CLINICAL STUDY

Does the expired-air carbon monoxide level reflect the severity of inflammation in COPD?

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Abstract

Objectives: **The aim of this study is to evaluate the expired-air carbon monoxide level which relates to the severity of inflammation in patients with chronic obstructive pulmonary disease (COPD).**
Design: **Cross sectional study.**
Setting: **Cukurova University, Faculty of Medicine, Department of Chest Disease, Out-patient clinic.**
Patients: **The characteristics of patients enrolled in this study were following; 20 ex-smokers with stable COPD (mean age: 68.8±7.2 years, FEV1: 45.6±16.6 % of predicted), 22 current smokers with stable COPD (mean age: 58.7±8.2 years, FEV1: 57.5±20.9 % of predicted), 20 healthy smokers (mean age: 55.9±6.0 years, FEV1: 86.7±14.2 % of predicted), and 20 healthy non-smokers (mean age: 60.8±9.2 years, FEV1: 95.3±13.5 % of predicted).**
Intervention: **CO level was measured in expired-air.**
Measurement and results: **The measurement of expired-air CO level was measured by DisCOver, carbon monoxide analyser. It is known that the level of expired-air carbon monoxide in healthy smokers (11.8±6.4 ppm) and in current smokers with COPD (11.1±7.4 ppm) is higher than in healthy non-smokers (1.7±0.7 ppm) and in ex-smokers with COPD (2.0±1.8 ppm) (p=0.0001).**
Conclusion: **We assumed that the level of expired-air carbon monoxide may not useful in assessing the severity of inflammation in COPD *(Tab. 1, Fig. 2, Ref. 23)*. Full Text (Free, PDF) *www.bmj.sk*.**
Key words: COPD, carbon monoxide, cigarette smoking, inflammation.

Oxidative stress has an important role in the pathogenesis and progression of COPD. In several studies has been reported an increase of oxidative stress markers in blood, expired-air, and urine in patients with COPD (1–8). Carbon monoxide (CO), which can be simply detected in expired-air, is produced ubiquitously in the body by heme oxygenase (HO) as a breakdown product of heme. HO-1, the stress-induced isoform, is also upregulated by oxidative stress (9). Thus, it is thought that expired-air CO level may be useful in assessing the airway inflammation in COPD patients.

Previous studies have shown that expired-air CO level in chronic inflammatory disease such as asthma, bronchiectasis, and COPD (both current smokers and ex-smokers) was higher than in healthy controls (2, 3, 10, 11, 12). However it was found that quitting smoking may decrease the expired-air CO level in smokers with COPD patients (13). On the other hand, it is known that expired-air CO level may increase due to active or passive cigarette smoking without any pulmonary disease. The effects of inflammation and smoking may interfere with expired-air CO level in current smokers with COPD. That's why several cut-off levels were suggested for expired-air CO level in smokers (6 or 8 ppm) and in patients with COPD (11 ppm) (13–15).

In this study we aimed to evaluate the measurement of the expired-air CO level which is non-invasive, more suitable and repeatable, in assessing the severity of inflammation in patients with COPD.

Patients and methods

In this study, 42 patients with stable COPD, 20 healthy smokers, and 20 healthy non-smokers, admitted to the outpatient clinic

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Tab. 1. Subjects characteristics.

Variable	Non-smokers n=20	Healthy smokers n=20 with COPD	Current smokers n=22 with COPD	Ex-smokers n=20	p
Age (y)	60.8±9.2	55.9±6.0	58.7±8.2	68.8±7.2	0.001
M/F	20/0	18/2	22/0	20/0	0.2
Smoking (pack-years)	–	38.0±19.5	40.5±19.6	40.0±1 0.	10.1
FEV1 (L)	2.7±0.5	2.8±0.5	1.7±0.7	1.2±0.4	0.001
FEV1 (% predicted)	95.3±13.5	86.7±14.2	57.5±20.9	45.6±16.6	0.01
FVC (L)	3.6±0.7	3.6±0.7	3.0±0.8	2.3±0.6	0.01
FVC (% predicted)	98.0±14.7	93.0±14.2	80.3±20.0	68.2±18.0	0.001
FEV1/FVC	77.0±4.6	76.7±4.9	55.3±10.6	46.5±11.3	0.01
Therapy (n)	–	–			
LAAC*			4	5	0.2
LABA**			11	18	0.06
Inhaled steroids			4	17	0.02
Theophylline			2	17	0.01

*LAAC – long acting anticholinergic, **LABA – long acting beta-2 agonist
Variable data are expressed as mean±SD

of Department of Chest Disease, were included. Demographic data of all participants were recorded, and pulmonary function tests, expired-air CO level were measured. The study was approved by local ethical commitee, and informed consent has been received from the participants.

