Original Article

Comparison of Airway Hyperreactivity in Chronic Obstructive Pulmonary Disease and Asthma

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Background: Airway hyperreactivity (AHR) has been described in patients with chronic obstructive pulmonary disease (COPD). However, the nature and characteristics of AHR in this disease have not been fully investigated.

Methods: AHR was examined in a sample of 33 patients with COPD and 25 with asthma and compared during continuous inhalation of stepwise increased concentrations of methacholine. Respiratory resistance (Rrs) was measured by the forced oscillation technique and the dose-response curves were recorded.

Results: The mean values for both forced vital capacity (FVC) and forced expiratory volume in 1s (FEV1) were well-preserved in subjects with asthma. In contrast, there was an obstructive ventilatory defect in patients with COPD, as evidenced by the FEV1/FVC ratio, which fell below 70%. Upon methacholine challenge, only 54.5% (18/33) of the patients with COPD had AHR, compared with 100% (25/25) of those with asthma. Analysis of the dose-response curves revealed that the patients with COPD had a significantly higher baseline Rrs, and thus lower baseline respiratory conductance (Grs), than those with asthma. The cumulative dose of methacholine capable of provoking a positive reaction was significantly higher in patients with COPD. The slope of the Grs was also less steep in responders with COPD. There was good correlation between the severity of AHR and the initial level of airway narrowing in patients with COPD ($r = 0.623$, $p < 0.01$), but not in those with asthma.

Conclusion: AHR is not uncommon in COPD, and it has different characteristics from that occurring in asthma.
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Symptomatic chronic obstructive pulmonary disease (COPD) is frequently associated with impaired ventilatory capacity which may result from airflow limitation, hyperinflation, ventilation-perfusion maldistribution, and increased dead space.[1] The pathologic basis of the largely irreversible airway obstruction is inflammatory with fibrotic changes in the peripheral airways and loss of elastic lung recoil. Airway hyperreactivity (AHR) has been described in COPD,[2,3] and it has been suggested that this

increased response to provocative stimuli may be involved in the deterioration of lung function.[4] Unlike asthma patients, however, not all patients with COPD present with AHR.[5,6] In addition, characteristics of the AHR in COPD are not fully understood because of differences in methods and dose schedules of the provoking agent used by various investigators.

Bronchial provocation with stimulants or allergens is a valuable and widely used technique to examine the hyperreactivity of airways, particularly for the diagnosis of bronchial asthma. The test is conventionally assessed by maximally forced spirograms.[7] Since the bronchial reactivity apparently may not be determined by a single dose-response relationship, multiple expiratory efforts are required following serial inhalations of increasing doses of the challenging agent. Repeated forced inspirations and expirations might induce bronchoconstriction. Although a rapid method for measurement of bronchial responsiveness has been described,[8] it requires a modification of the dose schedule to shorten the procedure. Moreover, the change in forced expiratory volume in 1s (FEV1) still remains to be determined following each dose.

It has been advocated that the total respiratory resistance (Rrs) measured by the forced oscillation technique might be a sensitive indicator of airway narrowing.[9,10] The measurement is made during continuous tidal breathing without intermittent maximal exhalations by the subjects. In fact, dose-response curves of Rrs during inhalation challenge have been obtained and analyzed by several investigators to examine bronchial responsiveness.[11,12] In the present study, we applied this method to evaluate the incidence, nature and characteristics of AHR in patients with COPD or asthma. The purpose of this study was to explore the similarities and differences in bronchial responses to methacholine challenge between patients with COPD and those with asthma.

METHODS

Patients

A total of 33 patients, 8 women and 25 men, with COPD, and 25 patients, 11 women and 14 men, with bronchial asthma were selected consecutively from our pulmonary clinic. All patients were followed up regularly by a chest physician, and were recruited on the basis of clinical and roentgenologic assessment in addition to pulmonary function test results. The diagnosis of pulmonary emphysema and/or chronic bronchitis fulfilled the criteria established by the American Thoracic Society.[13] The duration of COPD ranged from 3 to 8 years. All COPD patients were symptomatic and used bronchodilators including inhaled anticholinergic agents, and/or mucolytics. However, none of them used antibiotics, oral or inhaled corticosteroids, or domiciliary oxygen. We did not include those patients with clinical evidence of bronchiectasis, pulmonary tuberculosis, pneumoconiosis, unstable cardiovascular disease, or those with FEV1 values less than 50% of predicted.

