

Bronchial Responsiveness and Lung Function Related to Cigarette Smoking and Smoking Cessation

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Background: The relationships between bronchial responsiveness and both cigarette smoking and smoking cessation are still controversial.

Methods: To investigate the effects of cigarette smoking and smoking cessation on bronchial reactivity and the level of pulmonary function, bronchial responsiveness to methacholine using the forced oscillation method, the transfer factor, and spirometry were measured in 180 nonsmokers, 109 current smokers, and 82 ex-smokers. The following indices of bronchial responsiveness were used: (1) baseline respiratory resistance (Rrs); (2) the cumulative dose of methacholine (D_A) causing an increase in Rrs by twice the baseline values (bronchial sensitivity); and (3) the slope of linearly decreased respiratory conductance (SGrs) representing bronchial reactivity.

Results: Current smokers had significantly higher baseline Rrs ($p < 0.001$) and bronchial responsiveness than did nonsmokers and ex-smokers. In 24.7% of smokers, Rrs increased by twice or more upon challenge with methacholine (responders), compared with 0% of nonsmokers ($p < 0.0001$) and 19.5% of ex-smokers ($p = 0.28$). SGrs for responders among ex-smokers was found not to differ from that for responders among smokers. However, smokers had a significantly lower D_A of inhaled methacholine than did ex-smokers. Cigarette smoking was also associated with an appreciable reduction in FEV₁/FVC (forced expiratory volume in 1s/forced vital capacity), DLCO (carbon monoxide diffusing capacity), and DLCO/ V_A (alveolar volume).

Conclusion: There seems to be a partially reversible phenomenon that leads to improvement in airway responsiveness and DLCO upon smoking cessation. (*Chang Gung Med J 2002;25:645-55*)

Key words: cigarette smoking, smoking cessation, bronchial responsiveness, bronchial reactivity, lung function.

Cigarette smoking has been considered to be one of the most important etiologic factors for chronic airway obstruction.^(1,2) Diminished values for lung volumes or forced expiratory flows have been demonstrated in cigarette smokers.⁽³⁻⁵⁾ Conflicting results have been reported, however, for nonspecific

bronchial responsiveness (BR) to histamine/methacholine. Several studies^(6,7) have suggested that BR is not increased in asymptomatic cigarette smokers. On the contrary, many others have found greater responsiveness among smokers than among nonsmokers.⁽⁸⁻¹⁰⁾ These discrepancies may have resulted

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from differences in the methods of subject selection, and may depend on how BR is measured.

So far, the conventional methacholine provocation test for evaluating the airway responsiveness has usually been examined using spirometry, which mainly uses PD₂₀ FEV₁ (the dose of the agent causing a 20% decrease in forced expiratory volume in 1 s) as the index^(11,12) and requires multiple forced expiratory maneuvers. Since this procedure is time-consuming and might introduce false-positive results,⁽¹³⁾ sample sizes were usually small and not representative of the general population. Therefore, the effects of cigarette smoking on BR remain under debate.

The present study was designed to investigate relationships between methacholine BR and smoking habits in subjects with healthy, normal respiration using a rapid oscillation technique.^(14,15) By utilizing this method, it is possible to continuously measure changes in Rrs during quiet tidal breathing. Thus, minimum cooperation of the subject is required. In addition, the test is quite safe, reproducible, and can be completed in less than 20 min. Consequently, it is suitable to be used in epidemiologic surveys involving large population samples. In this study, spirometric parameters and DLCO were also measured to observe the adverse effects of cigarette smoking on the level of pulmonary function in a general population.

METHODS

All subjects were collected from those enrolled in a random, stratified sample of ethnic Chinese residents of Taipei City, Taiwan, who were invited to participate in a prospective epidemiologic study conducted by the Environmental Protection Administration of the Republic of China and National Taiwan University Hospital, to evaluate the long-term effects of air pollution on human health. Representative households were randomly selected from each of 15 districts into which the city was divided. The sampling rate was determined by the estimated population in each district. Stratification was based on the age and occupation of the heads of households.

