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RESEARCH

THE MEASUREMENT OF EXHALED CARBON MONOXIDE AND ARTERIAL CARBOXYHEMOGLOBIN CONCENTRATIONS IN MIDDLE-AGED AND ELDERLY PATIENTS WITH COPD

ABSTRACT

Introduction: Arterial blood carboxyhemoglobin concentrations and exhaled carbon monoxide concentrations have been suggested to be inflammatory markers. Arterial carboxyhemoglobin concentrations can be measured from blood gas samples and concentrations of carboxyhemoglobin can be measured from carbon monoxide in exhaled air.

We studied the relationship between arterial carboxyhemoglobin and exhaled carbon monoxide concentrations and disease severity. We evaluated whether arterial carboxyhemoglobin is useful for monitoring disease activity in patients with chronic obstructive pulmonary disease.

Materials and Methods: Fifty-seven middle aged or elderly patients who were admitted to the outpatient clinic were included in the study. Patients were stable for chronic obstructive pulmonary disease and all participants were ex-smokers. The carboxyhemoglobin concentrations were measured and arterial and venous carboxyhemoglobin concentration differences were calculated. Exhaled carbon monoxide concentrations in both control subjects and patients were measured.

Results: There were 13 controls and 44 patients with chronic obstructive pulmonary disease. There were no significant differences in age and smoking history (pack/year) between groups.

The arterial blood carboxyhemoglobin concentrations in patients with chronic obstructive pulmonary disease were higher than those in control subjects ($p<0.001$). There was a significant correlation between carboxyhemoglobin concentrations in arterial blood and exhaled carbon monoxide concentrations ($p<0.001$; r:0.71). Arterial carboxyhemoglobin was inversely correlated with force expiratory volume in one second ($p<0.001$; r:-0.74). Venous blood carboxyhemoglobin concentrations were higher in the chronic obstructive pulmonary disease group than in the controls ($p<0.05$). exhaled carbon monoxide levels of patients were significantly higher than controls ($p<0.001$).

Conclusion: Arterial carboxyhemoglobin is useful for monitoring disease activity in patients with chronic obstructive pulmonary disease.

Key Words: Aged; Middle Aged; Carboxyhemoglobin/Metabolism; Pulmonary Disease, Chronic Obstructive/Blood; Respiratory Function Tests.

ARAŞTIRMA

ORTA VE İLERİ YAŞLI KRONİK OBSTRUKTİF AKCİĞER HASTALARINDA EKSHALE KARBONMONOKSİD VE ARTERYEL KARBOKSİHEMOGLOBİN ÖLÇÜMÜ

ÖZ

Giriş: Arteryel kandaki karboksihemoglobin ve ekshale edilen havada ki karbonmonoksid düzeylerinin inflamatuar marker olabileceği ileri sürülmektedir. Arteryel karboksihemoglobin konsantrasyonu arter kan gazı analizleriyle ölçülür ve ekshale karbonmonoksid ölçümünden de arteryel karboksihemoglobin konsantrasyonu düzeyi tahmin edilebilir.

Bu çalışmada hastalığın şiddeti ve arteryel karboksihemoglobin ile ekshale karbonmonoksid arasında ki ilişki araştırıldı. Kronik obstruktif akciğer hastalığının aktivitesinin monitorizasyonun da arteryel karboksihemoglobinin yararlı olup olmadığı da değerlendirildi.

Gereç ve Yöntem: Polikliniğe başvuran orta ve ileri yaşlı toplam 57 hasta ve kontrol grubu çalışmaya dahil edildi. Stabil dönemdeki kronik obstruktif akciğer hastaları ve kontrol grubu exsmoker idi. Karboksihemoglobin düzeyi hem arter kanında hem de venöz kanda ölçüldü ve arteriovenöz karboksihemoglobin konsantrasyon farkı hesaplandı. Ekshale karbonmonoksid konsantrasyonu hasta ve kontrol grubunda ölçüldü. İstatistiksel analiz SPSS 17.0 kullanılarak yapıldı.