Patients in the asthma group had a history of breathlessness, cough, and recurrent attacks of wheezing. The onset of the disease was before the age of 35 years, and airway obstruction was largely reversible after medication. All of them had been diagnosed by a doctor as having asthma before entry into the study. The duration of asthma ranged from 5 to 23 years, and the severity was classified as mild to moderate because they had between 2 and 8 attacks of wheezing per year.

All subjects were in stable condition. None of them had been admitted to the hospital in the past 2 months because of secondary infections or acute exacerbations. This project was approved by the local Human Research Committee and informed consent was obtained from each subject.

Each subject underwent a physical examination. Health information such as respiratory symptoms, occupational histories, smoking habits and past histories of hypertension, diabetes, chronic lung and cardiac disease, and neuromuscular disorders were obtained from a questionnaire modified from those cited in the Epidemiology Standardization Project.[14] Laboratory investigations including determination of the blood eosinophil count and total serum immunoglobulin E (IgE) level were also conducted in each subject.

Pulmonary function tests

Subjects were not allowed to take bronchodilators for at least 12 hours prior to testing. Vital capacity (VC) and each forced expiratory spirogram were recorded with an automated plethysmograph (CS-828 FC, CHEST Inc., Tokyo, Japan). VC was mea-

sured by having each subject exhale completely, followed by a slow and maximal inhalation. Forced vital capacity (FVC), FEV1 and the FEV1/ FVC ratio were determined from the maximal expiratory flow volume curves. Inspiratory capacity (IC) was calculated as the sum of the tidal volume and inspiratory reserve volume. The thoracic gas volume was measured by the panting technique with the same body box to derive the residual volume (RV), total lung capacity (TLC) and RV/TLC ratio.

Methacholine challenge

Bronchial responsiveness was examined by a methacholine challenge and continuous measurement of total respiratory resistance (Rrs) during tidal breathing.[10] An astograph (TCK-6000, CHEST M.I. Inc., Japan), which employed the forced oscillation principle to record dose-response curves for bronchial provocation tests, was used in this study. In this apparatus, rapid oscillations of flow at the mouth were produced with a loudspeaker system driven by a low frequency sine-wave generator and power amplifier. Pressure oscillations at the frequencies of 5 Hz were then generated and applied to the mouth. The air flow at the mouth was measured with a Fleish No. 2 pneumotachometer (Hewlett-Parkard, Cupertino, CA, U.S.A.) and the mouth pressure was measured with a differential pressure transducer (MP 45-1, Validyne, Northridge, CA, U.S.A.). Spectral analysis of the resulting pressure and flow signals was performed by a computer. It yielded calculations of the Rrs and respiratory conductance (Grs), the reciprocal of Rrs.

The instrumentation also consisted of 12 nebulizers capable of generating aerosols with a particle size of less than 5 μm. Nebulizer 1 contained 0.9% normal saline; nebulizers 2-11 contained 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12.8, and 25.6 mg/ml of methacholine, respectively; nebulizer 12 contained 2.5 mg/ml of terbutaline as a bronchodilator. Rrs was directly recorded with an X-Y recorder (Graphtec WX-2400). Aerosols were delivered from each nebulizer for 1 min in sequence beginning with no. 1, and inhaled by the subject until the Rrs reached twice the baseline values. In that case, the methacholine challenge was terminated and terbutaline was administered immediately. The cumulative dose of methacholine (Dc) at the point where the Rrs started to increase prominently was calculated and expressed

as a methacholine unit. We defined the unit in a way similar to the method of Chai et al.,[15] i.e., 1 unit equals 1 min inhalation of 1 mg/ml methacholine. We also defined Dc as the indicator for bronchial sensitivity. Another calculated parameter was the Grs. Therefore, as the linear slope of the Grs (SGrs) decreased, the SGrs was used to represent bronchial reactivity.