A medical interview was scheduled for the subjects at the hospital where each of them completed a self-administered questionnaire.⁽¹⁶⁾ Answers to the questionnaire were used to identify population sub-

groups. Criteria for exclusion were a past history of cardiopulmonary, neuromuscular, pleural, or collagen vascular disease and/or occupational exposure that would suggest the presence of lung disease. Although participants with asthma and chronic bronchitis were excluded, those who had only respiratory symptoms such as a chronic cough and phlegm apparently resulting from cigarette smoking, but otherwise had "healthy respiration", were included in this survey. In addition, none of them had had airway infections within 2 weeks before entry.

A detailed history on smoking habits was collected by pulmonary specialists. The average number of cigarettes smoked per day, the number of years of smoking, and the number of pack-years smoked were calculated for each subject. We defined smokers as those who had smoked for more than 1/2 pack-year, and ex-smokers as those who had quit smoking for at least 6 months prior to testing. For each smoker, cigarette consumption was estimated and evaluated by smoking variables including duration of smoking (years smoked), smoking intensity (average and current cigarettes per day), and the number of pack-years.

Of the 737 randomly selected subjects from the general population, 122 (16.5%) were excluded by the questionnaire. A physical examination, posteroanterior and lateral chest roentgenograms, and an electrocardiogram were then performed on the remaining 615 subjects. This further excluded 97 subjects from the protocol, thereby reducing the number of subjects available for study to 518. Informed consent was obtained from each subject.

Maximal expiratory flow volume determination was conducted while subjects were seated and wore nose clips. An automated HI-501 spirometer (CHEST MI, Tokyo, Japan) was used to measure forced vital capacity (FVC), forced expiratory volume in 1s (FEV₁), the ratio FEV₁/FVC, forced expiratory flow at 75% of FVC (FEF₇₅), and mean forced expiratory flow during the middle half of FVC (FEF₂₅₋₇₅). Up to 3 trials were performed, and the average of 2 technically acceptable tests was reported. The tests had to agree within 5% of each other to be considered acceptable.

DLCO measurement were performed using an integrated and automated Chestac-65 lung function analyzer (CHEST Corp., Tokyo, Japan). The equipment and details of the methodology have been pre-

viously described.⁽¹⁷⁾ Tests were considered acceptable if the inspired volume was >90% of the subjects' vital capacity (VC). The alveolar volume (VA) was measured without correction for anatomic dead space. To correct the potential effect of CO back pressure in smokers, venous blood was drawn for measurement of carboxyhemoglobin using a CO-oximeter (OSM-3 Hemoximeter, Radiometer, Copenhagen, Denmark). The corrected DLCO values were then calculated according to the following equation: corrected DLCO = measured DLCO_i (1 - COHb%) / 100%. The average of 2 technically acceptable DLCO values were used in the final analysis. When duplicate tests were available, it was also required that the two DLCO values agree within 5%.

Measurements of total respiratory resistance (Rrs) and bronchial challenge were performed with an astograph (TCK-6000, CHEST MI). The device employs an oscillation technique and measures Rrs continuously during tidal breathing. Its principle and clinical application were described by Takishima et al.⁽¹⁴⁾ 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.

The nebulizers were driven by a constant air flow of 5 L/min from the air compressor of the apparatus. The patients were requested to clip their nose, connect their mouth to the breathing tube of the astograph, and continue quiet tidal breathing with the larynx relaxed. The nebulizers were then actuated in sequence beginning with no. 1 (1 min for each nebulizer). Rrs was directly recorded with an X-Y recorder (Graptex WX-2400). Aerosols were delivered from each nebulizer for 1 min in sequence and inhaled by the subject until Rrs reached twice the baseline values or subjects showed symptoms of intolerance such as difficult breathing or chest tightness. In that case, methacholine challenge was terminated, and terbutaline was immediately administered. Nebulization was continued to the last concentration (25.6 mg/ml) of methacholine if there was no apparent change in Rrs.

