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# Analysis of the Prognostic Value of Carboxyhemoglobin in Patients with Acute Coronary Syndrome

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## Abstract

**Aim:** While carbon monoxide is a gas that is toxic when introduced exogenously into the body, it also functions as a signaling molecule with regulatory roles in many physiological processes within the cardiovascular system. The aim of this study is to investigate the utility of endogenous carboxyhemoglobin (COHb) for estimating mortality within the first three months after admission among patients with acute coronary syndrome.

**Materials and Methods:** Our study was conducted on patients who came to the emergency service with a complaint of chest pain, met the inclusion criteria, were hospitalized in the cardiology clinic. Patients' demographic characteristics, coronary angiography results, electrocardiogram, blood gas assessment, and blood tests' prognosis were recorded.

**Results:** The average age was 61.52±13.19 (min: 21 - max: 93) and 164 (71.9%) patients were male. Angiography results showed that 110 (48.2%) patients had obstruction of the left anterior descending artery, and 82 (36%) patients had obstruction of the right coronary artery. In the analysis conducted after excluding patients who had been exposed to cigarette smoke before hospital admission, endogenous COHb level was not a statistically significant predictor of in-hospital mortality (p=0.248) or three-month mortality (p=0.26).

**Conclusion:** No statistically significant relationship was found between endogenous COHb levels and predicted mortality in patients diagnosed with acute coronary syndrome who were neither exposed to cigarette smoke nor had a history of smoking before hospital admission. However, we think that the small patient population, together with limitations in the study may have limited the findings.

**Keywords:** Carbon monoxide, acute coronary syndrome, myocardial infarction, unstable angina, acute coronary syndrome prognosis

## Introduction

It has been predicted that carbon monoxide (CO), which has a toxic effect, also acts as signal molecule which has a regulatory role in many pathophysiological processes that take place in the cardiovascular, immune and nervous system (1,2).This effect results from the modulation of soluble guanylate cyclase and upregulation of cyclic guanosine monophosphate production similar to nitric oxide (3). In addition, studies which show its anti-apoptotic, anti-inflammatory and vasodilatation effects have been conducted (2,4,5). On the other hand, endogenous production increases in a number of haematological diseases caused by the destruction of hemoproteins such as haemolytic anemia, hematoma, thalassemia and Gilbert's syndrome (6,7). It has also been found that endogenous CO production increases before treatment in critical diseases such as sepsis, septic shock and cirrhosis (8,9). Although carboxyhemoglobin (COHb) levels are high in healthy smoking adults, endogenous CO level increases in different inflammatory and oxidative pathological conditions (10). This study examines the usability of endogenous COHb in the prediction of mortality in the first three months after admission to hospital in acute coronary syndrome (ACS) patients (11).

## Materials and Methods

### Study Protocol

This study was planned prospectively and included 228 patients older than 18 years of age who presented to the

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Atatürk University Faculty of Medicine Emergency Clinic with symptoms suggestive of acute coronary artery disease, such as chest pain, shortness of breath, tachycardia, and back pain, and who were hospitalized in the cardiology clinic. On admission, in addition to an ACS assessment, a blood gas assessment was performed (Radiometer ABL 800-flex-Radiometer Medical ApS, Bronshoj, Denmark). In addition, the patient's demographic and clinical characteristics such as age and gender, exposure to cigarette smoke, past medical history, medications used, vital signs, coronary angiography results, echocardiography results, hospitalization duration, and prognosis were recorded. Patients who did not volunteer to participate in the study; patients with comorbid conditions that could affect blood CO levels; patients whose vital signs were unstable; patients who had cardiopulmonary arrest; patients who received respiratory support; patients with known chronic lung disease and patients who had smoked or been exposed to cigarette smoke immediately before arriving at the emergency service were excluded from the study (Figure 1). In addition, patients with incomplete echocardiographic or coronary angiographic data due to early discharge, referral to another center, or incomplete in-hospital evaluation were excluded from the analysis. The study protocol was approved by the Atatürk University Faculty of Medicine Ethical Board (ethical board number: B.30.2.ATA.0.01.00/, date: 08.12.2016).

