

Determining the diagnostic value of endogenous carbon monoxide in Chronic Obstructive Pulmonary Disease exacerbations

Nurettin Özgür Dogan,¹ Seref Kerem Corbacioglu,² Fikret Bildik,³ Isa Kilicaslan,⁴ Gül Pamukcu Günaydin,⁵ Yunsur Cevik,⁶ Volkan Ülker,⁷ Onur Hakoglu,⁸ Emre Gökçen⁹

Abstract

Objective: To determine whether endogenous carbon monoxide levels in exacerbations of Chronic Obstructive Pulmonary Disease patients were higher compared to healthy individuals and to investigate alteration of carbon monoxide levels across the three different severity stages of Global Initiative for Chronic Obstructive Lung Disease criteria related to Chronic Obstructive Pulmonary Disease exacerbations.

Methods: The prospective study was conducted from January to March 2011 at two medical institutions in Ankara, Turkey, and comprised patients of acute Chronic Obstructive Pulmonary Disease exacerbations. The severity of the exacerbations was based on the Global Initiative for Chronic Obstructive Lung Disease criteria. Patients with active tobacco smoking, suspicious carbon monoxide poisoning and uncertain diagnosis were excluded. healthy control subjects who did not have any comorbid diseases and smoking habitus were also enrolled to compare the differences between carboxyhaemoglobin levels. A two-tailed Mann-Whitney U test with Bonferroni correction was done following a Kruskal-Wallis test for statistical purposes.

Results: There were 90 patients and 81 controls in the study. Carboxyhaemoglobin levels were higher in the patients than the controls ($p < 0.001$). As for the three severity stages, Group 1 had a median carboxyhaemoglobin of 1.6 (0.95-2.00). The corresponding levels in Group 2 (1.8 [1.38-2.20]) and Group 3 (1.9 [1.5-3.0]) were higher than the controls ($p < 0.001$ and $p < 0.005$ respectively). No statistically significant difference between Group 1 and the controls (1.30 [1.10-1.55]) was observed ($p < 0.434$).

Conclusion: Carboxyhaemoglobin levels were significantly higher in exacerbations compared with the normal population. Also, in more serious exacerbations, carboxyhaemoglobin levels were significantly increased compared with healthy individuals and mild exacerbations.

Keywords: Chronic obstructive pulmonary disease, Carbon monoxide, Emergency medicine. (JPMA 64: 1037; 2014)

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality worldwide. COPD exacerbations also account for approximately 1.5 million emergency department (ED) visits per year.¹ In ED setting, physicians have to make decisions regarding hospitalisation or discharge for COPD patients. As a consequence, "Indications for Hospital Admission" and "Indications for ICU Admission" criteria were determined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) to help physicians in their discharge decisions.²

However, these criteria cannot be used efficiently due to overcrowding in ED and difficulties in immediate decision-making by ED physicians, thereby leading physicians to search for scores and indicators that tend to be easily measured.

Carbon monoxide (CO) is endogenously produced by the action of heme oxygenase 1 (HO-1) and heme oxygenase 2 (HO-2) on the heme from haemoglobin breakdown. HO-1 is a rate limiting enzyme, which is identified as inducible form and catabolises heme into three products: CO, free iron and biliverdin. HO-1 activity is induced in response to various conditions, including hypoxia, inflammation and oxidative stress.³⁻⁵ HO-1 can also function in signaling, which triggers a cytoprotective response.⁴ Respiratory epithelial cells and alveolar macrophages are common sites for HO-1 expression.⁶⁻⁸

In previous studies, carboxyhaemoglobin (COHb) levels in patients with exacerbations of COPD were reported to be significantly higher than those in control groups.^{9,10} The present study was planned to determine whether

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¹Kocaeli University, Faculty of Medicine, Department of Emergency Medicine, Kocaeli, ²Antakya State Hospital, Department of Emergency Medicine, Hatay, ^{3,4,8}Gazi University, Faculty of Medicine, Department of Emergency Medicine, Ankara, ⁵Atatürk Training and Research Hospital, Department of Emergency Medicine, Ankara, ⁶Keciören Training and Research Hospital, Department of Emergency Medicine, Ankara, ⁷Batman State Hospital, Department of Emergency Medicine, Batman, ⁹Malatya State Hospital, Department of Emergency Medicine, Malatya, Turkey.