The cumulative dose of methacholine (D_A) at the point where Rrs began to prominently increase

was calculated and expressed in methacholine units. We defined the unit in a similar way to the method of Chai et al.,⁽¹¹⁾ i.e., 1 unit equals 1 min inhalation of 1 mg/ml methacholine. We defined D_A as the indicator for bronchial sensitivity. Another calculated parameter was the respiratory conductance (Grs, i.e., the reciprocal of Rrs). Therefore, as the linear slope of Grs decreased, SGr_s was used to represent bronchial reactivity.

All data were coded, entered into a DEC 10-Cyber 175 computer system, and analyzed using the Statistical Analysis System (SAS Institute, Cary, NC, USA) software. Results are expressed as the mean ± SD. Values for lung function variables were also corrected for age and body size using the reference equations previously established by our laboratory,^(17,18) and were expressed as the percent predicted (%p). Statistical analyses used included analysis of variance followed by Scheffe's multiple comparison, and unpaired *t*-test when appropriate. Pearson's correlation coefficient was calculated to examine the association of D_A and SGr_s with anthropometric and smoking variables to methacholine challenge in responders. The differences in lung function data and bronchial reactivity between current smokers and ex-smokers were examined by unpaired *t*-test. Chi-square test was performed to compare the percentage of responders between nonsmokers and current smokers. The level of statistical significance was set at *p* = 0.05.

RESULTS

Of the 518 subjects who met the questionnaire criteria for having normal or healthy respiration, 409 (79%, all men) completed the bronchial challenge test. We were unable to collect an adequate number of female smokers because cigarette smoking is an infrequent habit in Oriental women. The final analysis was performed on a smaller sample because 38 subjects did not have an acceptable test, thereby reducing the study population to 371. There were 180 nonsmokers, 109 current smokers, and 82 ex-smokers. In Tables 1 and 2, the anthropometric and spirometric characteristics of these subjects by smoking category are compared. Observations on the smoking habits of Taiwanese men in the present study revealed that 85 (78%) of the current smokers had a smoking intensity of less than 1 pack per day,

Table 1. Anthropometric Characteristics and Smoking Habits of Subjects Studied

	Nonsmokers (N=180)	Current Smokers (N=109)	Ex-smokers (N=82)	<i>p</i> *
Age, yr	39.9 (14.1)	41.4 (11.0)	43.0 (11.2)	0.338
Height, cm	167.1 (5.5)	166.8 (6.0)	166.6 (4.6)	0.506
Weight, kg	65.3 (8.4)	66.6 (9.8)	67.2 (7.5)	0.237
BSA, m ²	1.71 (0.12)	1.74 (0.14)	1.75 (0.09)	0.181
Smoking duration, yr	‡	17.6 (11.3)	19.7 (11.6)	0.124
Smoking intensity, CPD*	‡	18.8 (8.4)	19.6 (9.0)	0.622
Pack-years	‡	18.3 (20.2)	20.3 (20.0)	0.482
Years of abstinence from smoking	‡	‡	5.6 (1.7)	‡
No. of subjects in each age interval, yr				
20-29	48	21	12	
30-39	51	27	29	
40-49	34	36	14	
50-59	24	12	18	
60-69	19	9	9	
70-79	4	4	0	
Total	180	109	82	

Abbreviations: BSA: body surface area; N: nonsmokers; C: current smokers; E: ex-smokers.

Numbers in parenthesis indicate the standard deviation.

*: The *p* value was calculated by ANOVA for the differences in anthropometric characteristics and by two-sample *t*-test for the differences in smoking variables among subjects studied.

‡: Cigarettes per day.

Table 2. Spirometric Data of the Study Population

	Nonsmokers (N=180)	Current Smokers (N=109)	Ex-smokers (N=82)	<i>p</i> *
Age, yr	39.9 (14.1)	41.4 (11.0)	43.0 (11.2)	0.338
FVC, L	3.82 (0.62)	3.85 (0.59)	3.86 (0.48)	0.685
FEV ₁ , L	3.22 (0.61)	3.18 (0.56)	3.13 (0.45)	0.590
FEV ₁ /FVC, %	84.0 (5.6)	82.5 (6.6)†	82.2 (6.5)†	0.018
FEF _{25-75%} , L/s	3.59 (1.17)	3.22 (1.45)†	3.28 (1.28)†	0.016
FEF ₇₅ , L/s	6.68 (1.67)	5.97 (1.54)†	6.04 (1.64)†	0.009

Abbreviations: FVC: forced vital capacity; FEV₁: forced expiratory volume in 1s; FEF_{25-75%}: mean forced expiratory flow at middle half of FVC; FEF₇₅: forced expiratory flow at 75% FVC; N: nonsmokers; C: current smokers; E: ex-smokers.

