutive years [9]. All were current tobacco smokers. Although none registered peak expiratory flow rates at home in order to definitely rule out the possibility of subclinical asthma, they all denied having ever experienced episodes of wheezy breathlessness within short time, with intervals of relative or complete freedom from symptoms [12].

Although all 95 subjects with chronic bronchitis had FEV_1 greater that 70% predicted a total of 28 (29%) showed FEV_1/FVC less than 70%. Most subjects had never consulted a doctor for pulmonary symptoms, and only four received any medication. Such subjects are only seldom seen by doctors. Still, more than half of the subjects showed hyperresponsiveness upon bronchial challenge with histamine.

The degree of bronchial responsiveness in the 79 asthmatics was significantly increased as compared to the subjects with chronic bronchitis. A great overlap was seen between the responsiveness of the subjects with chronic bronchitis and the asthmatics. The test, therefore, could not discriminate between the two groups.

We did not include a control group comprising nonsmoking healthy individuals. Earlier investigators showed that only 3% of nonsmoking healthy individuals between 20–60 yrs of age with normal ventilatory capacity exhibited methacholine hyperresponsiveness ($PC_{20}FEV_1$ <8 mg·ml^{-1}) with a Wright nebulizer [16]. COCKCROFT *et al.* investigated university students aged 20–29 yrs [17]. After bronchial challenge with histamine only 4.7% showed a threshold below 8 mg·ml^{-1} (Wright nebulizer); however, 9.3% of the students had asthma! As mentioned previously, we used a Pari Inhalier boy delivering double the dose of the Wright nebulizer.When comparing our results (multiplied by 2 due to the nebulizer) with the above-mentioned healthy individuals, a striking difference is seen in that our bronchitic subjects are substantially more reactive.

In agreement with our findings, earlier investigations have also found the bronchial responsiveness in subjects with chronic bronchitis and normal ventilatory capacity to be between the normal and the asthmatic range [18–21]. LAITINEN [22] found the responsiveness in subjects with chronic bronchitis and asthmatics to be identical; he did not state clearly, however, whether all of his subjects had normal ventilatory capacity. Also in young asymptomatic smokers the bronchial responsiveness has been shown to be increased compared to nonsmokers [23].

TAYLOR *et al.* [24], in their investigation of apparently healthy smokers, found no correlation between bronchial responsiveness, measured by bronchial histamine challenge, and tobacco consumption. Although asthmatics were excluded, they did not state the number of subjects with chronic bronchitis or rhinitis. We have demonstrated increased bronchial responsiveness with increasing tobacco consumption and with increasing age in our subjects with chronic bronchitis, but not in the asthmatics. Tobacco consumption could, though, explain only 5% of the variance in $PC_{20}FEV_1$ (r^2, table 2). Others have also found a significant correlation between tobacco consumption and bronchial responsiveness [25]. This indicates long-term tobacco consumption as a factor in developing increased bronchial responsiveness in nonasthmatics.

The significant correlation between FEV_1 % predicted and bronchial responsiveness was weak, explaining only approximately 7% (r^2) of the variance in responsiveness. In the asthmatics the correlation was somewhat stronger, FEV_1 % predicted explaining approximately 14% of the variance in $PC_{20}FEV_1$. Earlier investigations have found a much stronger correlation between prechallenge ventilatory capacity and bronchial responsiveness by including subjects with moderately to severely reduced ventilatory capacity [8, 21]. YAN *et al.* [8] found no correlation between bronchial responsiveness and FEV_1

% predicted in subjects with chronic bronchitis when only subjects with FEV_1 above 70% of predicted were investigated. They only investigated 13 subjects, however, and used another method than ours to determine the degree of responsiveness. Our results suggest that even within the normal range of ventilatory capacity, a correlation between initial ventilatory capacity and degree of bronchial responsiveness is found.

