Lung Diffusing Capacity for Carbon Monoxide (DLco-SB): the Influence of Cigarette Smoking

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ABSTRACT:

BACKGROUND:

Most tests of lung function used in the evaluation and follow-up of the pulmonary effect of smoking reflect airway function alone such as standard spirometry. Whereas, the best established test that reflect alveolar function is the single-breath carbon monoxide diffusing capacity (DLco-SB) especially when this is expressed per liter of alveolar volume (DLco/V_A). Accordingly, to study the effect of smoking on both airway and alveolar functions, it is necessary to use DLco/V_A test in addition to standard spirometry.

OBJECTIVE:

The present study was designed to evaluate the effect of cigarette smoking on lung diffusion, to correlate the effect of cigarette smoking and smoking cessation on lung diffusion and to find out whether the effect of cigarette smoking on lung diffusion is reversible.

SUBJECTS AND METHODS:

The effect of cigarette smoking on spirometric indicators of ventilatory function (FVC, FEV_1%, PEFR) and on lung diffusing capacity for carbon monoxide (DLco-SB/V_A) was evaluated on two occasions 6 months apart in 94 middle-aged, asymptomatic, male subjects, 56 smokers and 38 nonsmokers.

RESULTS:

All subjects were within the normal predicted spirometric and lung diffusion values (80-120%). The values of FVC, FEV_1, FEV_1/FVC% and PEFR averaged more than 94% in never smokers (n = 38, mean age 43.57 years), 85% predicted in smokers (n = 56, mean age 42.54 years). However, the mean rate of decrease in spirometric and lung diffusion values (DLco/V_A) between smoker and non-smokers were significant ($p<0.05$). fourteen subjects (14) who initially were smokers became sustained ex-smokers within six months of the first measurement, however, comparing the mean values of these parameters between the two groups reveals statistically significant differences ($p<0.05$); since that the values of DLco and DLco/VA in ex-smokers were significantly greater than those of current smokers and approached the values of those who had never smoked. In ex-smokers the mean values of DLco/V_A rose, averaging 90% predicted at the first assessment but 97% predicted six months later.

CONCLUSION:

The values of FVC, FEV_1, FEV_1/FVC%, PEFR and Lung diffusing capacity for carbon monoxide (DLco/V_A) were lower in smokers than in never smokers. Ex-smokers had spirometric and lung diffusion values similar to those of never smokers even when spirometric values and DLco/V_A were known to have been reduced while they were smoking.

KEY WORDS: dLco-SB, spirometry, smoking

INTRODUCTION:

It is well recognized that cigarette smoking has a deleterious effect on lung function. A diminished value for the single-breath carbon monoxide diffusing capacity (DLco-SB) has been reported in cigarette smokers [1, 2]. In addition to spirometry, it is often useful to determine the diffusion characteristics of a smoker's lungs (DLco) during their assessment in the pulmonary function laboratory, since that spirometry and DLco/V_A (Lung diffusing capacity for carbon monoxide expressed per liter of alveolar volume, (V_A)) reflect both airway and alveolar function[3]. Although the conventional single breath diffusing capacity (DLco-SB) test has been accepted as standard noninvasive test to assess the integrity of pulmonary vasculature, numerous pitfalls limit its

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utility. One factor is the effect of carbon monoxide (CO) in cigarette smoke, which raises carboxyhemoglobin (COHb) to as high as 10-15% in current smokers, whereas values are usually 1-2% in nonsmokers[4]. So that this factor in smokers will underestimates the percent of predicted DLco-SB values, unless additional adjustments are made for increases in COHb. Accordingly, standard DLco-SB test that use a breath-hold time of 10 seconds was considered in this study, therefore, DLco-SB when appropriately adjusted, would not change with increasing COHb [5, 6].

The present study was designed to evaluate the effect of cigarette smoking on lung diffusion, to correlate the effect of cigarette smoking and smoking cessation on lung diffusion and to find out whether the effect of cigarette smoking on lung diffusion is reversible.