*: The *p* value was calculated by ANOVA for the differences among various smoking groups.

†: Values significantly differ from those of nonsmokers by Scheffe's multiple comparison, *p* < 0.05.

and that 86 (79%) had a smoking duration of less than 20 years. Thus, Taiwanese men consumed fewer cigarettes than Caucasian subjects in terms of amount and duration of smoking.

It is of note that there were virtually no appreciable differences in the mean age and body size among normal nonsmokers, smokers, and ex-smokers with healthy respiration. In addition, the duration and intensity of smoking did not differ significantly between current smokers and ex-smokers.

Therefore, direct comparisons can be made to evaluate the effects of smoking and smoking cessation on lung function variables. For FVC and FEV₁, similar values were observed within smoking category groups (Table 2). However, the mean values of FEV₁/FVC, FEF_{25-75%}, and FEF₇₅ in nonsmokers were significantly higher than those observed in current smokers and ex-smokers. There were also no differences in these lung function variables between current and ex-smokers.

For DLCO and DLCO/VA, significant lower mean values were found among current smokers in comparison with nonsmokers and ex-smokers (Table 3). However, no such differences between nonsmokers and ex-smokers were noted. DLCO was already reduced in smokers even in the youngest age group of the present study. Thus, it appears that the decrease in DLCO occurs rapidly when one begins to smoke, regardless of smoking intensity. After correcting for the effects of age and body size, the %p DLCO and %p DLCO/VA of current smokers were still lower than those of nonsmokers and ex-smokers ($p < 0.005$). But there was a lack of significant differences in the %p VA values within smoking category groups.

As shown in Table 4, the baseline Rrs in current smokers was found to be higher ($p < 0.001$) than those of nonsmokers and ex-smokers. On the other hand, the Rrs in ex-smokers was comparable to that of normal nonsmoking subjects. Of more interest is the finding that in 24.7% of current smokers, Rrs increased by twice or more by the highest dose of

methacholine, compared with 0% of nonsmokers ($p < 0.0001$) and 19.5% of ex-smokers. Thus, current smokers had more-sensitive airways than nonsmokers according to the methacholine challenge test.

Current smokers had the lowest baseline respiratory conductance (Grs) among the 3 groups. Although baseline Rrs and baseline Grs were measured in all subjects, PD₃₅Grs and Cmin, by definition, were only able to be recorded in responders. In methacholine provocation, responders who had measurable PD₃₅Grs and who were smokers showed an increase in Rrs at the earlier dose steps than did ex-smokers. The Cmin of responders who had quit smoking was significantly higher than that of current smokers, indicating a decreased bronchial responsiveness in ex-smokers in terms of methacholine dose.

The dose-response curves of the airway to methacholine challenge in a responder and a nonresponder are displayed in Fig. 1. In responders, the prominent increase in Rrs by methacholine and sub-

Table 3. Pulmonary Diffusing Capacity by Smoking Habits

	Noonsmokers (N = 180)	Current Smokers (N = 109)	Ex-smokers (N = 82)	<i>p</i> *
DLCO, ml/min/mmHg	26.60 (5.48)	24.04 (4.12)†	27.66 (4.89)‡	< 0.001
VA, L (STPD)	5.09 (0.68)	5.16 (0.68)	5.19 (0.63)	0.625
DLCO/VA, ml/min/mmHg/L	5.33 (0.85)	4.67 (0.66)†	5.20 (0.61)‡	< 0.001

Abbreviations: DLCO: carbon monoxide diffusing capacity; VA: alveolar volume.

Numbers in parentheses indicate the standard deviation.