Statistical analysis

Results were expressed as the mean $\pm$ SD. Values for lung function variables were corrected for age and body size using previously established reference equations,[16,17] and were expressed as the percent predicted (%p). All data were coded, entered into a DEC10-Cyber 175 computer system, and analyzed using Statistical Analysis System (SAS Institute, Cary, NC, U.S.A.) software. The differences in lung function data and bronchial response between patients with COPD and asthma were examined by unpaired t-test. Pearson's correlation coefficient was calculated to examine the association between the FEV_1 and severity of AHR in responders. The chi-square test was performed to compare the percentages of responders between groups. The level of statistical significance was set at $p = 0.05$.

RESULTS

Table 1 shows the physical and clinical characteristics, and smoking habits of the subjects according to their disease grouping. Patients with COPD and asthma were similar in terms of body size and gender. Although the former group was slightly older than the latter, the difference was statistically insignificant ($p = 0.08$). In addition, more subjects with COPD had associated respiratory symptoms and there were more smokers in the COPD group than the asthma group. In both groups, the most common symptoms encountered were cough and chest tightness. Enhanced IgE synthesis, as reflected by a total serum IgE level of >100 IU/ml, was found in 84% (21/25) of asthmatic subjects. In contrast, only 9% (3/33) of patients with COPD had an abnormally increased IgE level. The eosinophil count in the peripheral blood was much higher in asthma patients than COPD patients.

The pulmonary function level of both study groups before bronchial provocation is summarized

Table 1. Physical and Clinical Characteristics of Subjects with COPD and Asthmatics

	Subjects with COPD	Asthmatics	p value
No., M/F	25/8	14/11	NS
Age, years	56.3 ± 14.5	48.7 ± 17.6	0.08
Height, cm	164.7 ± 6.4	162.5 ± 7.2	NS
BSA, m²	1.68 ± 0.13	1.63 ± 0.15	NS
Respiratory			
symptoms, n (%)	33 (100)	12 (48)	p < 0.001*
Cough	25 (76)	11 (44)	
Chest tightness	18 (55)	12 (48)	
Sputum	16 (49)	3 (12)	
Breathlessness	13 (39)	8 (32)	
Wheezing	10 (30)	9 (36)	
No. (%) of smokers	26 (79)	5 (20)	p < 0.001*
Blood eosinophil count, l/mm³	56 ± 23	248 ± 42	p < 0.001†
Total serum IgE, IU/ml	41.2 ± 18.7	236.5 ± 94.3	p < 0.001†

Abbreviations: COPD: chronic obstructive pulmonary disease; BSA: body surface area; IgE: immunoglobulin E; NS: not significant; *: From chi-square test; †: From unpaired t-test.

Table 2. Pulmonary Function Data

	Subjects with COPD (n = 33)	Asthmatics (n = 25)	p value*
FVC, L	2.74 ± 0.93	3.21 ± 0.84	NS
FVC, %p	93.8 ± 12.5	98.6 ± 10.2	NS
FEV1, L	1.62 ± 0.41	2.67 ± 0.63	NS
FEV1, %p	69.8 ± 14.5	88.6 ± 13.3	p < 0.001
FEV1/ FVC, %	60.3 ± 8.7	82.3 ± 6.9	p < 0.001
IC, L	2.37 ± 0.44	2.51 ± 0.56	NS
RV/TLC, %	39.4 ± 8.2	28.5 ± 4.7	p < 0.001
n (%) of broncho-dilator reversibility†			
Δ FEV1 11～14%	7 (21)		
Δ FEV1 6～10%	16 (49)	–	
Δ FEV1 < 5%	10 (30)		

Abbreviations: COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV1: forced expiratory volume in 1s; IC: inspiratory capacity; TLC: total lung capacity; RV: residual volume; %p: percent of predicted values; NS: not significant; *: From unpaired t-test; †: Based upon the response to 250 μg terbutaline and expressed in terms of prebronchodilator FEV1, as a percentage of post bronchodilator FEV1.