Study groups

***Group 1 (healthy non-smokers);* 20 healthy non-smoker adults with normal pulmonary function tests**

Group 2 (healthy smokers); 20 healthy smokers (at least 20 packs/year) adults with normal pulmonary function tests

Group 3 and 4 (patients with stable COPD); 42 patients with COPD whom postbronchodilatator FEV1/FVC ratio were less than 70% with consistent clinical findings according to GOLD criteria were included. These patients were divided into 2 groups: group 3 (22 current smokers) and group 4 (20 ex-smokers quitted smoking at least for previous year).

From the current smoker COPD patients, four were taking long acting anticholinergic agent and inhaled steroids, eleven were taking long acting beta-2 agonist, and two were taking theophylline tablets and the use of above mentioned drugs in ex-smokers patients with COPD was following: 5, 18, 17 patient. The smoking status of the all participants was questioned in details by the researcher. Current smokers in COPD group and in healthy smokers groups were active smokers during the measurement of expired-air CO level. One of the limitations of this study was that urine cotinine or COHb levels, which are reliable markers for smoking status, were not assessed in this study.

Patients with other systemic inflammatory diseases (diabetes mellitus, chronic renal and hepatic failure, connective tissue diseases), asthma, bronchiectasis, and atopy were excluded from the study. The state of atopy was evaluated by skin prick test. Eligibility criteria for patients with COPD to be included in the study were clinically stable disease with no worsening of symptoms and no need to increase doses of drugs within the previous 4 weeks.

Assays

Pulmonary function tests were measured with Super SPIRO (England). Test results were evaluated according to American Thoracic Society (ATS) criteria.

Measurement of expired-air CO level: Expired-air CO level was measured by DisCOver (MultiSPIRO, USA), an inexpensive, portable CO monitor that has previously been shown to be useful (16, 17). Expired air CO was measured on mornings between 8–10 hours a.m. in all groups. Healthy current smokers and current smokers with COPD have quitted smoking at least two hour ago before the measurement. The subjects were asked to exhale completely, inhale fully, and then hold their breath for 15 s, following breath holding, the subjects were asked to exhale slowly into to analyzer. Two successive recordings were made, and mean value was used in all calculations. The results were recorded from the monitor as unit of ppm.

Statistical analysis

Statistical analyses were performed using the statistical package SPSS v 12.0. For each continuous variable, normality was checked. One way ANOVA and student t test were used for normally distributed data. Since the data was not distributed normally, appropriate non-parametric test was chosen. Kruskal-Wallis test was used between groups more than 2. Since analysis of variance was significant, comparisons using the Mann-Whitney U test were applied. Bonferroni's correction was applied ($p<0.05/n$; where n=number of comparisons) when multiple comparison was made. Spearman Rho Correlation test was used between continuous variables. Results were presented as mean±SD.

Results

The demographic and clinical characteristics of the subjects in the groups were summarized in Table 1. The mean age in group 1 was 60.8±9.2, in group 2 it was 55.9±6.0, in group 3 it was

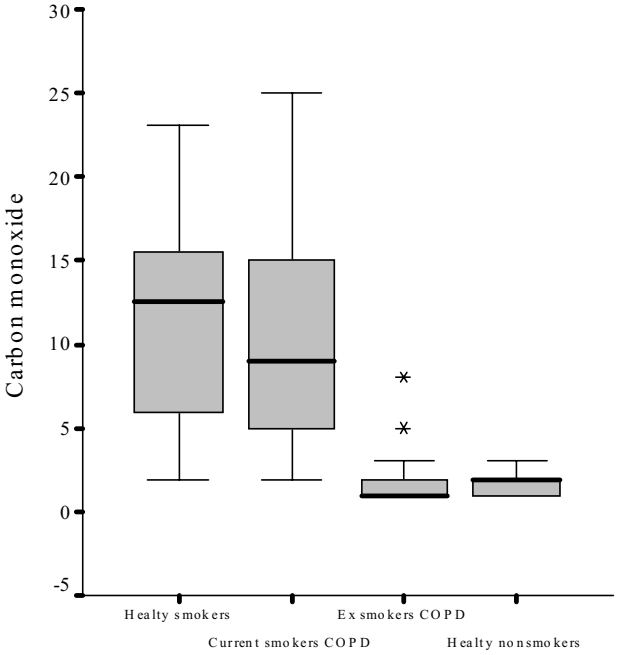

Fig. 1. Distribution of the expired-air CO levels in study groups.

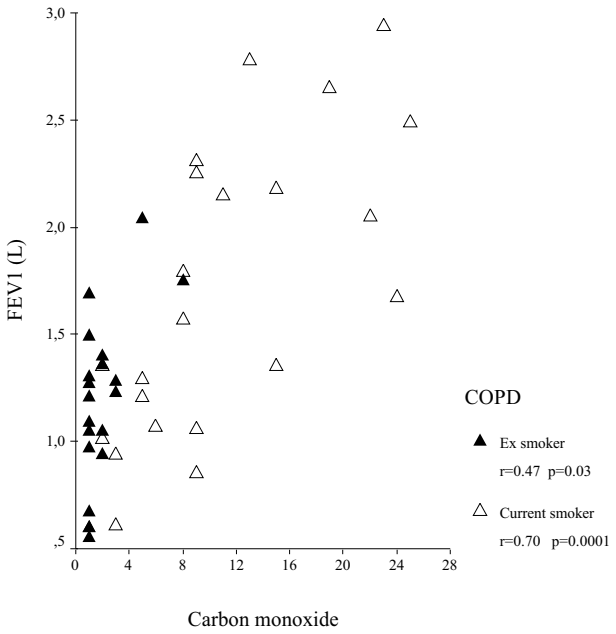

Fig. 2. Correlations between the expired-air CO and FEV1 in patients with COPD.