*: The *p* value was calculated by ANOVA for differences among various smoking groups.

†: Versus nonsmokers; $p < 0.001$.

‡: Versus current smokers; $p < 0.001$.

Table 4. Bronchial Responsiveness Assessed by Methacholine Challenge

	Noonsmokers	Current Smokers	Ex-smokers
n	180	109	82
No. (%) of responders	0 (0)	27 (24.7)	16 (19.5)
Baseline Rrs, cmH ₂ O/L/s	4.0 (0.7)	4.9 (1.0)*	4.1 (0.8)
L/s/cmH ₂ O	0.27 (0.06)	Baseline Grs, 0.20 (0.07)*	0.25 (0.06)
PD ₃₅ Grs in responders, unit	> 50	8.9 (3.2)†	11.2 (3.5)
Cmin in responders, mg/ml	> 25.6	6.7 (4.3)†	9.8 (4.8)

Abbreviations: Rrs: respiratory resistance; Grs: respiratory conductance; Cmin: the minimal concentration of methacholine at the point where Rrs began to increase; PD₃₅Grs, the cumulative dose of methacholine that resulted in a 35% decrease in Grs.

*: $p < 0.001$ comparing current smokers with ex-smokers or nonsmokers.

†: $p < 0.05$ comparing current smokers with ex-smokers. Only data of responders are shown.

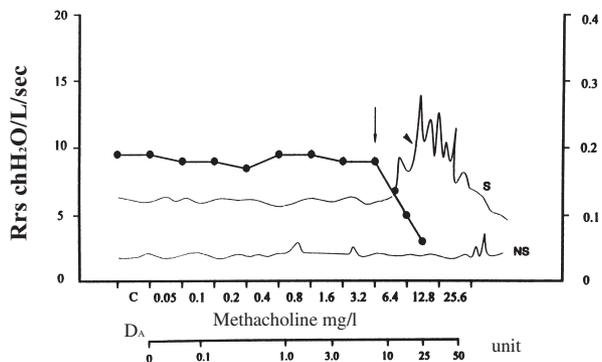


Fig. 1 Dose-response curves for methacholine provocation in a nonsmoker (NS), and a current smoker (S) who was a responder to the challenge. C, control; DA, cumulative dose of methacholine at which Rrs began to rise (arrow) in a positive reaction. Arrowhead: the point where terbutaline was administered to relieve bronchospasm. Note that the baseline Rrs in the smoker was higher than that of the nonsmoker. A dark circle represents the value for respiratory conductance (Gr).

sequent recovery by terbutaline inhalation produced a triangular curvilinear pattern. In contrast, the Rrs of nonresponders did not increase up to the maximum concentration.

In consideration that the DA of methacholine is capable of provoking a positive reaction, values were significantly lower in smokers (8.3; 4.1 units) than in ex-smokers (10.5; 4.2 units) (Fig. 2). In responders, similar values for SGrS in current smokers and ex-smokers were found, being 0.029; 0.016 and 0.026; 0.018 L/s/cmH₂O/min, respectively. Therefore, bronchial sensitivity did not correlate with bronchial reactivity in this study group, and bronchial reactivity was independent of smoking status in responders.

As shown in Table 5, neither DA nor SGrS were well correlated with age or anthropometric variables in either smokers or ex-smokers. In contrast, the correlations of DA and SGrS with smoking variables somewhat differed. The inverse correlations of DA to smoking exposure were weak for the amount of

