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Risk of late appearance of acute myocardial infartion after carbon monoxide (CO) intoxication

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ABSTRACT

***Background**: After acute carbon monoxide intoxication, there may be a higher risk for late adverse cardiac events. However, these patients are usually not followed to monitor the appearance of these effects. **Aim**: To follow patients seen at an emergency department for carbon monoxide intoxication, monitoring the appearance of myocardial infarction. To assess the predictive value for such complication of serum troponin, carboxyhemoglobin, and procalcitonin levels at the moment of intoxication. **Material and Methods**: We followed 237 patients receiving emergency care for carbon monoxide intoxication, with a serum carboxyhemoglobin of 5% or more, between 2010 and 2012. Levels of procalcitonin and troponin I were measured. Patients were followed for five years after the intoxication. **Results**: During the follow up period, 35 patients had a myocardial infarction. These patients had significantly higher carboxyhemoglobin, procalcitonin and troponin I levels at the moment of the intoxication than their counterparts who did not had a myocardial infarction in the follow up. A logistic regression analysis showed that age, carboxyhemoglobin levels, procalcitonin, troponin 1 and length of CO exposure were associated with a higher risk of myocardial infarction. Procalcitonin, troponin and carboxyhemoglobin levels had a high sensitivity and specificity to predict the appearance of myocardial infarction, with high areas under the receiver operating characteristic (ROC) curves. **Conclusions**: In patients with CO intoxication, carboxyhemoglobin, troponin and procalcitonin levels at the moment of the intoxication are significant predictors of the late appearance of myocardial infarction.*

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***Key words:** Carbon Monoxide; Emergency Service, Hospital; Myocardial Infarction; Poisoning; Procalcitonin.*

Riesgo de aparición de infarto agudo de miocardio en el largo plazo después de una intoxicación por monóxido de carbono (CO)

***Antecedentes**: Después de una intoxicación con monóxido de carbono, hay un mayor riesgo de desarrollar problemas cardiovasculares a largo plazo. Sin embargo, estos pacientes no son seguidos habitualmente para evaluar la aparición de estos eventos. **Objetivo:** Efectuar un seguimiento de pacientes que han sufrido una intoxicación con CO, evaluando la aparición de infarto del miocardio. Evaluar el valor de los niveles de troponina, carboxihemoglobina y procalcitonina para predecir la aparición de estos eventos. **Material y Métodos**: Seguimos 237 pacientes que fueron atendidos de urgencia por una intoxicación con CO, con*

niveles de carboxihemoglobina de 5% o más, entre 2010 y 2012. Se midieron los niveles de procalcitonina, troponina 1 y carboxihemoglobina y los pacientes fueron seguidos por cinco años después de la intoxicación. ***Resultados****: Durante el seguimiento, 35 pacientes tuvieron un infarto al miocardio. Estos pacientes tenían niveles significativamente más altos de procalcitonina, troponina 1 y carboxihemoglobina al momento de la intoxicación, que los pacientes que no tuvieron un infarto durante el seguimiento. Una regresión logística mostró que la edad, carboxihemoglobina, procalcitonina, troponina y la duración de exposición a CO se asociaron a un mayor riesgo de infarto. Procalcitonina, troponina 1 y carboxihemoglobina tuvieron una alta sensibilidad y especificidad para predecir la aparición de infarto, con áreas bajo la curva ROC (receiver operating characteristic) elevadas.* ***Conclusiones:*** *En pacientes con intoxicación por CO, la carboxihemoglobina, procalcitonina y troponina son predictores significativos de la aparición de infarto agudo de miocardio en el largo plazo.*

Palabras clave: *Atención Ambulatoria; Infarto del Miocardio; Intoxicación por Monóxido de Carbono; Monóxido de Carbono.*

Carbon monoxide (CO) poisoning, which is the leading cause of toxic deaths, also constitutes an important part of emergency room (ED) applications[1,2]. CO is a colorless, odorless, tasteless and non-irritant gas resulting from poor combustion of carbon-containing fuels. CO is a heavier gas than air and can accumulate quickly in poorly ventilated indoor environments. CO is bound to hemoglobin with an affinity 240 times higher than oxygen and disrupts the release and transport of oxygen to tissues by forming carboxyhemoglobin (COHb)[3,4].

CO, which can cause myocardial depression and hypotension, has a greater affinity to cardiac myoglobin than hemoglobin. CO, combined with myoglobin, leads to a decrease in partial oxygen in muscle tissue and causes rhabdomyolysis. Myocardial infarction (MI) is often associated with CO exposure. Even 5-10% increases in COHb levels in people with previous coronary artery disease (CAD) may trigger exercise angina. High levels of COHb may affect the myocardium even in young and healthy individuals[5,6].