$PC_{40}MEF_{50}$ could be measured in only 65 of the subjects with chronic bronchitis, since the critical value for discontinuing the challenge was a 20% fall in FEV_1. A fair correlation between $PC_{20}FEV_1$ and $PC_{40}MEF_{50}$ was demonstrated (r=0.65). However, since measurement of MEF_{50} and $PC_{40}MEF_{50}$ did not give further information on hyperresponsiveness or the other parameters, and since the measurement is more troublesome, we do not recommend MEF_{50} and $PC_{40}MEF_{50}$ to be measured in subjects with chronic bronchitis.

In asthmatics, the slope of the dose-response curve is mainly dependent on the starting airway calibre [7]. In our subjects with chronic bronchitis, the slope of the dose-response curve for $PC_{20}FEV_1$ showed no significant correlation with FEV_1 % predicted, other ventilatory capacity values, or bronchial responsiveness ($PC_{20}FEV_1$). However, all subjects had FEV_1 above 70% predicted. A significant correlation between the slope of the dose-response curve for $PC_{20}FEV_1$ and the tobacco consumption was, however, demonstrated. The slope of the $PC_{20}FEV_1$ could therefore prove useful as an early indicator of lung disease from tobacco consumption. Future studies, which are in progress, with registration of annual decline of ventilatory capacity, will hopefully clarify this issue.

In asthma, the bronchial hyperresponsiveness is associated with the severity of disease and need for medication [26], and the hyperresponsiveness can be reduced by inhaled steroids [27]. Investigations of inhaled steroids in subjects with chronic bronchitis with normal ventilatory capacity are lacking. Treatment with sodium cromoglycate in subjects with chronic bronchitis has caused a small but significant reduction of the bronchial hyperresponsiveness to fog challenge [28].

LIM *et al.* [29] recently reported the results of bronchial histamine challenges performed before and after a 4 yr observation period in 27 current smokers with apparently normal FEV_1 and chronic bronchitis. They found a significant correlation between airway responsiveness ($PC_{20}FEV_1$) measured at the end of the observation period and the annual decline in FEV_1, but they did not report the correlation between the decline in FEV_1 and the degree of responsiveness observed prior to the observation period. Similar results have been shown previously [30]. The magnitude of increased bronchial responsiveness in smokers shown in this study again suggests cessation of smoking. Prospective analyses of bronchial responsiveness and decline in FEV_1 are in progress.

In conclusion we found that 52 of 95 subjects with FEV_1 above 70% predicted and with chronic bronchitis had increased bronchial responsiveness measured as $PC_{20}FEV_1$ upon challenge with inhaled histamine. The degree of responsiveness was significantly less than that found in a group of asthmatics, but substantially higher than that reported in normal individuals. The degree of responsiveness in subjects with chronic bronchitis was significantly correlated to prechallenge ventilatory capacity, age and tobacco consumption but not to sex.

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Comparison de la réactivité des voies aériennes chez les fumeurs bronchitiques et chez les asthmatiques. T. Engel, J.H. Heinig, O. Madsen, M. Hansen, E.R. Weeke.

RÉSUMÉ: Une hyperréactivité bronchique, exprimée en PC_{20} VEMS après provocation par inhalation d'histamine, a été retrouvée chez 52 de 95 fumeurs dont le VEMS est supérieur à 70% des valeurs prédites, mais qui sont atteints de bronchite chronique. Le degré de réactivité était systématiquement inférieur à celui trouvé chez les asthmatiques pairés, mais nettement supérieur à celui observé chez les sujets normaux. Le degré d'hyperréactivité est en corrélation significative avec les valeurs de base de la capacité ventilatoire, l'âge et la consommation de tabac, mais sans rapport avec le sexe. PC_{40} MEF_{50} a montré le même type de distribution que PC_{20}VEMS, mais n'a pas ajouté d'information complémentaire. La pente de la courbe dose-réponse du MEF_{50} n'a de corrélation avec aucun des paramètres mesurés. La pente des courbes dose-réponse du VEMS, par contre, montre une corrélation significative avec la consommation de tabac. Il y aurait lieu d'investiguer dans quelle mesure le degré d'hyperréactivité bronchique pourrait constituer un indice d'incapacité future.
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