Bulgular: Kırk dört kronik obstruktif akciğer hastası ve 13 kontrol grubu çalışmaya katıldı. Gruplar arasında yaş ve sigara içme süresi (paket/yıl) açısından fark saptanmadı.

Arteryel karboksihemoglobin konsantrasyonu kronik obstruktif akciğer hastalarında kontrol grubundan anlamlı olarak yüksekti ($p<0.001$). Arteryel karboksihemoglobin konsantrasyonu ile ekshale karbonmonoksid arasında korelasyon mevcuttu ($p<0.001$; r:0.71). Arteryel karboksihemoglobin birinci saniyedeki zorlu ekspirasyon volümünün yüzde prediktif değeri ile ters ilişki idi ($p<0.001$; r:0.71). Venöz karboksihemoglobin konsantrasyonu kronik obstruktif akciğer hastalarında kontrol grubundan yüksekti ($p<0.05$). Ekshale karbonmonoksid düzeyi hastalarda kontrol grubundan anlamlı derecede yüksekti ($p<0.001$).

Sonuç: Arteryel karboksihemoglobin kronik obstruktif akciğer hastalığının aktivasyonun monitorizasyonunda faydalıdır.

Anahtar Sözcükler: Yaşlı; Orta Yaşlı; Kronik Obstruktiktif Akciğer Hastalığı; Arteryel Karboksihemoglobin düzeyi; Solunum Fonksiyon Testi.

Introduction

Chronic obstructive pulmonary disease (COPD) is a global health problem and is characterized by airflow obstruction and inflammation of airways. Many factors are associated with the pathogenesis of COPD, including oxidative stress, inflammatory cells, and some mediators (1).

Exhaled carbon monoxide (CO) and arterial blood carboxyhemoglobin concentrations (Hb-CO) increase in inflammatory pulmonary diseases (2). In patients with COPD, airflow limitation calculated by force expiratory volume in one second (FEV1) inversely correlates with several inflammatory indicators, such as nitric oxide (NO) levels in exhaled air (3, 4), 4-hydroxy-2-nonenal levels in the lung (5), and sputum interleukin-8 levels (6).These have been suggested as markers for monitoring the production of reactive oxygen species in the lung, and inflammation in the airway and lung in patients with COPD (3, 5).

Heme oxygenase (HO) is expressed in airway epithelial cells (7), endothelial cells (8), and alveolar macrophages (9). Carbon monoxide (CO) is produced endogenously by HO, and is known to be present in measurable quantities in the exhaled air of normal subjects (10, 11). Stimulation of HO by oxidant stress and proinflammatory cytokines (12) in airways, and lung inflammation, are suggested to cause the increased levels of exhaled CO in patients with inflammatory pulmonary diseases (9, 11, 13).

Arterial blood carboxyhemoglobin (Hb-CO) concentrations are correlated with exhaled CO concentrations (10), and have been proposed to be an inflammatory marker in inflammatory pulmonary disease, including bronchial asthma, acute pneumonia, and silicosis (14).

Arterial Hb-CO concentrations can be measured via the measurement of blood gas. The concentration of carboxyhemoglobin (Hb-CO) is often estimated from measurements of carbon monoxide in exhaled air.

In this study, we studied the relationship between Hb-CO concentrations and disease severity and we investigated whether the presence of airflow obstruction significantly alters the relationship between exhaled CO and Hb-CO. We evaluated whether arterial Hb-CO is useful to monitor disease activity in patients with chronic obstructive pulmonary disease (COPD).

Materials and Methods

This study was conducted in the Chest Medicine and Tuberculosis Clinic in a large training and research hospital. The protocol was approved by the local ethics committee and all participants signed informed consents before their enrollment.

Patients and Controls

Fifty-seven middle aged or elderly consecutive patients who were admitted to the outpatient clinic were enrolled in the study.