Table 3. Data on AHR in Subjects with COPD and Asthma

	Subjects with COPD (n = 33)	Asthmatics (n = 25)	p value*
Baseline Rrs, cmH₂O/L/s	5.2 ± 1.4	4.3 ± 1.2	0.02
Baseline Grs, L/s/cmH₂O	0.18 ± 0.05	0.24 ± 0.06	< 0.001
No. (%) of responders	18 (54.5)	25 (100)	< 0.001†
Dc in responders, unit	6.5 ± 5.2	1.2 ± 0.9	< 0.001
SGrs in responders, L/s/ cmH₂O /min	0.045 ± 0.021	0.062 ± 0.027	0.008

Abbreviations: Rrs: respiratory resistance; Grs: respiratory conductance; Dc: cumulative dose of methacholine at which Rrs began to rise in a positive reaction; SGrs: the linear slope of Grs; *: From unpaired t-test; †: From chi-square test.

in Table 2. The mean values of the FEV1 and the FEV1/ FVC ratio in COPD patients were consistently lower than those of asthma patients. An obstructive ventilatory defect was present in the COPD group because the mean ratio of the FEV1/ FVC was < 70%. In addition, although the IC was not different, the RV/TLC ratio was significantly higher among patients with COPD. Thus, the pulmonary function in asthma patients was well-preserved and better than that found in patients with COPD.

As shown in Table 3, the baseline Rrs in COPD patients was significantly higher than that in those with asthma. However, a more prominent difference in the Grs between groups was noted. Only 54.5% of COPD patients had a Rrs increased by twice or more by the highest dose of methacholine, compared to 100% of the asthma patients. Although both baseline Rrs and Grs were measured in all subjects, Dc and SGrs, by definition, were only able to be recorded in responders. In the methacholine provocation, the mean values for Dc in responders who had COPD were significantly higher (6.5 ± 5.2 units) than in those who had asthma (1.2 ± 0.9 units), suggesting relatively less severe AHR in patients with COPD in terms of methacholine dose. We did not find a particularly significant relationship between SGrs and FEV1 in either the COPD or asthma group (r = − 0.125 and 0.094, 95% confidence interval [CI], − 0.172 to − 0.068 and 0.039 to 0.147, respectively; p > 0.1).

The dose-response curves of the airways to methacholine challenge in two responders with asthma and COPD are displayed in Figs. 1 and 2. In both responders, the pronounced increase in Rrs by
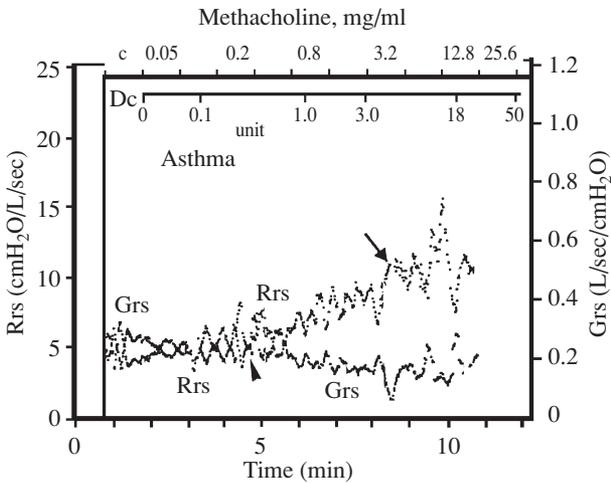