Cardiac troponins (cTn) are structural proteins involved in the regulation of skeletal and cardiac muscle contraction with tropomyosin. The complex of troponins T, I and C enables the interaction of actin and myosin with calcium mediated and fine filaments. Troponins are sensitive and specific markers of heart muscle damage[7,8].

Procalcitonin (PCT) has been introduced as a new marker of inflammation. The original product of the Calc-1 gene is the 141-amino acid chain of pro-thermicutonin, the C-cells of the thyroid gland are bound by the N-terminus of the endoplasmic reticulum, where it is cleaved by an endopeptidase and ascends to PCT[9]. PCT concentration is undetectable or low in healthy subjects[10]. Recent studies have found that PCT levels correlate with the degree of atherosclerosis in coronary artery disease patients and are even associated with a negative outcome[11].

The aim of this study was to evaluate the cTn, PCT and COHb levels of patients presenting with ED due to CO intoxication, and the risk of MI that may develop late after treatment and discharge. Determining the parameters predicting the risk of MI that may develop in the late stage of CO intoxication could provide close monitoring and early treatment of the patients.

Material and Methods

Study design and population

In this cross-sectional cohort study; between January 2005 and December 2012, 1,869 patients older than 18 years of age who presented to ED for CO poisoning were screened. 237 patients (129 female, 108 male; mean age 55.17 ± 9.84 years; range 29 to 98 years, 54.4% female) with serum PCT were included in the study.

At the time of admission to the ED, known coronary artery disease (CAD) or other known heart disease, such as valvular diseases or rhythm disorders, cerebrovascular disease, congestive

heart failure, chronic liver disease, dialysis due to chronic renal failure, infectious, inflammatory disease or malignancy, patients with severe anemia or other hematologic diseases and erythrocyte suspension in the last six months, and patients with hemogram and biochemical tests and serum levels of COHb, cTn and PCT were excluded from the study.

A five-year follow-up registry after discharge from CO poisoning patients through an annual automation system was reviewed. During this period, patients who did not have access were called by telephone and CAD was questioned. Diagnoses, admission dates, contact information and demographic, clinical and laboratory data are included in the registry system of our hospital. Patient information was reached by call and/or hospital records. CO poisoning patients in the late period; CAD was divided into two groups as developing and non-developing.

Procalcitonin; PCT was studied in 20-30 minutes with Mini Vidas device. Results were considered to be higher than the normal range of 0-0.05 ng/ml.

The patients' COHb levels were obtained from arterial blood gas analyses using the Acobas®b221 Blood Gassystem (Roche, Basel, Switzerland). A diagnosis of CO poisoning was made according to the medical history and a COHb level > 5%. CO exposure time was defined as the approximate duration of CO inhalation.

Troponin I levels, which were evaluated with in fifteen-minutes after patients were admitted to ED, were measured with a one step immunofluorometric assays and wich method using three monoclonal antibodies (AQ90 Flex, Radiometer Medical ApS, Brønshøj, Denmark). The conventional definition of elevated troponin level is when this value exceeds the 99th percentile value of a healthy reference population and elevated test level, which is > 0.05 ng/ml, for our laboratory, was accepted aspositive. Additionally, nonelevated test level, which is ≤ 0.05ng/ml, was accepted as negative.

Recurrent electrocardiography (ECG) of the patients with high cTn I levels at the time of admission to the emergency department was performed and troponin follow-up was performed. Patients diagnosed with acute MI in the late post-discharge period were examined for cTn I at 0, 6 and 12 consecutive hours in ED. Patients with ST elevation in the ECG were taken to the coronary angiography laboratory. AMI diagnoses were determined by cardiologists and emergency medicine specialists in our hospital based on AHA diagnostic criteria. ECGs of the patients; Twelve leads were taken with Cardiofax ECG-9132K (NihonKohden, Tokyo, Japan) at the bedside for ED admission.

The study was made in following the Declaration of Helsinki for Human Researchand was approved by the institutional review board. All patients were given written informed consent and the study was approved by Cumhuriyet University Medical School Ethical Committee.

Statistical Analysis

The data obtained from this study was analyzed by SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software package. Shapiro Wilk's was used because of the number of units. Mann-Whitney U test was used to examine the differences between the groups because the variables did not come from the normal distribution. Chi-square analysis was used to examine the relationships between groups of nominal variables. Fisher's exact test was used wjen appropriate and Spearman correlation analysis was performed in Monte Carlo Simulation with RxC tables. In addition, logistic regression was used for univariate and multivariate analyzes of variables. Univariate analysis was used to measure the relationship of variables with CAD development. Variables that were statistically significant in univariate analysis were used in multivariate logistic regression risk model by advanced step method to determine independent prognostic factor for CAD development. 0.05 was used as the level of significance when interpreting the results, and P values less than 0.05 were considered as significant.