58.7±8.2, and in group 4 it was 68.8±7.2 ($p<0.05$). In the pulmonary function tests, the mean FEV1 level (1.2±0.4 L) was lower in ex-smokers with COPD than in current smokers with COPD (1.7±0.7 L) ($p=0.001$).

The expired-air CO levels of all groups were shown in Figure 1. The expired-air CO levels were not significantly different between healthy smokers (11.8±6.4 ppm) and current smokers with COPD (11.1±7.4 ppm) ($p>0.05$). However, the expired-air CO levels in both groups were significantly higher than in healthy non-smokers (1.7±0.7 ppm), and ex-smokers with COPD (2.0±1.8 ppm) ($p=0.0001$).

While there was no correlation between FEV1 (L) and expired-air CO level in healthy non smokers and smokers groups ($r=0.10$, $p=0.5$), there was a positive correlation between FEV1 (L) and expired-air CO level in current smokers with COPD group ($r=0.70$, $p=0.0001$) and ex-smokers with COPD group ($r=0.47$, $p=0.03$) (Figure 2).

Discussion

In this study, we have found that the expired-air CO level was significantly higher in healthy smokers and current smokers with COPD than in healthy non-smokers and ex-smokers with COPD. In addition, we found that there was a positive correlation between expired-air level and FEV1 in patients with COPD groups.

Several studies revealed that oxidative stress products were increasing by advanced age (18, 19). However, in one study an opposite result was encountered (20). In our study, although the mean age of ex-smoker COPD group was higher, the expired-air CO level, a marker of oxidative stress, was lower. We assumed that age may not be a determinant factor of the expired-air CO level.

Exhaled CO is potentially influenced by cigarette smoking. The half-life of alveolar CO level was reported to be 150 minutes in chronic smokers (13). Some studies suggested that the high level of exhaled CO may be a useful indicator of cigarette smoke (12, 21, 22). In our study, we asked the patients to stop smoking at least two hours ago before measuring the exhaled air CO level. Urine cotinine and COHb level were not evaluated in this study and it was a study limitation.

Another studies showed that the expired-air CO level was higher in patients with COPD than in both current smoking and non-smoking healthy controls (2, 12, 13). It is postulated that the high levels of exhaled CO found in COPD patients are caused by inflammatory cytokines or reactive oxygen species-induced HO-1 expression and therefore that the measurement of exhaled CO may reflect the airway inflammation. In this study, we found that the expired-air CO level was significantly higher in current smokers with COPD than in ex-smokers with COPD group, but we did not found the difference compared to healthy smokers. In contrast to the results of previous studies, the expired-air CO level in ex-smokers with COPD was almost similar to the healthy non-smokers. This may be explained by two reasons: First, the effect of cigarette on expired-air CO disappeared specially in the ex-smoker COPD group and the second, which was noticeable for us, was the positive correlation between expired-air CO level and FEV1.

Some studies showed that the expired-air CO level was lower in ex-smokers with COPD than in current smokers with COPD

(12, 13). Togores et al have reported that severe airflow limitation might have a negative effect on the expired-air CO level (22). Machado et al showed that α_1-antitrypsin deficiency have low exhaled levels of CO compared with healthy controls and patients with non-α_1-antitrypsin deficient COPD (23). It is worth to mention that the level of expired-air CO level was lower, too. Two main reasons might be associated with this finding. Firstly, in COPD patients with severe airflow limitation it is reported that expired-air CO level might be abnormal due to existence of abnormal ventilation/perfusion ratio and emphysematous changes in lung (23, 24). In this study, we found a positive correlation between FEV1 and expired-air CO level, so we can assume that the severe airflow limitation especially in ex-smokers with COPD might be the cause of low expired-air CO level. Secondly, although a previous study revealed that inhaled steroids have no effect on expired-air CO level (2), in our patients with COPD not only inhaled steroids were used, but also LABA and theophylline. In English literature, no published data were found about the effect of LABA and theophylline on the expired-air CO level. But we speculated that these drugs may affect the expired-air CO level in patients with COPD groups.

In conclusion, we found that expired-air CO level was not different in the ex-smokers with COPD and in the healthy non-smokers, similarly between current smokers with COPD and healthy smokers. These results suggested that expired-air CO level may not be useful in assessing the severity of inflammation in patients with COPD.

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