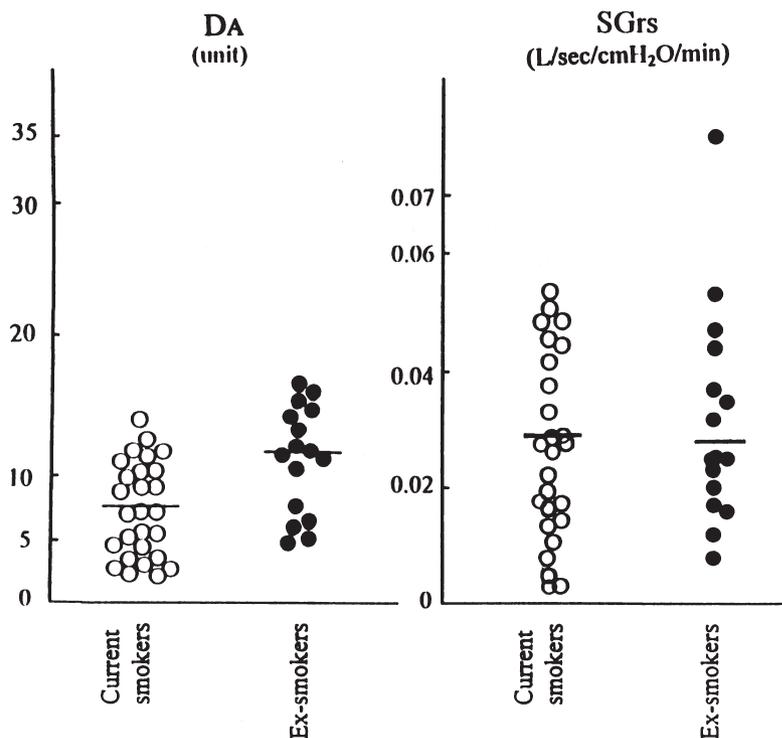


Fig. 2 Values for DA and SGrS in current smokers and ex-smokers, both groups of which were responders to methacholine challenge.

Table 5. Correlation of Bronchial Sensitivity (DA) and Bronchial Reactivity (SGrS) with Age, Body Size, and Smoking Variables in Responders

Variable	Current Smokers		Ex-smokers	
	DA	SGrS	DA	SGrS
Age, yr	-0.122	0.076	-0.094	0.053
Height, cm	0.097	0.113	0.088	0.074
Weight, kg	0.022	0.038	0.043	0.018
Smoking duration, yr	-0.302*	0.085	-0.281*	0.074
Smoking intensity, PPD	-0.120	0.033	-0.109	0.052
Pack-yrs	-0.424*	0.106	-0.354*	0.125

*: $p < 0.001$.

Abbreviations: PPD, pack per day.

Table 6. Mean Values of Spirometric Variables in Responders by Smoking Status

Variable	Current smokers (N=27)		Ex-smokers (N=16)	
	FVC (%p)	93.5 ; 4.6	92.7 ; 4.4	
FEV ₁ (%p)	90.3 ; 4.2	91.8 ; 5.0		
FEV ₁ /FV (%)	75.9 ; 6.4*	80.1 ; 6.2		
FEF _{25%-75%} (%p)	72.5 ; 14.2	77.9 ; 16.1		

*: $p < 0.05$.

smoking per day, but were much stronger for smoking duration and pack-years. This relationship is present regardless of smoking status. On the other hand, SGrS was not closely related to any of the smoking variables.

In Table 6, the spirometric data of responders are compared according to their smoking habits. It is evident from this table that values for FEV₁/FVC were lower in smokers than in ex-smokers among responders. Thus, smoking responders have a higher degree of airflow limitation than their ex-smoking counterparts. There were no differences in values for FVC, FEV₁, and FEF_{25-75%} between these two groups.

DISCUSSION

Our results clearly demonstrate that smokers with healthy respiration show an increased BR to methacholine inhalation compared with normal non-smokers and ex-smokers. The effects of cigarette smoking on nonspecific BR is a matter of debate.^(6,8,9) The lack of consistent data in the literature may be due to the small sample sizes studied and the criteria

employed for subject selection. In fact, epidemiologic surveys involving large populations are often limited by the methodology for measurement of BR.

The conventional bronchoprovocation test by means of inhalation challenge^(11,12) for a given bronchoconstrictor stimulus (antigen, methacholine, histamine, etc.) is a time-consuming procedure. Subjects are required to perform deep inspirations and repeated forced expiratory maneuvers in order to obtain a predicted fall in FEV₁. Furthermore, forced expiration itself might induce bronchoconstriction. Using the present oscillation technique, we were able to conduct measurements of BR on a large number of subjects who were a representative sample from the general male population in a Taiwan metropolitan area.