Results

Main patients' characteristics are shown in Table 1. Baseline characteristics, age, CO exposure time, red cell distribution width (RDW), mean platelate volum (MPV), PCT, COHb and cTn were statistically significant (Table 1).

The gender of the patients with late CAD after CO intoxication was not statistically significant with chi-square test, but diabetes mellitus, hypertension, tobacco use and mortality and MI development were statistically significant (Table 2).

Table 1. Baseline characteristics of study patients

	All patients n: 237	Patients with (-) CAD n: 202	Patients with (+) CAD n: 35	Z	p-value
Mean age(y)	55,17 ± 9,84	54,21 ± 9,88	60,12 ± 13,07	**-3,737**	0,001
Famale Male	129 (%54,4) 108 (%45,6)	109 (%84,5) 93 (%86,1)	20 (%15,5) 15 (%13,9)		0,727
CRP (mg/L)	4,07 ± 6,16	3,92 ± 5,93	4,95 ± 7,39	-0,214	0,831
CO ET (h)	2,99 ± 1,51	2,65 ± 1,33	4,97 ± 0,89	**-8,112**	**0,001**
WBC(10^3/uL)	10,28 ± 3,77	10,40 ± 3,77	9,61 ± 3,78	-1,014	0,311
RDW (%)	15,08 ± 2,29	14,92 ± 2,27	16,04 ± 2,21	**-2,654**	**0,008**
MPV (fL)	7,97 ± 0,81	7,82 ± 0,74	8,82 ± 0,64	**-6,598**	**0,001**
MCHC (g/dL)	33,26 ± 1,19	33,25 ± 1,19	33,26 ± 1,19	-0,633	0,526
MCV (fL)	87,11 ± 8,94	87,15 ± 8,82	86,86 ± 9,97	-0,041	0,967
MCH (pg)	29,57 ± 2,27	29,52 ± 2,29	29,86 ± 2,12	-1,044	0,297
PCT (ng/dL)	0,31 ± 0,51	0,12 ± 0,20	1,42 ± 0,34	**-11,699**	**0,001**
COHb (%)	31,62 ± 9,83	28,22 ± 5,14	51,25 ± 7,03	**-9,253**	**0,001**
Tn (ng/dL)	0,55 ± 1,41	0,04 ± 0,14	3,53 ± 1,71	**-9,238**	**0,001**

CAD: Coronary Artery Disease, (+):Positive; (-):Negative; CRP: C reactive protein; CO ET: Carbon monoxide exposure time; WBC: White blood cell; RDW: Red cell distrubution width; MPV:Mean Platelate Volume; MCHC:Mean Corpuscular Hemoglobin Concentration; MCV; Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobine; COHb: Carboxyhemoglobin; Tn:Troponin, PCT: Procalcitonin.

MI developed in 35 (14.7%) of 237 patients after 60 months follow-up of patients discharged after CO poisoning. All patients with MI had cTn, COHb, PCT, duration of exposure to CO, MPV and RDW elevation. In terms of MI, age, duration of CO exposure, cTn, PCT, COHb, MPV and RDW values were significant for univariete analysis. Corrected multivariete binary logistic recession analysis was performed for this purpose. There was a strong positive correlation between these values and MI. MI was also found to be high in diabetes, hypertension and tobacco users.

In univariate analysis, age, exposure to CO, mortality, COHb, PCT, cTn, MPV and RDW levels were found to have a prognostic value. White blood cell (WBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), C-reactive protein (CRP) MI were statistically insignificant. In addition, in multivariate Binary Logistic regression analysis, age, CO exposure time, mortality, COHb, PCT, cTn, MPV and RDW were associated with increased CAD risk (Table 3).

Patients with high levels of COHb, cTn and PCT at the time of admission to ED had a higher mortality in the acute period. In addition, it was determined that COHb level was above 40% in all patients who developed late mortality during the 60 months follow-up period and the duration of cTn, PCT, CO exposure was high and RDW and MPV were elevated, both in uni and multivariate analyses.

There was no significant correlation between CAD and CRP after CO intoxication. However, statistically strong correlation was found between age, exposure time to CO, mortality, COHb, PCT, cTn, MPV and RDW (Table 4).