Correspondence: Nurettin Özgür Dogan. Email: nurettinozgurdogan@gmail.com

endogenous COHb levels in former smokers presenting with COPD exacerbation were higher than the non-smoking controls, and to determine whether COHb levels were associated with the severity of COPD exacerbation as defined by the GOLD criteria.

Patients and Methods

The prospective study was conducted from January to March 2011 at two EDs related to a university hospital and a training/research hospital in Ankara, Turkey. Both the institutions are high-volume tertiary healthcare facilities in the region. Patients of acute COPD exacerbations admitted to the two EDs were consecutively enrolled. Ethical committee approval for the study was obtained and patients were asked to sign an informed consent before they were enrolled. If the patients were unable to sign the informed consent due to medical reasons, the legal guardians or relatives were asked to sign the form.

Those who refused to give consent were excluded from the study and so were those with active tobacco smoking (active smoker in the preceding three months), suspicious CO poisoning and uncertain COPD diagnosis. Besides, healthy control subjects, who did not have any comorbid diseases and smoking habitus, were also enrolled in the study to compare differences between COHb levels. To investigating the active smoking status, the patients were asked to define the last day when they had smoked.

The COPD diagnosis in the enrolled patients was confirmed via hospital records indicating spirometric tests, which were previously performed in outpatient clinics. The severity of the disease was subsequently classified by an ED physician into three categories, according to the recommendations of the GOLD guidelines.² Group 3 refers to patients with the need of intensive care unit (ICU) treatment; Group 2 refers to patients with the need of hospitalisation after the ED visit; and, lastly, Group 1 refers to patients who did not meet the aforementioned criteria of hospitalization or ICU treatment and needed to be discharged (Table-1).

All vital signs were recorded in the ED triage area on arrival. The blood gas analysers (for COHb levels; Roche Omni S, Roche Diagnostics®) and hematologic/biochemical analysers were well-standardised in both institutions. COHb measurement was done simultaneously at the beginning of the therapy via arterial blood samples. Historical data was obtained from the patients or her/his relatives after ED treatment was set up.

After initial assessment and therapeutic interventions, the physicians were asked to make a decision regarding the severity of exacerbation among the three patient groups.

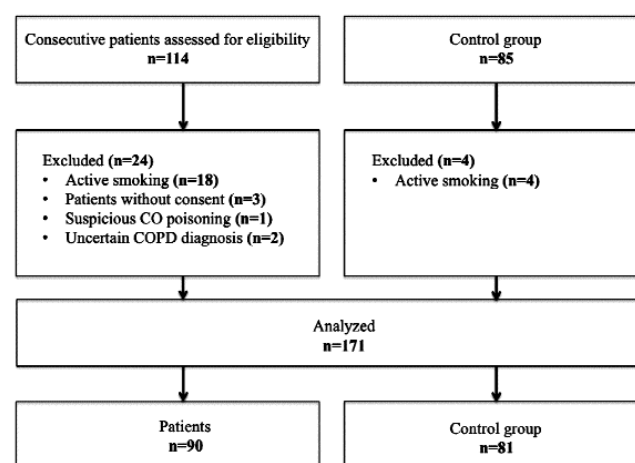
Statistical analysis was performed using SPSS 15.0. In all cases, Shapiro-Wilk test was applied to test for normal distribution. Results for normally distributed data were shown as mean $\pm$ standard deviation (SD). Non-normally distributed data was expressed by median and interquartile range (IQR).

To compare differences between patients and controls, Student t-test and Mann Whitney U test were performed for variables with normal and non-normal distribution, respectively. Continuous variables were compared among COPD severity groups using the Kruskal-Wallis test. A two-tailed Mann-Whitney U test with Bonferroni correction was done after the Kruskal-Wallis test to assess differences among the three patient groups. Categorical variables were evaluated using Pearson Chi-square test. Spearman correlation was used for the relationship between COHb values and other laboratory parameters. $P < 0.05$ was accepted as statistically significant.