We studied 13 control subjects and 44 patients with COPD. Patients with COPD were classified according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (1). Seven patients were classified into GOLD II (moderate), 19 into GOLD III (severe), and 18 patients into GOLD IV (very severe) COPD.

Patients were stable for COPD (had not had exacerbation at least for 4 weeks: white blood count (WBC), neutrophils, sedimentation, C-reactive protein (CRP) of patients were normal and there were not any symptom of exacerbation like worsening of patient's respiratory symptoms) and all participants (including controls) had been ex-smokers for at least 3 months (Patients and controls declared that they were exsmokers at least 3 months). Passive smokers, both patients with COPD and control subjects were excluded. None of the COPD patients had received oral or inhaled corticosteroids for 3 months.

Measurement of Arterial and Venous Blood Hb-CO and Exhaled CO

We drew blood from the radial artery and the median cubital vein in patients with COPD and in control subjects. We measured the Hb-CO concentrations with a spectrophotometer, and calculated the arterial and venous (a-v) Hb-CO concentration differences. We also measured exhaled CO concentrations in the control subjects and patients with electrochemical sensor (EC50; 50 Bedfront). To avoid the influence of ambient CO on Hb-CO, Hb-CO and exhaled CO levels were measured at least 5 hours after arrival in a room in the hospital with low ambient CO. Spirometry was evaluated for each participant. The size of the measurement error (ΔCO) was calculated from the difference between Hb-CO and exhaled CO. Each measurement for both patients and controls was made on the same day for each person.

Statistical Analysis

SPSS 17.0 (Chicago IL, USA) was used for statistical analysis. The age, Hb-CO concentrations, (a-v) Hb-CO difference, ex-

Table 1— The Characteristics and Results of Patients With COPD and Control Subjects

	Patients n:44	Controls n:13	P
Age (yr)	64.3±8.1	62.7±5.9	p>0.05
Smoking History(pack/year)	56.8±25.1	53.3±18.2	p>0.05
FEV1(% pred)	40.7±10.6	100.2±18.7	p<0.001
FVC (%pred)	53.1±10.2	95.6±16.6	p<0.001
FEV1/FVC (%)	58.2±8.9	82.9±7.7	p<0.001
Venous Hemoglobine(mg/dl)	14.8±1.3	14.3±0.7	p>0.05
Exhaled CO (ppm)	5.3±1.4	1.3±0.8	p<0.001
%CO	1.4±0.2	0.7±0.2	p<0.001
PaCO2 (mmHg)	40.8±6.2	36.3±1.8	p<0.05
PaO2 (mmHg)	64.6±10.9	76.5±6.1	p<0.001
SaO2 (%)	91.4±4.3	95.1±1.0	p<0.05
Hb-CO (%) arterial	3.2±0.5	1.6±0.5	p<0.001
Hb-CO (%) venous	2.3±1.0	1.7±0.8	p<0.05
ΔCO	1.76±0.6	0.80±0.49	p<0.001
(A-V)Hb-CO (%)	0.82±0.97	-0.12 ±0.83	p<0.05

Values are mean ± sd. FEV1: Forced expiratory volume one second, FVC: Forced vital capacity, Exhaled CO: Exhaled carbondioxide, Hb-CO: Carboxyhemoglobin, ΔCO: Measurement Error.

haled CO concentrations, arterial partial pressure of O_2 (PaO_2) and CO_2 ($PaCO_2$) values, ΔCO, FEV_1, FVC and FEV_1/FVC in each group were reported as mean ± SD. Statistical analysis of these values was performed using nonparametric tests. The Mann Whitney U test was used for comparing groups. Correlation analysis was done with Pearson correlation tests. Significance was accepted as p<0.05.

Results

The characteristics of patients with COPD and control subjects are shown in Table 1. The mean age of patients was 64.3±8.1 years (45-80) and that of controls was 62.7±5.9 years (54-70). There was no statistically significant difference in age and smoking history (pack/year) between normal control subjects and patients. All control subjects and patients were ex-smokers.

