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Original Contribution

COHgb levels predict the long-term development of acute myocardial infarction in CO poisoning☆

Hakki Kaya, MD [a,*], Abuzer Coşkun, MD [b], Osman Beton, MD [a], Ali Zorlu, MD [a], Recep Kurt, MD [c], Hasan Yucel, MD [a], Hakan Gunes, MD [c], M. Birhan Yılmaz, MD [a]

[a] Department of Cardiology, Cumhuriyet University Medical School, Sivas, Turkey
[b] Department of Emergency, Sivas State Hospital, Sivas, Turkey
[c] Department of Cardiology, Sivas State Hospital, Sivas, Turkey

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ABSTRACT

Background: There are several studies evaluating the cardiac effects of carbon monoxide (CO) poisoning during the acute period; however, the number of studies evaluating the long-term cardiac effects is limited.
Objective: The present study aimed to evaluate the effects of blood carboxyhemoglobin (COHb) levels, elevated due to CO poisoning on the long-term development of acute myocardial infarction (AMI).
Methods: This cross-sectional cohort study included a total of 1013 consecutive patients who presented to the emergency department (ED) due to CO poisoning, between January 2005 and December 2007. The diagnosis of CO poisoning was made according to the medical history and a COHb level of greater than 5%. In terms of AMI development, the patients were followed up for an average of 56 months.
Results: At the end of follow-up, 100 (10%) of 1013 patients experienced AMI. Carboxyhemoglobin levels at the time of poisoning were higher among those who were diagnosed with AMI compared to those who were not (55% ± 6% vs 30% ± 7%; $P < .001$). Using a multivariate Cox proportional hazards model with forward stepwise method, age, COHb level, CO exposure time, and smoking remained associated with an increased risk of AMI after adjustment for the variables found to be statistically significant in a univariate analysis. According to a receiver operating characteristic curve analysis, the optimal cutoff value of COHb used to predict the development of AMI was found to be greater than 45%, with 98% sensitivity and 94.1% specificity.
Conclusion: In patients presenting to the ED with CO poisoning, COHb levels can be helpful for risk stratification in the long-term development of AMI.

1. Introduction

Carbon monoxide (CO) is a tasteless and odorless gas that consists of carbon and oxygen atoms and has very low atmospheric concentrations [1,2]. Normally also found in the human body in low concentrations, CO is believed to play important roles in vasoregulatory, anti-inflammatory, antiapoptotic, and antiproliferative processes in the metabolism [3,4]. However, in case of exposure to high doses, it is highly toxic to the human body [2,5]. It is acknowledged that CO poisoning is very common worldwide and accounts for more than half the poisonings that result in death [2,6]. Although CO poisoning is commonly encountered in the emergency services, due to its nonspecific symptoms, it can be easily overlooked when a detailed history is not obtained [7,8].

Carbon monoxide is known to have cardiotoxic effects and causes electrical, functional, and morphological changes in the heart. It has been shown that, in CO poisonings, there are increased cardiac biomarkers, such as brain natriuretic peptide, troponin, creatine kinase, and creatine kinase-MB, and electrocardiographic abnormalities such as ST elevation, T-wave changes, premature atrial beat, and sinus tachycardia [9,10]. It has also been reported that CO poisoning may lead to acute myocardial infarction (AMI) and cardiogenic shock with acute pulmonary edema, although this is rare [11–15].

To diagnose poisoning, the level of carboxyhemoglobin (COHb), produced by the binding of CO to the heme proteins in hemoglobin (Hb), is used. The blood level of COHb is normally lower than 2% to 3% but varies between 5% and 13% in smokers. However, it is greater than 20% in cases of CO poisoning [2]. There are some studies regarding the cardiovascular effects of CO poisoning during the acute period; however, the literature contains only a limited number of studies on the long-term cardiac effects of elevated COHb levels as a result of such poisonings [9,10,13–17]. The purpose of the present study was to examine the effects of elevated COHb levels due to CO poisoning on long-term AMI development.

2. Materials and methods

This cross-sectional cohort study included consecutive patients older than 16 years, who presented to the emergency department

☆ Conflict of interests: None.