A post hoc power analysis was performed to determine the average power of tests used in the study (G-Power 3.1.3, Universitat Kiel, Kiel, Germany). To determine the association between former smokers presenting with COPD and non-smoking controls regarding endogenous COHb levels, the sample size was found adequate to achieve a statistical power of 0.99 (effect size=0.8; $\alpha=0.05$).

Results

Initially, 114 patients were assessed for eligibility, but 24(21%) had to be excluded for various reasons. Likewise, of the 85 healthy controls, 4(4.7%) were left out. The final



CO: Carbon dioxide
COPD: Chronic Obstructive Pulmonary Disease

Figure-1: Patient flowchart.

Table-1: Main features of three groups regarding severity of COPD exacerbations.**Group 1**

- ◆ Patients, who do not meet the criteria in Group 2 and 3
- ◆ Able to use long acting bronchodilators
- ◆ Patient, if previously ambulatory, is able to walk across room
- ◆ Arterial blood gases are stable in ED follow-up
- ◆ Patient fully understands correct use of medications
- ◆ Follow-up and home care arrangements have been completed
- ◆ Patient, family, and physician are confident that the patient can manage successfully at home

Group 2

- ◆ Marked increase in intensity of symptoms
- ◆ Severe underlying COPD
- ◆ Onset of new physical signs (e.g., cyanosis, peripheral oedema)
- ◆ Failure of an exacerbation to respond to initial medical management
- ◆ Presence of serious comorbidities (e.g., heart failure, newly occurring arrhythmias)
- ◆ Frequent exacerbations
- ◆ Older age
- ◆ Insufficient home support

Group 3

- ◆ Severe dyspnoea that responds inadequately to initial emergency therapy
- ◆ Changes in mental status (confusion, lethargy, coma)
- ◆ Persistent or worsening hypoxaemia ($pO_2 < 40$ mm Hg) and/or severe/worsening respiratory acidosis ($pH < 7.25$) despite supplemental oxygen and noninvasive ventilation
- ◆ Need for invasive mechanical ventilation
- ◆ Haemodynamic instability / Need for vasopressors

COPD: Chronic Obstructive Pulmonary Disease.

sample size, as such, had 90(79%) patients and 81(95%) controls (Figure-1). According to the historical characteristics of the patients, hypertension in 46(51%), heart failure in 26(29%) and diabetes mellitus in 20(22%) were the leading co-morbid diseases. Lung cancer was not observed in the study group.

The mean age of the patients was 68.90 ± 9.55 years, and the mean age of the controls was 67.31 ± 7.27 years ($p < 0.219$).

COHb values of the patients and the controls were not distributed normally. While the patient group had a median of 1.70 (IQR: 1.10-2.20), the control group had a median of 1.30 (IQR: 1.10-1.55) ($p < 0.001$).

According to the GOLD severity criteria, 28(31%) patients were in Group 1; 50(55.5%) in Group 2; and 12(13.3%) in Group 3. Group 1 had a median COHb value of 1.6 (IQR: 0.95-2.00). Group 2 had 1.8 (IQR: 1.38-2.20) and Group 3 had 1.9 (IQR: 1.5-3.0) which were both higher than the control group ($p < 0.001$ and $p < 0.005$ respectively) (Figure-2). No statistically significant difference between Group 1 and the control group was observed ($p < 0.434$).

Among the three patient groups, no statistically significant difference was found according to age, COHb level, body temperature, blood pressure (systolic and

Table-2: Ages, vital signs and laboratory values of patients according to severity of COPD exacerbations.