Although relationships between smoking habits and airway responsiveness have been reported by several investigators, the characterizations of subjects studied may be a source of potential bias. For example, Rijcken and coworkers⁽¹⁹⁾ conducted histamine challenge tests to observe the distribution of BR in both symptomatic and asymptomatic subjects, in which the men with wheezing tended to have lower mean values of VC and FEV₁ than did the men who were asymptomatic or had only cough and phlegm. In a report by Cerveri and colleagues,⁽⁸⁾ the relationship between smoking habits and BR was studied in completely asymptomatic subjects with normal lung function, in which a higher frequency of subjects with lower FEV₁ and FEF_{25-75%}, compared to that of nonsmokers, was found in the group of heavy smokers. It is of interest to note that our respiratory healthy smokers already had lower DLCO, FEV₁/FVC, and FEF_{25-75%} values than did normal nonsmokers. Thus, different results may be obtained as a reflection of differences in stages of developing airflow limitation.

It is well documented that the effects of cigarette smoking on increased BR is dose-related.^(20,21) Pack-years was consistently found to be correlated with the proportion of current smokers who showed a positive challenge test. The relationship between other smoking variables and BR is somewhat vague. A significant effect on BR of smoking intensity (number of cigarettes per day or PPD; 1 pack=20 cigarettes) was demonstrated by Rijcken and colleagues⁽²²⁾ and Cerveri and associates.⁽⁸⁾ On the con-

trary, Casale and coworkers⁽²³⁾ failed to establish a significant relationship between BR and daily number of cigarettes. Instead of smoking intensity, years of smoking appeared to have a significant correlation with D_A in the present study. The discrepancy of these findings related to the association of smoking variables with nonspecific BR may be explained by differences in the number and age range of subjects studied, and the highest cumulative dose of methacholine or histamine inhaled (sometimes less than 5 mg).⁽⁸⁾

Although smoking is an important factor in increased loss of lung function, the mechanisms are, to a wide extent, unknown. There are now many ongoing investigations to understand the pathogenesis and to determine the early signs of chronic obstructive pulmonary disease (COPD) with the aim of making early intervention possible. Our data indicate that current smokers had significantly lower values for FEV_1/FVC , $FEF_{25-75\%}$, and FEF_{75} than did non-smokers, suggesting the presence of subclinical airflow limitation. Since active cigarette smoking has been shown to cause an acute increase in airway resistance in normal volunteers in the laboratory,^(24,25) and there was indeed an increased Rrs in current smokers in the present study, the adverse effects of cigarette smoking on spirometric values may be explained by increased resistance to airflow.

Previous observations concerning the relationship between airway caliber and BR were inconclusive. Yan and coworkers⁽²⁶⁾ found that there was a good correlation between FEV_1/FVC and $PD_{20}FEV_1$ values in subjects with COPD but not in asthmatic subjects. Cerveri and colleagues⁽⁸⁾ demonstrated that smoking habits affected bronchial reactivity in normal subjects even in the absence of airway obstruction. However, there were no significant differences in FEV_1 and $FEF_{25-75\%}$ between subjects with lower and those with higher bronchial reactivities. O'Conner and coworkers⁽²⁷⁾ reported that passive smoking was associated with significantly lower pulmonary function (although in the normal range), but not with increased BR among young adults denying asthma. It has also been suggested that BR predicts respiratory symptoms independent of pulmonary function level.^(19,28)

Several investigators have demonstrated the effect of acute bronchitis on airway reactivity.⁽²⁹⁻³¹⁾ In

a murine model, Martin and associates⁽²⁹⁾ were able to determine that BR was heightened in mice infected with *Mycoplasma pneumoniae* at days 7 and 14, but was not at day 21. In the clinical setting, patients suffering from upper respiratory tract infections may precipitate an abnormal response to inhaled challenge tests for as long as 7 weeks.⁽³⁰⁾ Therefore, infection-induced BR should be considered in a population survey. However, only a relatively small proportion (around 1/3) of acute bronchitis patients develop bronchial hyperresponsiveness, and some of them were diagnosed with asthma in the 5 years subsequent to their bronchitic episode.⁽³¹⁾ Thus, many investigators have chosen 2 to 4 weeks after colds to exclude BR related to airway infection.^(8,10)