Fig. 1 Dose-response curves during methacholine provocation in an asthmatic patient. C, control; Dc, cumulative dose of methacholine at which Rrs began to rise (arrow). Arrowhead: the point where terbutaline was administered. See text for the definitions of other abbreviations.
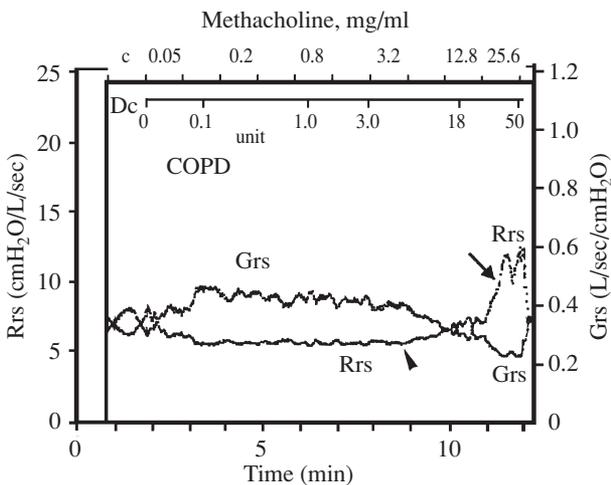

Fig. 2 Dose-response curves during methacholine provocation in a responder with COPD. C, control; Dc, cumulative dose of methacholine at which Rrs began to rise (arrow). Arrowhead: the point where terbutaline was administered. Note that the bronchial reactivity (SGrs, the slope of Grs during a response to the challenge) was less profound than that in Fig. 1. See text for the definitions of other abbreviations.

methacholine inhalation produced a triangular curvilinear pattern. The shape and position of the curves describe the sensitivity and reactivity of the airways to the provoking agent. The SGrs (the bronchial reactivity) during a positive reaction was also less steep in patients with COPD than in those with asthma (Table 3).

In this study, the relationship between the initial airway caliber and the magnitude of bronchial responsiveness in responders was examined. PD35Grs is the cumulative dose of methacholine which results in a 35% decrease in Grs and its position is affected both by the Dc and SGrs, so we chose PD35Grs as the indicator to estimate the magnitude of a response. It is evident from Fig. 3 that there was a good correlation between the percent of predicted values of the initial FEV1 and PD35Grs values in the patients with COPD (r = 0.623, 95% CI, 0.785 to 0.472, $p < 0.01$), while no significant correlation (r = 0.157, 95% CI, 0.083 to 0.229, $p > 0.1$) was found between these two variables in asthma patients. Thus, the level of airway obstruction could modify the dose-response curves in COPD, but not in asthma. The configuration of the curves during AHR to methacholine in patients with COPD is a function of their initial level of airway narrowing.
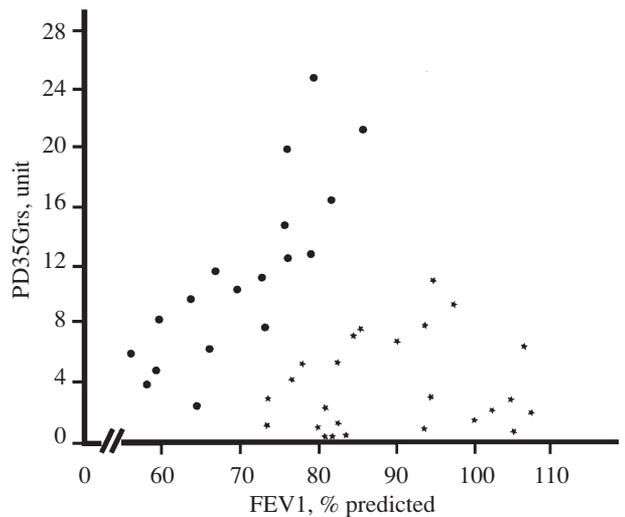

Fig. 3 The relationship between PD35Grs and FEV1 in subjects with asthma and COPD. ●: COPD; ★: asthma. See text for the definitions of abbreviations.

DISCUSSION

Although both COPD and asthma are characterized by similar respiratory symptoms such as airway obstruction and inflammation, they are etiologically distinct disease entities.[18,19] Association of an inherited allergic constitution (atopy) and the risk of developing reversible bronchospasm have been found in asthma. By contrast, COPD is a disease of late adult life associated with cigarette smoking, and is manifested by irreversible reduction in expiratory flow rates, although there may be a limited improvement in FEV1 in response to bronchodilator therapy. Since full understanding and prevention of both asthma and COPD are not satisfactory at present, methods to differentiate the diseases are required for better management and an improved prognosis.