Variables	Group 1 Median (IQR)*	Group 2 Median (IQR)*	Group 3 Median (IQR)*	p value**
Age (years)	71 (61.5-78.5)	69 (63.75-74.00)	78.5 (65.50-80.75)	0.116
Body temperature (°C)	36.75 (36.6-37.3)	37.00 (36.7-38.0)	36.90 (36.6-37.6)	0.238
Heart rate (beat per minute)	85.5 (80-100)	110 (100.5-122.0)	96 (85-110)	<0.001 †
Systolic BP*** (mmHg)	133.5 (120-140)	140 (120-160)	140 (100-150)	0.165
Diastolic BP*** (mmHg)	80 (74-90)	80 (70-96)	75 (60-100)	0.472
O2 saturation (%)	86.5 (83-90)	82 (77-88)	66.5 (60-80)	<0.001 †
Respiratory rate	17 (15-20)	24 (19.5-34.8)	23 (15-24)	<0.001 †
pH	7.40 (7.37-7.41)	7.40 (7.37-7.44)	7.24 (7.16-7.28)	<0.001 †
pO2 (mmHg)	54.9 (52.8-68.6)	49.5 (43.0-64.8)	44.25 (33.3-56.6)	0.014 †
pCO2 (mmHg)	38.5 (35.3-44.0)	40.8 (32.8-48.5)	56.85 (55.0-70.0)	<0.001 †
Lactate (mmol/L)	12 (10-14)	13 (11.75-20.25)	17.5 (5-28)	0.468
Haemoglobin (mg/dL)	13.25 (11.7-14.3)	13.6 (11.6-14.8)	12.25 (11.3-15.2)	0.688
Leukocyte	9800 (6600-13500)	12900 (7700-16000)	10950 (8800-16200)	0.295
Glucose (mg/dL)	101.5 (90-126)	136 (116.5-182)	175.5 (108-224)	0.001 †

*IQR: Interquartile range

**Kruskal-Wallis test

***BP: Blood pressure

† p value < 0.05

COPD: Chronic Obstructive Pulmonary Disease

O2: Oxygen

pO2: Pressure of oxygen

pCO2: pressure of carbon dioxide

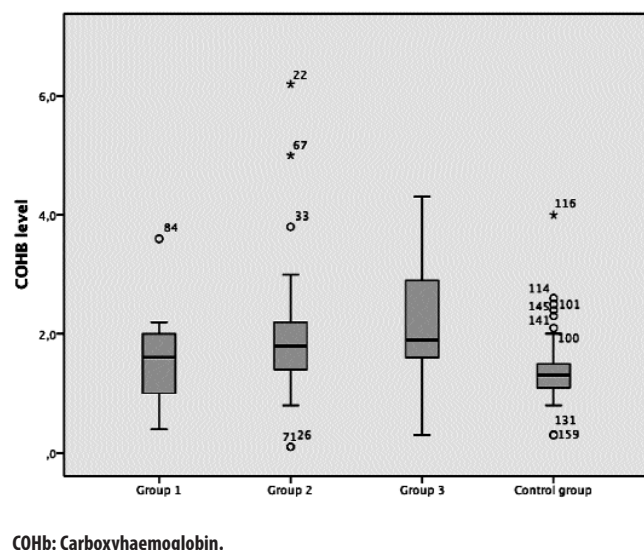


Figure-2: The distribution of COHb levels among patients and control group.

diastolic), lactate, haemoglobin and leukocyte levels (Table-2). Only Group 2 was found to be more tachycardic compared to Group 1 ($p < 0.001$), and no differences were found between the other groups with regard to the heart rate. According to arterial oxygen saturation levels, all three groups were found different from each other. The level of statistical difference was 0.011 for Group 1 and 2, and < 0.001 for comparison of Group 1 - 3 and Group 2 - 3. According to arterial blood samples, Group 3 was found more acidotic ($p < 0.001$) and more hypercapnic ($p < 0.001$).

No correlation was found between COHb levels and lactate levels ($p < 0.837$), pH levels ($p < 0.812$) and systolic blood pressures ($p < 0.461$). A statistically significant correlation was observed between COHb levels and pressure of oxygen (pO_2) ($p < 0.001$; $r = -0.405$), pressure of carbon dioxide (pCO_2) ($p < 0.005$; $r = +0.294$) and arterial oxygen saturations ($p < 0.002$; $r = -0.325$).