Optimal cut-off values of PCT, cTn and COHb to determine 5-year cardiac follow-up positivity in the ROC curve: PCT: m> 0.855; sensitivity 98.7% and specificity 97.3%; cTn: > 0.980; sensitivity 97.1% and specificity 96.6%; COHb:> 42.00; sensitivity 97.8% and specificity 95.3% (p = 0.001, Figure 1).

Table 2. Chi-square test of coronary artery disease related to gender, mortality and variable risk factors

		Coronary Artery Disease		χ^2	p-value
		Negative n (%)	Positive n (%)		
Gender	Female	109 (46)	20 (8,4)	0,122	0,727
	Male	93 (39,2)	15 (6,3)		
Mortality	No	202 (85,2)	0 (0)	**47,784**	**< 0,001**
	Yes	27 (11,4)	8 (3,4)		
HT	No	155 (65,7)	18 (7,6)	**8,418**	**< 0,004**
	Yes	47 (19,9)	16 (6,8)		
DM	No	154 (65)	13 (5,5)	**21,907**	**< 0,001**
	Yes	48 (20,3)	22 (9,3)		
Tobacco	No	141 (59,5)	12 (5,1)	**16,446**	**< 0,001**
	Yes	61 (25,7)	23 (9,7)		

HT: Hypertension, DM: Diabetes Mellitus.

Table 3. Univariate and Multivariate Analysis of Variables with Myocardial Infarction

	Coronary Artery Disease							
	Univariate				Multivariate			
	Cox R sqaure	HR	95% CI	p-value	Cox R square	HR	95% CI	p-value
Age	0,056	1,077	1,033-1,122	< 0,001		1,492	1,718-1,870	< 0,001
CO ET	0,271	3,952	2,545-6,136	< 0,001		4,266	4,592-8,632	< 0,001
PCT	0,530	40,003	20,287-90,013	< 0,018		42,017	22,872-94,004	< 0,001
COHb	0,511	1,651	1,342-2,031	< 0,001	0,567	1,919	1,843-2,487	< 0,001
Tn	0,538	86,814	9,633-782,409	< 0,001		40,035	1,576-1016,755	< 0,004
Mortality	0,029	5,610	3,501-8,989	< 0,001		0,114	0,039-0,331	< 0,001
MPV	0,204	8,923	4,194-18,984	< 0,001		9,230	6,941-21,849	< 0,027
RDW	0,025	1,192	1,030-1,379	< 0,019		1,236	1,045-1,461	< 0,001
WBC	0,006	0,941	0,848-1,044	> 0,252				
MCV	0,000	0,996	0,959-1,036	> 0,857				
MCH	0,003	1,065	0,918-1,236	> 0,407				
MCHC	0,001	1,068	0,793-1,440	> 0,663				
CRP	0,003	1,024	0,974-1,076	> 0,361				

CI: Confidence Interval, HR: Hazard Ratio.

Table 4. Spearman correlation coefficients for late-period coronary artery disease

	Myocardial Infarction	
	r	p-value
PCT	0,762	< 0,001
COHb	0,602	< 0,001
Tn	0,601	< 0,001
CO ET	0,528	< 0,001
Mortality	0,449	< 0,001
RDW	0,173	< 0,008
MPV	0,430	< 0,001
Age	0,243	< 0,001
CRP	0,014	> 0,831

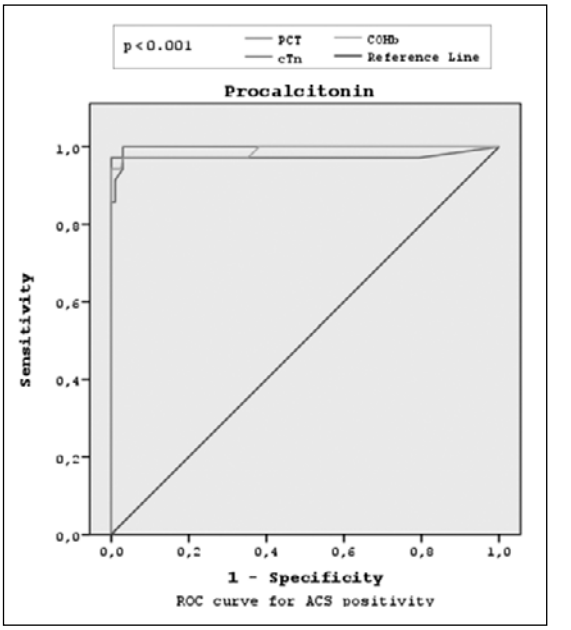

Figure 1. ROC curve analysis according to procalcitonin coronary artery disease positivity.