Hemodynamic instability was defined as any of the following: systolic blood pressure <90 mmHg, requirement for vasopressor support, need for invasive or non-invasive mechanical ventilation, or cardiopulmonary arrest at admission. These patients were excluded to avoid the confounding effects of hypoxia and exogenous oxygen therapy on COHb measurements.

### Statistical Analysis

For statistical analyses, the data were recorded with the Statistical Package for Social Sciences (SPSS 20) program. A Paired-sample t test was used to compare dependent variables that were normally distributed. All data were expressed as average ± standard deviation and $p<0.05$ level was considered as statistically significant.

To test the predefined study hypothesis, a minimum sample size of 128 patients was calculated to detect an effect size of 0.80 with a statistical power of 80% and a type I error rate of 0.05. A total of 228 patients were included in the final analysis, exceeding the required sample size.

## Results

During the study period, 736 patients with a diagnosis of coronary artery disease were admitted to the cardiology clinic from the emergency department. One hundred forty-nine patients declined to participate in the study. Patients with chronic lung disease (n=120); those with a history of smoking or exposure to cigarette smoke before admission (n=160); those referred to the emergency service already intubated or receiving respiratory support with unstable hemodynamics (n=66) and patients for whom echocardiography and angiography data could not be retrieved from the hospital automation system

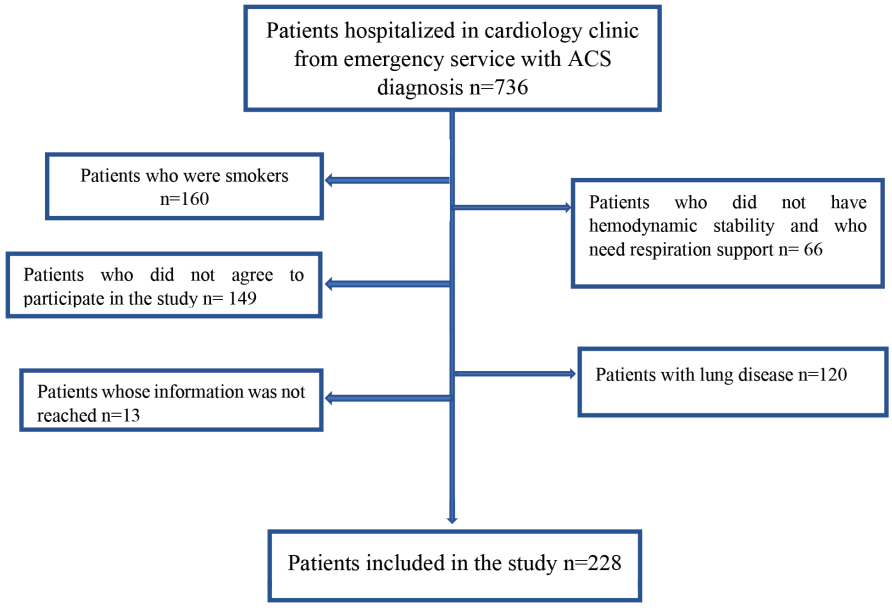


**Figure 1.** Flow chart of the patients included in the study
ACS: Acute coronary syndrome

(n=13) were excluded from the study, resulting in a final sample of 228 patients (Figure 1).

Of the patients included in the study, 164 (71.9%) were male and average age was 61.52±13.19 (21-93). When the patients' medical histories were examined, 192 (84.2%) had a history of hyperlipidemia, 91 (39.9%) had a history of hypertension, and 71 (31.1%) had a diagnosis of diabetes. When the history of drug use for existing comorbid diseases was examined, 42% (n=96) used aspirin, 25% (n=57) used a beta-blocker, and 15.8% (n=36) used an antilipidemic (Table 1).