* Corresponding author at: Departments of Cardiology, Cumhuriyet University Medical School, Sivas, Turkey. Tel.: +90 3462581807; fax: +90 3462191268.
E-mail address: drhakkikaya84@gmail.com (H. Kaya).

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(ED), due to CO poisoning, between January 2005 and December 2007. All CO exposures were related to the heating system malfunction and accidental. Patients with known coronary artery disease (CAD) or other known heart disease, for example, valvular diseases or rhythm disorders, were excluded. The study was made in accordance with the Declaration of Helsinki for Human Research and was approved by the institutional review board.

The diagnoses; dates of admissions; and demographic, clinical, and laboratory data with contact information are shown in the registry system of our hospital. Patients admitted to our hospital with the diagnosis of AMI after CO intoxication are also displayed in our system. In our study, if a diagnosis of myocardial infarction was not shown after intoxication in the registry system, we contacted the patients by telephone and asked whether they were admitted to another hospital with diagnosis of AMI after CO intoxication. Eventually, all patients were contacted via call and/or hospital records, and outcomes that were related development of AMI during an average of 56 months after the CO poisoning were assessed.

The patients' COHb levels were obtained from arterial blood gas analyses using acobas b 221 Blood Gas system (Roche, Basel, Switzerland). A diagnosis of CO poisoning was made according to the medical history and a COHb level greater than 5%. *Carbon monoxide exposure time* was defined as an approximate duration of CO inhalation. A diagnosis of AMI was determined by cardiologists in our hospital and based on the definitions of the joint committee of the American College of Cardiology/American Heart Association. *Hypertension* was defined as blood pressure greater than or equal to 140/90 mm Hg on more than 2 occasions during office measurements or being on antihypertensive treatment. *Diabetes mellitus* was defined as a fasting blood sugar level greater than or equal to 126 mg/dL or being on antidiabetic treatment.

3. Statistical analysis

Continuous variables were expressed as mean ± SD or median (min-max) in the presence of abnormal distribution; and categorical variables, as percentages. Receiver operating characteristic curve analysis was performed to identify the optimal cutoff point of COHb (at which sensitivity and specificity would be maximal) for the prediction of the development of AMI. Areas under the curve (AUCs) were calculated as measures of the accuracy of the tests. We compared the AUC with use of the *Z* test. Comparisons between the groups of patients were made by the use of a χ^2 test for categorical variables, independent-samples *t* test for normally distributed continuous variables, and Mann-Whitney *U* test when the distribution was skewed. Kaplan-Meier curves were used to display the development of AMI in 2 patient subgroups, defined as having no increased or increased COHb levels based on a cutoff value. We used univariate analysis to quantify the association of variables with the development of AMI. Variables found to be statistically significant in univariate analysis were used in a multivariate Cox proportional hazards model with forward stepwise method to determine the independent prognostic factor for the development of AMI. All statistical procedures were performed using SPSS software version 14.0 (SPSS, Inc, Chicago, IL). $P = .05$ was considered as statistically significant.

4. Results

The mean age of the patients was 36 ± 16 years (40% males, 50% females) with a mean follow-up period of 56 months (range, 17-95).

After follow-up, 100 (10%) of the 1013 experienced AMI. Patients were classified into 2 groups: those who were diagnosed with AMI or not. The baseline characteristics and laboratory data are presented in Table 1. Carboxyhemoglobin levels were higher among those who were diagnosed with AMI compared with those who were not (55% ± 6% vs 30% ± 7%; $P < .001$). In addition, the mean age, CO exposure time, glucose, triglyceride, white blood cell (WBC), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) levels, the presence of hypertension (HT), and smoking were higher among those patients who were diagnosed with AMI compared with those patients who were not diagnosed. Furthermore, high-density lipoprotein (HDL) was lower among the patients who were diagnosed with AMI.