Increased airway responsiveness to non-specific stimuli such as histamine, methacholine and cold air inhalation is generally regarded as a hallmark of asthma. However, AHR also can be found in persons with acute airway infections[20] or COPD.[2,3] Moreover, the prevalence and nature of AHR in COPD are somewhat different from those observed in asthma.[2,21] Our study demonstrated that although AHR is not uncommon in patients with COPD, the incidence is much lower than that found in those with asthma. This implies that the threshold to induce responses to a methacholine challenge may not be the same in the two groups. Impaired spirometric function is also not a prerequisite for AHR since all the subjects with asthma in this study had normal ventilatory capacity. Therefore, the prevalence of AHR in subjects with airflow limitation is not necessarily related to the level of resting airway obstruction.

Bronchial challenge in subjects with severe airway obstruction may induce bronchospasmotic attacks during the procedure, which requires immediate management. For safety reasons, we excluded patients with a FEV1 of <50% of predicted. Therefore, the characteristics of AHR in severe or very severe COPD could not be delineated by our study. Nevertheless, because AHR is now regarded as an "early sign" of decline in ventilatory function and aggravation of respiratory symptoms,[4] how the AHR manifests itself in severe airway obstruction is of relatively minor importance.

While inhalation challenge with antigens, methacholine and histamine has been widely used to assess AHR, the procedures have not yet been standardized. Investigators need to address the issue of these varying methods, which may make it difficult to compare data in different studies. For example, different provoking agents may produce different bronchial response patterns in subjects. Even when the same agent is used, the dose range tested and the number of points determined on the dose-response curves can be different. Enarson and coworkers[7] conducted methacholine inhalation tests with concentrations from 0.5 to 16 mg/ml to explore the association between bronchial hyperresponsiveness and asthma, asthma-like symptoms and chronic bronchitis in epidemiologic groups. In a report by Hodgins and colleagues,[4] a single dose of methacholine (either 5 mg/ml or 25 mg/ml) was employed to study the relationship between nonspecific bronchial responsiveness and the development of chronic airflow obstruction. Hospers et al. analyzed the inhalation challenge data of Netherlands inhabitants,[22] in which 5 sequential aerosol inhalations of histamine (1 mg/ml, 4 mg/ml, 8 mg/ml, 16 mg/ml, 32 mg/ml) were applied to observe whether airway hyperresponsiveness is a risk factor for mortality from COPD. In our study, both bronchial reactivity and sensitivity were recorded continuously within the full test range (0.05 mg/ml to 25.6 mg/ml) of the bronchoconstrictor agent. Consequently, the shape and position of the dose-response curves obtained were more sharply and accurately delineated than what would be obtained by an intermittent method.

How can the observed characteristics of AHR in subjects with COPD and asthma be explained in terms of the present knowledge of their pathologic features? Data from previous studies suggest that the degree of AHR is related to some extent to the severity of airway obstruction in COPD.[23] Indeed, the pathologic processes present in COPD may include bronchitis, bronchiolitis and pulmonary emphysema. Inflammation of the bronchial tree, along with increased secretions, causes a narrowed airway with a thickened wall. It has been demonstrated that the thickness of the airway wall can affect both the position and shape of the dose-response curves during challenge studies.[24,25] Moreover, loss of elastic recoil reduces the load against which the bronchial muscle contracts in a response to provoking stimuli. Thus,

the airway disease in COPD can lead to or enhance AHR. The present results also showed a close relationship between PD35Grs and the initial FEV1 values in responders with COPD. It seems possible that the subjects who developed airflow limitation subsequently developed AHR.

The situation in asthma is somewhat different from that observed in COPD.[26,27] The pathologic changes in the respiratory tract of these two diseases are different in nature and site. Airway obstruction, thickening of the muscle layer and inflammation also occur in asthma. However, there is little loss of elastic recoil of the lung. The narrowing of bronchial airways is usually reversible by administration of bronchodilator drugs. In this study, although the subjects with asthma had normal values for the FVC and FEV1, all had AHR and were extremely sensitive to methacholine provocation. Therefore, the degree of AHR in subjects with asthma is not correlated with their initial airway caliber. This implies that AHR may have already existed in the absence of airflow limitation and may precede the development of airway obstruction. Since this observation is in contrast to what is observed in COPD, the modes of action of methacholine on the airways may not be the same among subjects with COPD and asthma.