When the admission complaints of the patients who were thought to have ACS were examined, 215 (94.5%) had chest pain; on taking anamnesis, 85 (37.3%) patients reported circumstances that increased angina symptoms.

On echocardiography performed after hospital admission, 69 (30.3%) of patients had an ejection fraction below 40%. No statistical association was found between ejection fraction and COHb level (p=0.521). In our study, wall motion disorder was found in 45 (19.7%) patients and no statistically significant association was found between wall motion disorder and endogenous COHb (p=0.172)

When the patients' ECGs were examined, depression was present in 17.1% (n=39), elevation in 36.8% (n=84), and T negativity was present in 30.3% (n=69). 82 (36%) patients with ST elevation myocardial infarction (STEMI) and 112 (49.1%) patients with non-STEMI were included in the study. Angiography was performed in 194 (85.1%) patients who were treated as inpatients for ACS. 110 (48.2%) patients had left anterior descending artery (LAD) obstruction, and 82 (36%) had right coronary artery (RCA) obstruction. No statistical association was found between COHb levels (RCA: p=0.797, LAD: p=0.826, circumflex: p=0.411) and the presence of lesions in any coronary artery among patients who received angiography (p=0.293). Angiography revealed 157 (68.9%) patients with coronary artery obstruction higher than 50%; no statistically significant association was found between the degree of obstruction and endogenous COHb (p=0.498).

**Table 1. Demographic characteristics of the patients hospitalized in cardiology clinic from the emergency service**

| Characteristics | |
|---|---|
| **Age** | 61.52±13.19 (min: 21-max: 93) |
| **Gender** | |
| Male | 164 (71.9%) |
| **Comorbid diseases in the anamnesis** | |
| Hyperlipidemia | 192 (84.2%) |
| Hypertension | 91 (39.9%) |
| Diabetes | 71 (31.1%) |
| By-pass operation | 37 (16.2%) |
| Congestive heart failure | 33 (14.5%) |
| Cerebrovascular disease | 20 (8.8%) |
| Renal failure | 14 (6.1%) |
| **Medications used** | |
| Aspirin | 96 (42%) |
| Beta blocker | 57 (25%) |
| Antihyperlipidemic | 36 (15.8%) |
| ACE* inhibitor-ARB** | 34 (14.9%) |
| Clopidegrol | 34 (14.9%) |
| Calcium canal blocker | 22 (9.6%) |
| **Admission complaint** | |
| Chest pain | 215 (94.5%) |
| Dyspnea | 24 (10.5%) |

*ACE: Angiotensin-converting enzyme, **ARB: Angiotensin receptor blocker

When patients' treatments were examined, it was found that 225 (98.7%) patients received medical treatment, 147 (64.5%) patients received percutaneous intervention, 104 (45.6%) patients received a stent, and 8 (3.5%) patients underwent bypass operation.

When the patients' mortality rates were examined, 16 (7%) died during hospitalization, 3 (1.3%) died within a month, and 4 (1.8%) died within three months. Endogenous COHb level was not a statistically significant predictor of in-hospital mortality, one-month mortality (p=0.248), or three-month mortality (p=0.26).

## Discussion

Endogenous CO is increasingly recognized as a biologically active molecule with cytoprotective, anti-inflammatory, and vasodilatory properties, primarily mediated through the heme oxygenase (HO) pathway. Experimental and clinical studies have demonstrated that HO-1 induction and subsequent CO production may increase in response to ischemic and oxidative stress. Therefore, COHb has been proposed as a potential surrogate marker reflecting endogenous CO activity and systemic stress responses (2,12,13).