Table 1
Baseline characteristics of study patients

	All patients (n = 1013)	AMI not (n = 913)	AMI (n = 100)	*P*
Baseline characteristics				
Age (y)	36 ± 16	33 ± 13	65 ± 13	<.001
Male/female	402/611	363/550	39/61	.883
HT	309 (30%)	257 (28%)	52 (52%)	<.001
DM	221 (22%)	200 (22%)	21 (21%)	.936
Current smoking	287 (28%)	206 (23%)	81 (81%)	<.001
CO exposure time (h)	3.2 ± 2.2	2.8 ± 1.6	7.0 ± 3.0	<.001
Laboratory findings				
COHb (%)	32 ± 10	30 ± 7	55 ± 6	<.001
Glucose (mg/dL)	123 ± 44	122 ± 43	136 ± 53	.013
BUN (mg/dL)	19 ± 9	19 ± 9	19 ± 9	.455
Creatinine (mg/dL)	1.0 ± 0.4	0.9 ± 0.3	1.0 ± 0.3	.063
AST (IU/L)	25 (5-216)	24 (5-216)	42 (14-126)	<.001
ALT (IU/L)	23 (5-223)	20 (5-223)	39 (9-105)	<.001
ALP (IU/L)	92 (9-497)	86 (9-497)	150 (40-378)	<.001
Calcium (mg/dL)	9.3 ± 0.8	9.3 ± 0.8	9.2 ± 0.9	.121
Sodium (mmol/L)	138 ± 9	138 ± 9	138 ± 5	.804
Potassium (mmol/L)	4.6 ± 0.7	4.6 ± 0.7	4.7 ± 0.6	.387
Magnesium (mg/dL)	2.1 ± 0.4	2.1 ± 0.4	2.0 ± 0.4	.055
Chlorine (mmol/L)	100 ± 9	100 ± 9	100 ± 7	.436
Triglycerides (mg/dL)	139 ± 79	137 ± 78	152 ± 82	.063
Cholesterol (mg/dL)	172 ± 66	172 ± 68	172 ± 54	.962
HDL (mg/dL)	35 ± 9	35 ± 9	32 ± 8	.013
LDL (mg/dL)	109 ± 47	109 ± 47	109 ± 41	.868
CRP (mg/L)	1.7 (0.01-37.1)	1.5 (0.01-37.1)	4.96 (0.01-23.2)	<.001
WBC ($10^3/\mu L$)	10.2 ± 3.8	10.0 ± 3.8	11.4 ± 3.3	.001
RBC ($10^6/\mu L$)	4.7 ± 0.7	4.7 ± 0.7	4.7 ± 0.7	.956
Hb (g/dL)	14.1 ± 1.9	14.0 ± 1.9	14.0 ± 1.8	.983
Hematocrit (%)	42 ± 7	42 ± 7	42 ± 6	.888
MCV (fL)	88 ± 7	88 ± 7	87 ± 8	.686
RDW (%)	14.7 ± 1.9	14.7 ± 1.8	14.8 ± 2.0	.560
Platelet ($10^3/\mu L$)	252 ± 76	252 ± 77	257 ± 72	.538
MPV (fL)	8.5 ± 1.0	8.5 ± 1.0	8.5 ± 1.0	.738

Abbreviations: BUN, blood urea nitrogen; RBC, red blood cell; MCV, mean corpuscular volume; RDW, red cell distribution width; MPV, mean platelet volume.

The results of the univariate and multivariate Cox proportional hazards analyses for the development of AMI are depicted in Table 2. Age, current smoking, COHb level, CO exposure time, the presence of HT, glucose, ALT, AST, ALP, HDL, CRP, and WBC levels were found to have a prognostic significance in the univariate analysis. However, in the multivariate Cox proportional hazards model with forward stepwise method, only age, COHb, CO exposure time, and smoking remained associated with an increased risk of AMI after adjustment for the variables found to be statistically significant in the univariate analysis.

The receiver operating characteristic curve analysis of COHb is shown in Fig. 1. According to the receiver operating characteristic curve analysis, the optimal cutoff value of COHb, to predict the development of AMI, was found to be greater than 45%, with 98% sensitivity and 94.1% specificity (AUC, 0.998; 95% confidence interval, 0980-0994).

We also demonstrated the probability of future AMI in a patient with CO poisoning over time, based on the COHb cutoff value ($P = .001$; Fig. 2).

5. Discussion

To the best of our knowledge, for the first time in the literature, we demonstrated that high COHb levels on admission, long CO exposure time, older age, and smoking could independently predict the long-term development of AMI in patients who were admitted to the ED with CO poisoning.