The arterial blood Hb-CO concentrations in patients with COPD (3.20%±0.55) were significantly higher than those in control subjects (1.60%±0.57; p<0.001). Among the patients with COPD, Hb-CO concentrations in patients at GOLD 4 (3.59%±0.47; n=18) and GOLD 3 (3.05%±0.38; n=19) were higher than in patients at GOLD 2 (2.57%±0.39; n =7) (Figure 1).

There was a significant correlation between arterial Hb-CO and exhaled CO (p<0.0001; r=0.71). Arterial Hb-CO was inversely correlated with FEV1% (p<0.0001; r=-0.74) (Figure 2).

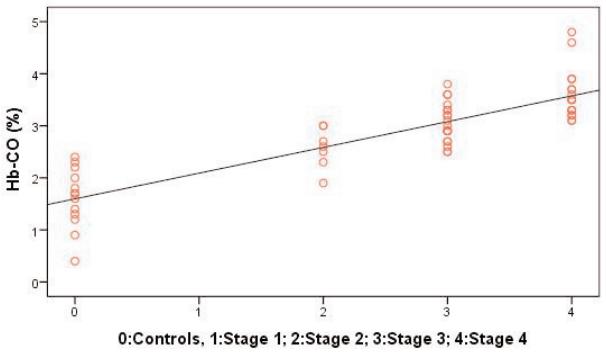

Figure 1— Hb-CO concentrations of patients and controls.

Venous blood Hb-CO concentrations were higher in the COPD group (2.38±1.0) than in controls (0.12±0.83; p<0.05). There were no differences among COPD stages. The difference between arterial and venous Hb-CO was higher in the patient group (0.85%±0.9) than in controls (0.12%±0.8; p<0.05).

Exhaled CO levels of patients (5.32±1.49; n=44) were significantly higher than those of controls (1.31±0.85; n=13; p<0.001). There were no significant differences among COPD stages for exhaled CO levels.

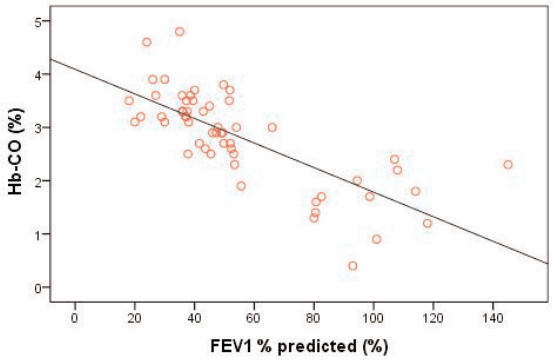

Figure 2— Correlation between FEV1 and Arterial Hb-CO in COPD patients (p<0.001, r=-0.74).

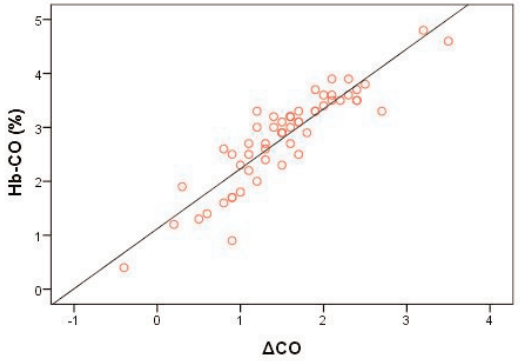

Figure 3— Correlation between Arterial Hb –CO and ¢CO (p<0.001, r=0.90).

ΔCO was significantly different between patients and controls (Table 1). GOLD 4 COPD patients' ΔCO levels were significantly higher than those for GOLD 2 COPD patients. There were no significant differences among the other groups. ΔCO was inversely correlated with FEV1% (p<0.001; r=-0.54) (Figure 3).

Discussion

The present study demonstrated that arterial Hb-CO and exhaled CO concentrations in patients with COPD were higher than those in control subjects, in people who were elderly and middle aged.