In the present study, there was an association between cigarette smoking and a lower level of lung function, and between cigarette smoking and bronchial hyperresponsiveness. Thus, appropriate interpretation of our results with respect to the natural history of COPD may involve the recognition of the role played by increased BR in the development of chronic airway obstruction. There are several possibilities. First, bronchial hyperresponsiveness precedes the occurrence of airway obstruction, and leads toward the latter; second, hyperresponsiveness is simply an effect of airway obstruction; and finally, hyperresponsiveness of the airway is not dependent on airway caliber. Although we are unable to give a definite answer to these speculations, our data obviously did not show that increased BR resulted from obstructed airways, because the spirometric values in our smokers were within a normal range.

Several investigators^(4,32) have reported that the onset of defects in pulmonary diffusion appears to occur early in cigarette smokers. Although alveolar destruction and loss of gas exchange surfaces can lower the DLCO, such anatomical changes associated with pulmonary emphysema, one of the major consequences of smoking exposure, do take time to develop. In addition, impairment of FEV_1/FVC observed in this study was not of sufficient magnitude to be regarded as clinical evidence of airway obstruction. Thus, it is unlikely that such a reduced FEV_1/FVC would account for the lower DLCO in our current smokers. Moreover, Rankin and associates⁽³³⁾ demonstrated that impairment of diffusion could occur in the absence of impaired ventilatory

function.

It is well known that COHb% is increased in smokers. This might reduce the DLCO in a manner similar to mild anemia. However, since correction for COHb% was made in our sample, carboxyhemoglobin alone cannot explain the lower DLCO in smokers. On the other hand, since nicotine is a cutaneous vasoconstrictor,⁽³⁴⁾ the potential effect of nicotine in causing pulmonary vasoconstriction and inducing changes in regional blood flow by reducing pulmonary perfusion should also be considered.

On smoking cessation, the improvement in DLCO among ex-smokers was rather rapid, though a time course of improvement could not be defined. The mean %pDLCO of men who quit smoking within the past 5 years (N=46) was already 105.63%, and was 105.20% for those off cigarettes for more than 5 years (N=36). Therefore, it does appear that there is improvement in DLCO with smoking cessation, and the effects of cumulative cigarettes consumption are in part reversible. This may be explained by the abolition of the aforementioned processes or factors responsible for the decrease in DLCO associated with smoking.

Although there may be slower rates of decline in pulmonary function and improvement in survival,⁽³⁵⁾ smoking cessation does not necessarily result in a complete recovery of the impaired functional level. Cerveri and coworkers⁽⁸⁾ noted that bronchial reactivity for ex-smokers was found not to differ from that of normal nonsmokers. Knudson and colleagues⁽²⁾ suggested that both reversible and irreversible phenomena were present with respect to the effects of smoking cessation on the DLCO. In the present study, giving up smoking produced no improvement in FEV₁/FVC or FEF₂₅₋₇₅%. In addition, there was still an increased BR in ex-smokers compared to nonsmokers, despite the similar values for baseline Rrs between the 2 groups of subjects. Thus, the effects of smoking on deterioration of lung function, to some extent, are irreversible.

In conclusion, our study provides evidence that cigarette smoking is associated with increased BR, which can occur in the absence of apparent airway obstruction. A link between cigarette smoke exposure and a decreased level of pulmonary function was also demonstrated. Since not all smokers develop bronchial hyperresponsiveness, it is feasible to

closely follow-up the lung function level of those who continue to smoke and are responders to bronchial challenge. The functional impairment resulting from cigarette smoking, however, is at least partially reversible and can be rapid upon smoking cessation. But we were unable to determine the exact duration of smoking or smoking cessation required for producing or reversing the functional deficit because our data are cross-sectional and should be interpreted with caution. Further investigations on patients with COPD are necessary to assess the cumulative effects of smoking exposure.

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