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COHb Level and High-Sensitivity Cardiac Troponin T in 2012 in Bursa, Turkey: A Retrospective Single-Center Study

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Abstract

Background: Intoxication due to carbon monoxide (CO) is one of the most common types of poisoning. Cardiac effects of carboxyhemoglobin (COHb) range from simple arrhythmias to myocardial infarction.
Objectives: The current study aimed to investigate the relationship between blood carboxyhemoglobin and high-sensitivity cardiac troponin T (hs-cTnT) level with a highly sensitive assay in patients with acute carbon monoxide poisoning.
Patients and Methods: This retrospective study was conducted on 141 (54 males and 87 females) patients, with acute CO intoxication, admitted to the Sevket Yilmaz research and education hospital emergency unit during a one-year period (January 2012 - January 2013). The patients were divided into three groups based on COHb levels: Group I, mild COHb level <15%; Group II, COHb between 15% and 25%; Group III, severe acute CO intoxication COHb levels > 25%. COHb, hs-cTnT (Stat), creatine kinase (CK) and creatine kinase-myocardial band (CK-MB) levels were measured on admission.
Results: The mean age of the patients was 38 ± 16 years. COHb levels ranged from 8 to 35. hs-cTnT levels on inclusion in this study were slightly different between the groups (P = 0.05). COHb levels with hs-cTnT values were weakly correlated (r = 0.173, P = 0.041); on the other hand, CK-MB levels were not correlated with COHb (r = 0.013, P = 0.883).
Conclusions: In patients without clear signs of myocardial infarction, even mild CO poisoning was associated with quantifiable circulating levels of hs-cTnT when TnT was measured using a highly sensitive assay in the current study patients. Plasma levels of the hs-TnT and CK-MB assays were not correlated with the COHb levels in the current study patients.

Keywords: Carbon Monoxide Poisoning, Troponin T, Cardiac

1. Background

Intoxication due to carbon monoxide (CO) is one of the most common types of poisoning, and one of the most important toxicological global causes of morbidity and mortality (1). A weak association between carboxyhemoglobin (COHb) level and patients' clinical picture is documented (2).

CO binds rapidly to hemoglobin with greater affinity than oxygen (O_2) and forms COHb, which leads to a decrease in the O_2 carrying capacity of the blood resulting in tissue hypoxia. Therefore, organs with high oxygen demand, such as heart, brain and lungs are most sensitive to hypoxia (3-6). Cardiac effects of COHb range from simple arrhythmias to myocardial infarction (7-9).

Cardiac troponins (cTn) are structural proteins unique to the heart. The release of cTn into the circulation occurs as a consequence of cardiomyocyte injury (10). Highly sensitive-cTn (hs-cTnT) assays are developed recently, enabling measurements of concentrations that are 100-fold lower than those of the ones previously measurable (11).

2. Objectives

The current study aimed to assess whether or not myocardial damage occurs in patients with CO poisoning. The study investigated the relationship between blood carboxyhemoglobin and hs-cTnT level with a highly sensitive assay in patients with acute CO poisoning.

3. Patients and Methods

The current retrospective study was conducted at the Sevket Yilmaz Training and research hospital that is a state tertiary hospital with 1050 beds, located in the eastern Bursa, Turkey.

The study used the data available in the hospital clinical data warehouse, a centralized data repository integrating information in several databases including the order entry database and the laboratory results database of the hospital. Patients diagnosed with CO poisoning were included in the study and their corresponding electronic charts were reviewed for data collection. Prescription data were linked to detailed clinical information including patient demographics, diagnosis, clinical characteristics (including past medical history, smoking status), CO source (charcoal or fire), vital signs at presentation, physical examination characteristics, COHb levels, treatment therapy, complications in erectile dysfunction (ED), and laboratory data; the latter included specimen collection date, time, and location (for example: intensive care unit).

Two-hundred-seventeen cases admitted to the emergency medicine unit of the hospital in 2012, (January 2012 - January 2013) with the diagnosis of acute CO intoxication were selected by census method. Seventy-six patients whose additional diagnoses indicated chronic ischaemic heart disease, heart failure, myocarditis, muscular dystrophy, polymyositis, implanted cardiac resynchronization device, chronic inflammatory disease, and chronic renal failure were excluded. The overall study population included 141 subjects (87 females (62%) and 54 males (38%); 70% of the poisonings occurred in the winter, 24% in spring and 6% in autumn.

The study was approved by the Sevket Yilmaz research and education hospital ethics committee (No. 2013/7-4) and was in compliance with the Helsinki declaration; informed consent was not assumed necessary because of the retrospective observational nature of the study and all steps were taken to ensure the anonymity of the data.

Blood samples were first collected (on admission) in the emergency department and four hours later in the intensive care unit (ICU). Routine laboratory data (COHb, creatine kinase-myocardial band (CK-MB) and high-sensitivity cardiac troponin T (hs-TnT) were recorded. COHb levels were measured by a blood gas analyzer (OMNI S, Roche Diagnostics Penzberg, Germany) supported by a CO-oximetry panel. hs-cTnT and CK-MB levels were determined by an Elecsys 2010 autoanalyzer (Roche Diagnostics, Penzberg, Germany) using commercial assays. According to the manufacturer of the hs-cTnT STAT assay, the lower limit of detection was 3 ng/L, and the 99th percentile in healthy volunteers was 14 ng/L. For quality assurance purposes, the laboratory participates in an external quality assessment scheme run by Labquality, Helsinki, Finland. At the time of the present study, the QC program reported average values obtained in 107 participating laboratories. All of the data were within ± 2 SDs of the mean values.