In stable conditions, the Hb-CO concentrations in patients at GOLD IV stage were higher than those in patients at GOLD II stage and GOLD III stage. Hb-CO concentrations also inversely correlated with FEV1.

These findings suggest that measurement of Hb-CO may be a useful marker of severity of COPD. In this study, increased Hb-CO in patients with COPD is consistent with that observed in previous studies in patients with COPD, bronchial asthma, pneumonia, and interstitial lung disease (15,16), in which increased Hb-CO might relate to inflammation in the airway and/or lung parenchyma. Airway inflammation (17) and production of reactive oxygen species(18) might be associated with increased Hb-CO(12) in patients with COPD.

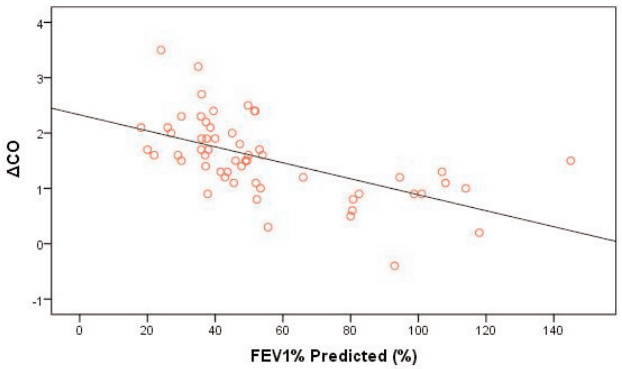

Figure 4— Correlation between ΔCO and FEV1 (p<0.001, r=-).

Yasuda et al. reported that Hb-CO concentration was inversely correlated with both FEV1 and arterial blood O2 (PaO2) concentrations (2). In 4 patients with FEV1 less than 40%, Hb-CO concentrations were higher than 1.4% and in 5 patients with FEV1 less than 50%, Hb-CO concentrations were higher than 1.2%. In our study, FEV1 levels were <40% in 23 patients and Hb-CO concentrations were higher than 1.4% in these patients. These findings suggest that measurement of Hb-CO may be a useful marker of severity of COPD.

In severe airway obstruction, arterial Hb-CO might be increased because of reabsorption of CO and estimation of Hb-CO concentrations from exhaled CO may yield inaccurate results, but this might reflect endogenous production of CO (2). In the current study, patients exhaled CO levels were significantly higher than those of controls and Hb-CO concentrations were correlated with exhaled CO.

In several studies ΔCO levels have been found to be higher in patients with inflammatory pulmonary diseases and COPD patients. ΔCO levels were higher in severe COPD than in stable disease (19).

Our results show that the magnitude of ΔCO increases in direct proportion to the degree of airflow obstruction. ΔCO levels were higher in GOLD 4 COPD than in GOLD 2 COPD (p<0.05), and ΔCO was correlated with arterial Hb-CO concentrations. The current results indicate that the magnitude

of ΔCO caused by airflow limitation is clinically relevant in subjects with severe degrees of airflow obstruction and that lungs produce most of the endogenous CO.

There were some limitations of our study; firstly we evaluated exsmokers with anamnesis of patients, we could not measure any parameter that shows objective criteria for smoking cessation, we should measure urine cotine concentrations; secondly we classified COPD only spirometric findings of patients and finally we didn't calculate the exacerbation risk of patients. In assessment of exacerbations, all patients and controls evaluated with clinical symptoms, radiologic and laboratory findings.

In conclusion, arterial Hb-CO measures are useful in the monitoring of disease activity in patients with chronic obstructive pulmonary disease (COPD). Patients needed to stop breathing for 20 seconds to measure the exhaled CO concentrations. This procedure was difficult to accomplish for patients with COPD. Hb-CO concentrations can be measured at the same time as the blood gas analysis. The measurement of arterial Hb-CO concentration may be a simple and valuable marker to monitor disease activities in patients with COPD.

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