Discussion

Even though CO is highly recognised as a reason for intoxication by physicians, results of recent studies have started to reveal that CO increases by endogenous production and leads to high COHb levels in some diseases, primarily in pulmonary diseases that cause hypoxia and inflammatory stress. One study determined COHb levels as $0.55 \pm 0.02\%$ in the control group, $0.81 \pm 0.02\%$ in patients with stable COPD, $1.09 \pm 0.04\%$ in patients with exacerbation of COPD, and indicated this difference as statistically significant.⁹ Another study determined exhaled CO levels as 7.4 ± 1.9 ppm in ex-smoker patients with COPD and 3.0 ± 0.3 ppm in the

control group, and this difference was statistically significant.¹⁰

One study on the importance of COHb levels in some pulmonary diseases, COHb mean value was found to be $0.65 \pm 0.03\%$ in the control group, while it was $1.13 \pm 0.14\%$ in asthma patients, $1.05 \pm 0.01\%$ in patients with pneumonia and $0.93 \pm 0.03\%$ in patients with idiopathic pulmonary fibrosis (IPF), and it was statistically significant.¹¹ In another study on asthma patients, exhaled CO levels were 1.4 ± 0.2 ppm in patients with stable asthma, and 4.6 ± 0.4 ppm in patients with asthma attacks.¹²

Similar to previous studies, we also determined a significant difference between patients presenting to the ED with COPD exacerbations and the controls (1.7% versus 1.3%). Following this finding, another major concern for us was to determine whether or not this data could be used in administering patients with COPD exacerbations, particularly in predicting severity of exacerbations. As a new data, the results of our study suggested that COHb levels were increased in more serious COPD exacerbations compared with mild exacerbations.

As it is a well-known fact in ED practice, one of the major problems in COPD exacerbations is predicting its severity and determining which patients should be hospitalised. Even though there exist some clinical guidelines in order to assist physicians, the validity of these guidelines has not been proven in clinical practice. For instance, in a study, 384 patients with COPD exacerbations were followed in 29 hospitals. Their hospitalisation criteria were compared with the GOLD guidelines after their reasons for hospitalisation had been analysed and, in the light of their findings, two of the criteria were found to be incompatible with the guidelines.¹³ Given the overcrowding in EDs and the need for urgent decisions, different methods are required that will enable determination of the severity of exacerbations in COPD patients.

One study revealed the relationship between COHb values and the stable COPD stage.⁹ In the same study, it was also shown that COHb values of the patients with COPD exacerbations were negatively correlated with pO_2 and positively correlated with pCO_2 and C-reactive protein (CRP) values. Most importantly, it proved that COHb values can be correlated with the severity of the exacerbation by showing that COHb values of the patients with COPD exacerbations were inversely correlated with forced expiratory volume in 1 second (FEV1).⁹ However, in another study regarding exhaled CO, no correlation was found between CO levels and

respiratory function tests.¹⁰ Moreover, in the earlier of the two studies⁹ it is not clear that pCO₂ and CRP values, which are shown to be correlated with COHb, are related with the severity of COPD exacerbations. Additionally, in the study where 960 patients with COPD exacerbations were hospitalised, it was found that pCO₂ and CRP values were not related with mortality.¹⁴

Although a significant association between respiratory diseases and endogenous CO production may exist, the literature about this relationship still remains unclear. A recent study demonstrated that endogenous COHb levels showed an increase in patients with community-acquired pneumonia and COHb concentrations correlated within pneumonia severity index groups.¹⁵ Respiratory tract infections were one of the trigger factors of COPD exacerbations. The finding may explain the increase in COHb levels in severe exacerbations via underlying respiratory tract infection.

In our study, there are several limitations. First, the study population is relatively small, although COHb levels were found to be significantly higher in COPD exacerbations compared with healthy individuals and mild exacerbations. Second, serial measurement of COHb values could have been considered for our three groups to demonstrate the value of COHb in the follow-up period.

Conclusion

COHb values were higher in patients with severe COPD exacerbations, and there was a weak negative correlation with pO₂ and positive correlation with pCO₂ in terms of COHb values. Although it seems impossible at this stage to conclude that these high COHb values can help us in predicting the clinical severity of COPD exacerbations, the study indicated that endogenous COHb levels in former smokers presenting with severe COPD exacerbation were higher than non-smoking controls and mild exacerbations.

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