SUBJECTS AND METHODS:

Ninety four (94) healthy, asymptomatic, male subjects (56 smokers and 38 nonsmokers, aged 35-45 years) with normal medical history, physical examination and within the normal predicted spirometric values (80-120%) were studied. In other words, subjects with FEV_1% more than 75% predicted were included with respect to subjects who were excluded from this study because of low spirometric values suggestive of undiagnosed airway obstruction (FEV_1% below 70% or an FEV_1 less than 75% predicted). In addition, subjects with the following criteria were excluded: History of neuromuscular, musculoskeletal or cerebrovascular diseases that could affect the test performance, signs of anemia or chest disease on physical examination and obese subjects (BMI > 30).The demographic and anthropometric parameters of the study group are given in tables (1).

Table 1: Demographic and anthropometrical data of the studied groups.

Parameter	Age (years)	Height (cm)	Weight (kg)	BSA (m^2)	BMI
Smokers n = 56 males	42.54 ± 3.26	171.9±7.02	67.63 ± 8.9	1.92 ± 0.15	24.59±1.83
Nonsmokers n = 38 males	43.57 ± 3.27	170.6 ± 6.8	69.83 ± 7.4	1.91 ± 0.13	24.05±1.62
P value	0.274	0.431	0.827	0.183	0.121

Values are expressed as mean ± SD.
P value greater than 0.05 is considered to be statistically not significant.

Subjects involved in this study were selected for their consistency of smoking or non-smoking habit as assessed by questionnaire at the beginning of the work. Healthy nonsmokers include subjects who had never smoked in the past while the healthy smokers are those who had a smoking background of at least one pack-year (pack-year = number of packs of cigarettes smoked per day multiplied by the number of years of smoking). In other words, only consistent smokers of more than 15 cigarettes a day were included. For the purpose of assessing the reversibility of smoking effects, the smokers group was classified into current smokers and ex-smokers. Current smokers included those who were still smoking at least in the last 6 months period preceding the study (56 subjects). Ex-smokers were those smokers who had given up their smoking habit more than 6 months (quitting smokers; 14 subjects), in which spirometry and DLco were performed on two occasions, at the beginning and end of the 6 months.

Measurements:

The standing height and body weight were measured; therefore, body surface area (BSA) and body mass index (BMI) were automatically computed according to the following equations [7]:

BSA= [Wt (kg) 0.425 X Ht (cm) 0.725] X 0.007184

BMI= Weight (kg) / (Height (m)) ^{2}

Spirometry and DLco-SB were measured using a computer-based automated system (Master Lab Proversion 4.3, JAEGER Gmbh-Germany)[8]. Standard lung function protocols based on the American Thoracic Society recommendations (ATS 1995)[9] were followed. Current smokers were asked to stop smoking at least 4 hours before the test. Tests were performed at 10-12 am, an ambient temperature of 13-23 C and relative humidity of 45-50%. Pulmonary function tests were performed in a sitting

position with nose clips. Forced expiratory volume in one second (FEV_1), FEV_1 %, forced vital capacity (FVC) and PEFR were obtained. Furthermore, static lung volumes; total lung capacity (TLC) and residual volume in addition to alveolar volume (VA) were calculated indirectly by diluting the Helium in the lungs (dilution technique)[10,11]. The hemoglobin of each subject involved in this study (gram %) was estimated and the DLco results were corrected to a standard hemoglobin concentration of 14.6 g/dl [12,13].

Statistics:

All data obtained were statistically analyzed using the Statistical Package for the Social Science (SPSS, version 17). The mean, standard deviation, minimum and maximum limits of the variables were obtained from the descriptive and frequency programs. The student's t-test for paired and unpaired samples was used for data analysis where appropriate. However, differences were regarded as significant when the P value was less than 0.05.

RESULTS:

As it is clear from table (1) that represents the demographic and anthropometrical parameters of the studied subjects, there were no significant differences between nonsmokers and smokers regarding Age, Height, Weight, BSA and BMI ($p<0.05$).

Table(2) shows the percent predicted pulmonary function values (DLco, DLco/V_A, TLC, FVC, FEV_1% and PEFR) of all subjects involved in this study. It was noticed from this table that all pulmonary function parameters of nonsmokers were within the normal predicted limits (80-120%), which further supported the criteria for inclusion as reference healthy subjects [14]. Moreover, when the values of DLco, DLco/VA, TLC, FEV_1% and PEFR of smokers were compared with that of nonsmokers, results had revealed that smoking caused significant decrease in DLco, DLco/VA, FEV_1% and PEFR ($p<0.05$) which improved after smoking cessation.

On the other hand, the TLC and FVC had not changed significantly with smoking ($P>0.05$).