Does the presence of AHR also lead to an acceleration of airflow limitation and eventually cause airway obstruction? Vedal et al. reported that increased AHR is associated with airway obstruction in working populations.[28] In a 5-year longitudinal study, Hodgins et al. were able to demonstrate that the development and persistence of AHR were strongly associated with higher rates of FEV1 decline in a group of miners and working nonminers.[4] Although both smoking and mining were independently associated with FEV1 declines, these factors did not substantially modify the effect of AHR. Our results also showed that in responders with COPD, the more severe the airway obstruction, the more profound the response to methacholine challenge. Consequently, AHR may be a risk factor for airflow limitation in chronic airway disorders.

It is well known that cigarette smoking can cause chronic airway obstruction. Since our data demonstrated an association between AHR and an obstructed airway in COPD, it would be of interest to recognize the role played by cigarette smoking in the development of AHR. However, conflicting results have been reported for nonspecific AHR to histamine/methacholine in smokers. Jensen and coworkers found a greater responsiveness among smokers than nonsmokers.[29] On the contrary, Cockroft et al. suggested that bronchial responsiveness is not increased in asymptomatic smokers.[30] This study was not intended to establish a causal model of the relationship between cigarette smoking and AHR. Our finding that the prevalence of AHR in the 33 patients with COPD (most of whom were smokers) was 54.5% is insufficient to conclude that cigarette smoking causes AHR. Further investigations are required to resolve this question.

In conclusion, AHR is not uncommon and occurs in a considerable proportion of patients with COPD. Compared with asthma, the AHR in COPD is less sensitive and less intense in terms of the provocative dose of methacholine and the rate of decrease in Grs during a positive reaction. There is also a relationship between the severity of AHR and the degree of airway obstruction in patients with COPD. The differences in characteristics of AHR between asthma and COPD suggest that the mechanism and structural changes causing the abnormal responses may not be the same in these two diseases. Further investigations are required to determine the need for treatment with medication and its effectiveness on the responses.

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慢性阻塞性肺病之氣道高反應性：與氣喘病所見之比較

楊錫欽　林本源

背　景： 罹患慢性阻塞性肺病 (COPD) 之病人會出現氣道高反應性，於文獻上已有報告；但由於各個研究在進行時所使用之方法及激發劑量並不相同，此種氣道高反應性的本質及特徵仍然不十分清楚。

方　法： 我們針對 33 位 COPD 病人及 25 位氣喘病人以強制振盪法進行支氣激發試驗。病人係連續吸入濃度逐漸提高之 methacholine，同時測量呼吸阻力 (Rrs)，並記錄其劑量-反應曲線，再比較兩組病人之結果。

結　果： 氣喘組病人仍具有良好之肺功能，其平均用力肺活量 (FVC) 及一秒量 (FEV1) 均為正常；COPD 組之病人則已有阻塞性換氣障礙，因其 FEV1/ FVC 比值 < 70%。激發試驗結果顯示 54.5% (18/33) COPD 病人有氣道高反應性，而氣喘病人則為 100% (25/25)。COPD 病人有比氣喘病人基礎值高之呼吸阻力，較低之呼吸傳導度 (Grs)；而且試驗反應為陽性之 COPD 病人，其氣管敏感度 (sensitivity) 及支氣管反應度 (reactivity) 均較氣喘病人為低 (亦即需要較大的激發劑量，與被激發時具有較平坦的 Grs 斜率)。

結　論： 氣道高反應性在 COPD 病人並不罕見，此一高反應性與其氣道縮窄的程度有關，但在氣喘病人則沒有這種情形。
(長庚醫誌 2010;33:515-23)

關鍵詞： 氣道高反應性，methacholine 激發，呼吸阻力，慢性阻塞性肺病