Discussion

There are few studies on the late effects of CO intoxication. As far as we can search in the literature, we have not been able to detect a study to determine the risk of late development of COHb, cTn and PCT levels in ED applications of patients diagnosed with CO intoxication.

Since CO poisoning can be acute or chronic, cardiac damage is based on 2 mechanisms: the first is ischemic damage and COHb binds to both proteins instead of oxygen; the second is toxic damage directly caused by CO[13-18]. As a result, endothelial damage occurs due to enzymes induced during apoptotic process and free radical formation[19]. CO has shown to trigger venous, arterial and even stent thrombosis and has a prothrombotic effect[20-23]. Myocardial damage includes areas of focal necrosis, more prominent in the subendocardium. Focal perivascular infiltrations and punctate hemorrhages may also be observed. Cardiac biomarkers such as brain natriuretic peptide, troponin, creatinkinase and creatinkinase-MB and CO elevation, T wave changes, premature atrial beat and sinus tachycardia have been shown to be associated with CO intoxication[24,25].

Gender and age differ in many studies in the literature. In our study, most patients were women and the mean age was 55 years. Kaya et al.[26], reported an incidence of 60% of women and age mean was 36.36 years while in Durak study[27] 72% were male with an age mean of 33 years. Coşkun et al.[28] study showed a 60% of women with an age mean of 53 years. Age differences among series may be due to particular demographic characteristics.

While there are many studies on acute effects of CO intoxication, late effects are very few or case-level studies. Henry et al.[29] found that death due to acute myocardial injury in patients with CO intoxication occurred after 7.6 years. In a study with a mean follow-up of 10.6 years after CO intoxication, this condition was reported as an independent predictor of all mortality events in the long term[30].

Cardiac damage may occur in the acute phase of CO intoxication but may also occur in the late period. Arrhythmias such as palpitations, sinus tachycardia, atrial fibrillation, ventricular extrasystole may be observed. In severe cases, bradycardia and atrioventricular complete block may be seen[31]. It may trigger angina pectoris and MI in patients with ischemic heart disease. ST segment and T wave changes can be seen in ECG. There may be transient right and/or left ventricular wall movement disorders[32].

The underlying cause of coronary artery disease is atherosclerosis, an inflammatory disease. Kafkas et al.[33] measured PCT, IL-6, CKMB, tro-

ponin I and C-reactive protein levels in AMI at admission and at certain hours and found PCT levels to be elevated in patients with AMI. Eren et al.[34] have shown that increased PCT levels are associated with the degree of atherosclerosis in patients with CAD and peripheral arterial disease.

In our study, PCT was found to be high due to inflammation, which is the basis of CAD and also triggered by CO poisoning. It was observed that PCT was noticeably low in patients without MI and with low COHb and cTn. These findings support the reports indicating that PCT may be elevated in silent, secondary or MI cases due to inflammatory events following CO intoxication.

Sinning et al.[35] reported that increased PCT levels at baseline were associated with increased cardiovascular event rate and higher mortality at follow-up. Ataoğlu et al.[9] measured PCT levels at the time of admission and after 48 hours in patients with ACS and reported that high PCT concentrations showed increased 6-month mortality in patients with severe myocardial injury after infarction at 48 hours after admission. We found a significant relationship between mortality and PCT levels from blood samples taken at the time of admission to the emergency department for CO poisoning. At the same time, this relationship was found to be present with COHb, cTnI, RDW and MPV levels. COHb, PCT and cTnI elevations were found to be associated with increased mortality in CAD, consistent with the literature.

In the study of Kalay et al.[36] it is the first study to show that high COHb level is an independent predictor for MI in the long term. Increased Tn due to CO intoxication and COHb were associated with blood levels and CO exposure, whereas the present study showed that increased COHb levels and long-term CO exposure were independent predictors of MI development.

In our study, cTn, PCT and COHb levels increased with increasing CO exposure time. However, as shown, the rate of cardiac injury and mortality was also increased.

Study limitations

The biggest limitation of the study was that it was single-centered and retrospective. Therefore, it was difficult to access some data. Some of these were the failure to regain control PCT, cTn, arterial blood gas, COHb levels after admission to ED, and angiography and echocardiography results were other limitations. There was no history of drug use that could affect CAD prognosis.

Conclusion

In case of CO intoxication, patients should be evaluated for immediate effects, even if they are asymptomatic with emergency treatment. Considering the PCT, COHb and cTn levels evaluated in our study, it can be a guide in providing follow-up and early treatment by predicting future cardiac problems. In addition, further studies are needed to show how the immediate treatment of CO intoxication affects late effects.

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