In order to examine the effect of smoking, smokers were classified according to smoking history into 42 current smokers (smoking for at least six months prior to study) and 14 ex-smokers (stopped smoking for at least 6 months). Likewise and apart from the percent predicted FVC and TLC, all lung function parameters had decreased significantly in current smokers as compared to nonsmokers. On the other hand, lung function parameters were not significantly different between ex-smokers and nonsmokers indicating an improvement in the ventilatory and diffusion function of the lungs following smoking cessation. This is clear since that the values of DLco and DLco/VA in ex-smokers were significantly greater than those of current smokers and approached the values of those who had never smoked ($p<0.05$).

Adjustment of DLco for hemoglobin (Hb-adjusted DLco):

The measured DLco was adjusted for hemoglobin level according to the method described by Cotes and co-workers [12, 13] and following the recommendation of the American Association of Respiratory Care (AARC, 1999) [14].

Hb-adjusted DLco = measured DLco X [(I0.22+Hb) / 1.7 X Hb]……. (Cotes, 1993)

Table (3) shows the effect of hemoglobin correction on mean DLco values obtained from all subjects studied. All subjects had Hb values above 14g/dl and when DLco values were corrected for Hb, all groups showed little but statistically non significant differences (0.5 ml/min/mmHg) between the measured and Hb-corrected DLco values ($P>0.05$). However, this difference seemed to be of little clinical significance because Hb was within the normal range when compared with those with Hb values below 14g/dl [9,13].

Table 2: The percent predicted (%P) pulmonary function values of 94 healthy, male subjects involved in this study with respect to their smoking status.

Parameter	Nonsmokers (N) n = 38	Current Smokers (C) n = 56	Ex-smokers (E) n = 14
%p FVC (L) rang	96.60 ± 10.21 85.00 – 119.23	94.45 ± 9.62 80.00 ± 107.5	95.54 ± 9.81 83.00 – 115.00
FEV_1 % rang	91.73 ± 7.43 80.7 – 107.35	82.21 ± 6.30* 75.00 – 112.23	90.68 ± 6.93** 77.00 –108.55
% PEFR (L/min) rang	94.62 ± 7.55 82.00 – 110.00	89.49 ± 5.67* 80.00 – 110.05	93.84 ± 6.94** 80.91 – 108.45
%p DLCO (ml/min/mmHg)	94.09 ± 8.20 29.85 ± 4.35	87.65 ± 9.92* 25.42 ± 2.87	92.09 ± 9.42** 27.62 ± 2.82
%p DLCO/V_A (ml/min/mmHg/L)	101.87 ± 8.41 4.65 ± 0.66	90.59 ± 10.52* 4.49 ± 0.49	97.44 ± 9.63** 4.62 ± 0.44
%p TLC (L)	92.23 ± 7.9 6.46 ± 0.62	91.11 ± 8.79 6.19 ± 0.59	91.51 ± 8.42 6.43 ± 0.61

Values are expressed as mean ± SD.
P value less than 0.05 is considered to be statistically significant.
* C versus N
** E versus C
%p DLCO = Hb adjusted DLCO

Table 3: Effect of Hemoglobin (Hb) correction on mean DLco values.

Group	Hb (g/dl)		DLco (ml/min/mmHg)	Hb-corrected DLco	P value
	Range	Mean ± SD			
Smokers n = 56	14.6 -16.0	15.14± 0.59	25.42±2.87	25.19±3.5	P = 0.06
Nonsmokers n = 38	14.2 -15.8	14.89± 0.89	29.85±4.35	29.49±3.86	P = 0.06
Ex-smokers n = 14	14.1-15.3	14.92± 0.97	27.62±2.82	27.17±2.38	P = 0.07

Values are expressed as mean ± SD.
P value greater than 0.05 is considered to be statistically not significant.

DISCUSSION:

The effect of smoking on lung diffusing capacity for CO (DLco) has long been a matter of intensive research. Early investigations of McGrath and Thomas (1959) and of Anderson and shepherd (1969) did not demonstrate an effect of smoking on DLco[15,16]. In contrast, lower DLco values in smokers have been demonstrated by a subsequent study with an average difference of approximately 5 ml/min/mmHg between smokers and nonsmokers [17]. These values are close to what has been found in the present study as shown in table 2. However, before blaming cigarette smoking as a causative factor for reducing DLco and DLco/V_A, many variables known to affect lung diffusion have to be excluded, on the top of which is lung volume. In the present study, no significant differences in the %p FVC or %p TLC were observed between smokers and nonsmokers, consequently, a major variable which is the total surface area available for diffusion may be blamed as a cause for the differences in DLco and DLco/V_A

observed between smokers and nonsmokers [18].