Although endogenous CO production increased in case of ischemic stress (12), we concluded that it was not effective in predicting short-term mortality in patients diagnosed with ACS. However, in a study conducted by Kobayashi et al. (13), it was concluded that endogenous CO can be useful in evaluating cardiovascular stress risk. We believe that this difference between the two studies results from the fact that while increasing endogenous production by causing free hem release from hem-increasing proteins such as haemoglobin, myoglobin and cytochrome in case of ischemic stress, it is not an effective method in determining mortality (12). This discrepancy may be explained by several factors. First, ACS-related mortality is influenced by a multifactorial interplay among clinical severity, extent of myocardial injury, hemodynamic status, and established prognostic markers, such as left ventricular systolic

function, coronary anatomy, and biochemical markers. In this complex clinical setting, the isolated contribution of COHb may be insufficient to independently predict mortality (11,14).

While CO has a toxic characteristic disrupting cellular respiration, it is formed endogenously as a result of the breakdown of hem through HO enzyme and through photooxidation, lipid peroxidation and xenobiotic metabolism (15). It is known that CO, which is synthesized naturally in our body, has physiological functions such as anti-inflammatory, anti-oxidative, anti-apoptotic, vasodilation, angiogenesis and vascular remodeling in low concentrations (16,17).

It has been shown in experimental animals that blood COHb levels can be used to predict HO activity (15). In addition, it has been associated with increased HO-1 expression and elevated COHb levels. It is thought that increased HO-1 expression and high COHb level is associated with more serious course in patients who have critical disease, chronic obstructive pulmonary disease, systemic inflammatory response syndrome, acute respiratory distress syndrome and acute ischemic disease (16,18). One notable example is the retrospective study by Kakavas et al. (18), which examined the relationship between COHb level and prognosis in patients with pulmonary embolism. Univariate logistic regression analysis showed that COHb and methemoglobin levels were associated with mortality, while multivariate analysis showed that COHb was an independent predictor of in-hospital mortality. In our study, no data were found indicating that it is effective in evaluating in-hospital mortality in ACS patients. In patients diagnosed with pulmonary embolism. This can result from a number of chronic clinical situations, such as previous deep vein thrombosis, malignancy, immobilization, and bleeding disorders. We believe that the significant result reported in Kakavas et al.'s study (18) may be attributable to chronic diseases affecting COHb levels.

A large number of studies have been conducted to find out in-hospital and short term mortality in patients diagnosed with ACS (19). In studies conducted, it has been found that the relationship between type B natriuretic peptide (20), platelet neutrophil ratio (21), uric acid (22) and angiographic scoring system and serum albumin level (23) is effective in finding out mortality (24,25,26). However, in our study, endogenous CO was not significantly associated with mortality.

### Study Limitations

The present study is a cross-sectional analysis conducted at a single institution. The number of subjects was relatively low. Therefore, prospective studies with larger sample sizes are needed.

Because the number of mortality events was relatively low, multivariate regression analysis could not be performed. Another important limitation of this study is the lack of detailed subgroup-level COHb distribution data for survivors and non-survivors at different follow-up time points. Although mortality outcomes were recorded, the available dataset did not allow a reliable post hoc comparison of COHb levels between survivors and non-survivors. Therefore, such analyses could not be performed and should be addressed in prospective studies that include predefined subgroup analyses.

## Conclusion

There is no globally accepted mortality marker that can be used in daily practice for patients with ACS. The results of our study showed that endogenous COHb was not effective in predicting in-hospital and three-month mortality in patients with ACS. Although no statistically significant association was shown in our study, we think that the efficacy of endogenous COHb can be demonstrated more accurately with a larger number of patients and in multicultural studies.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Atatürk University Faculty of Medicine Ethical Board (ethical board number: B.30.2.ATA.0.01.00/, date: 08.12.2016).

**Informed Consent:** This is prospectively study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: A.Ü., Z.Ç., Concept: A.Ü., Z.Ç., Design: A.Ü., Z.Ç., Data Collection or Processing: A.Ü., Z.Ç., Analysis or Interpretation: A.Ü., Z.Ç., Literature Search: A.Ü., Z.Ç., Writing: A.Ü., Z.Ç.

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