Despite that values of DLco/V_A are sensitive to uneven distribution of inspired gas, of the diffusion-alveolar volume ratio, and of the perfusion-diffusion ratio, the results of Cotton et al. 1998[19] suggested that the lowering effect of smoking on DLco was due to smoke-related changes in alveolar capillary diffusion, rather than due solely to alterations in the distribution of ventilation. Thus, another factor, which can interfere with lung diffusion, is the ventilatory function of the lungs. Referring back to table 2, all spirometric parameters of smoker subjects were well within the normal predicted range (80-120%) indicating normal ventilatory function, thus eliminating another important factor which might alter lung diffusion. Since that lung diffusion in smokers may be influenced by the presence of carboxyhemoglobin (COHb) in mixed venous blood[11], in the present study, subjects were asked not to smoke on the morning of the test in order to minimize the carboxyhemoglobin (COHb) level (AARC, 1999)[14]. However, other investigators have pointed out, this factor alone cannot account for the lower DLco in current smokers[2]. Although carboxyhemoglobin (COHb) is often increased in smokers[6], the American Thoracic Society recommendation for adjusting the DLco for COHb remains optional [20].

In order to answer the question whether DLco decrement in smokers is reversible or not, the smokers group was classified into current and ex-smokers. The higher values of DLco and DLco/V_A in ex-smokers than those of current smokers (table 2) were supported by several studies, since they noted that ex-smokers tended to have values similar to persons who never smoked [20,21]. Cumulative smoking history had an irreversible effect: although ex-smokers on average always had a higher DLco than continuing smoker, DLco tended to be lower in ex-smokers who had accumulated more pack years of smoking. Hence in the early years of smoking the predominant factor reducing DLco in smokers is likely to be the reversible factor and to be found in a high proportion of smokers. Irreversible changes are due to emphysema which develops in a smaller proportion of smokers and later in the smoking history by observing DLco and DLco/V_A values lower than those predicted on the basis of standard factors (age, height, gender) plus factors expressing the average effects of cumulative cigarette consumption and current smoking. [21]. The fact that DLco changes as a function of hemoglobin concentration is well known. DLco value may be corrected if the subject's hemoglobin is known [22]. Different methods for Hb adjustment have been reported. The method of Cotes and associates 1993[12] in which DLco is adjusted to a standard Hb concentration of 14.6 g/dl is most widely used and it has been utilized in this study according to the recommendations provided by the American Association for Respiratory Care (AARC, 1999). As shown in the data given in table 3, the adjustment of DLco for hemoglobin seemed to have a small non significant effect on the measured DLco value because all subjects herein had Hb values within the normal range (above 14 g/dl, which is near the upper normal limit [9,13].

Concerning the relationship between alveolar volume (VA) and DLco, the observed differences between DLco and DLco corrected per alveolar volume (DLco/V_A) among the studied groups (table 2), were in consistent with the studies of Lebecque, P., Mwepu, A., Veriter, C., et al.[23] and Nabors, L..K., Baumgartner. W. A., Janke, S. J. et al.[24]. Despite the mechanism of alteration in DLco-single breath with alveolar volume is not yet known, in 1986 Lebecque et al. had investigated the existence of hysteresis in human lungs in vivo. They conclude that two mechanisms need to be considered: an active filling of the capillary bed, or more likely, an unfolding of the alveolar capillary membrane. Whereas, a more recent study conducted by Nabors et al 2003 has demonstrated that when alveoli are inflated, the stretched alveolar walls draw their capillaries into oval cross sections that caused the disk-shaped red blood cells to be oriented near alveolar gas, thereby minimizing diffusion distance thus accelerating gas diffusion.

CONCLUSION:

The present study revealed that the reduction in spirometric and lung diffusing capacity for carbon monoxide (DLco/V_A) found in cigarette smokers is commonly reversible. In addition, to study the effect of cigarette smoking on lung function, it is necessary to allow not only for conventional spirometry, but also for DLco/V_A test.

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