As part of the treatment, all the patients inhaled high flow normobaric oxygen and were monitored and followed up in ICU. Treatment continued until clinical findings stabilized and serum COHb levels decreased to target levels of 5%.

3.1. Statistics

The patients intoxicated with CO were divided into three groups depending on COHb levels: Group I, mild COHb level < 15%; Group II, COHb levels < 25% and > 15%; Group III, severe acute CO intoxication COHb levels > 25%. Samples with hs-cTnT below the limit of blank (i e, 3 ng/L) were assigned a value of 1 ng/L.

Distribution of continuous data was assessed with the Shapiro-Wilk test of normality. Results were not normally distributed and non-parametric statistical tests were therefore used. The comparisons between the medians of three groups were performed by the Kruskal-Wallis test and the post-hoc Dunnett tests were used to examine the significance levels between groups. Spearman rank analysis was used to assess associations between COHb, CK-MB and hs-TnT levels. Statistical analysis of the data was performed by the SPSS 21. 0 (SPSS, Chicago, IL) and P values of < 0.05 were considered significant.

4. Results

One-hundred-forty of the patients were poisoned at home and only one of the patients was poisoned at work and they used coal or wood for heating. The predominating symptoms were nausea (n = 89), headache (n = 86), dizziness (n = 47) and vomiting (n = 28).

Tachycardia was determined in 35% of the cases (n = 50). Demographic data and the general characteristics of the patients are presented in Table 1. There were totally 141 patients with the mean age of 37.4 ± 16.6 years. COHb levels ranged from 8 to 35 (median 23, mean 22.0 ± 6.6%) on admission. The patients intoxicated with CO were divided into three groups depending on their COHb levels: Group I, mild COHb level < 15% (n = 29); Group II, COHb between 15% and 25% (n = 67); Group III, severe acute CO intoxication COHb levels > 25% (n = 45) (Table 1) (12).

Median hs-cTnT increased with increasing COHb level (Kruskal-Wallis P = 0.05; Table 1). When the post-hoc Dunnett test was performed, hs-cTnT levels were not statistically different between the groups. CK-MB levels did not differ between the three groups (Kruskal-Wallis; P = 0.48).

COHb levels with hs-TnT values were weakly correlated (r = 0.173, P = 0.041); on the other hand, CK-MB levels were not correlated with those of the COHb (r = 0.013, P = 0.883) (Table 2).

On admission, 5 of the 141 patients had elevated serum CK-MB levels and 20 had elevated serum hsTnT levels (> 14 ng/L), only three of the patients with cardiac markers were elevated on the follow-up period.

Table 1. Demographics and Plasma Concentrations of Biochemical Markers in the Patients at Admission[a]

Parameters	Group 1	Group 2	Group 3	P Value
Number				
Male	15	19	20	
Female	14	48	25	
Age, y	37 ± 15	36 ± 17	41 ± 16	0.23
COHb	12.0 (4.0)	22.0 (4.0)	28.0 (5.0)	< 0.01
CK-MB	1.88 (1.18)	1.85 (0.97)	1.95 (1.34)	0.48
hs-TnT	1.0 (6.0)	1.1 (9.4)	5.0 (12.0)	0.05

Abbreviations: CK-MB, creatine kinase-myocardial band; COHb, carboxyhemoglobin; hs-TnT, high-sensitivity cardiac troponin T.
[a]Values are expressed as median (interquartile range) or mean ± SD.

Table 2. Correlation Analysis Between COHb and hs-TnT

	r	P Value
CK-MB, ng/mL	0.013	0.883
hs-TnT, ng/L	0.173	0.041

Abbreviations: CK-MB, creatine kinase-myocardial band; hs-TnT, high-sensitivity cardiac troponin T.

5. Discussion

The findings of the cohort current study of patients with COHb intoxication hs-cTnT levels were slightly higher in severe toxicated patients than in mild toxicated patients without significant correlation between COHb and hs-cTnT levels.

Cardiac troponins are components of the contractile apparatus of cardiomyocytes and are released during myocardial necrosis. Serum troponin elevation is a specific and well established myocardial necrosis biomarker, and can detect extremely small amounts of myocardial necrosis (< 1.0 g) (12, 13). Very low, but detectable amounts of hs-cTnT levels may reflect a normal biological process of myocyte turnover and it may also be associated with an increased cell turnover (14, 15). The proposed mechanisms of cardiac troponin release include apoptosis, cellular release of proteolytic degradation products, increased cell wall permeability, and formation and release of membranous blebs (11).

Cardiac troponins are markers of all heart muscle damage, not just myocardial infarction. Many acute diseases are associated with elevated cTn in the absence of acute ischemic heart disease that can occur for many reasons (16). Direct toxic effects of circulating cytokines and chemotherapies can cause severe myocardial toxicity as severe sepsis and septic shock (12, 16). Recent data showed that one can detect the effects of some toxic chemotherapy by monitoring cTn (16). Carbon monoxide poisoning is an archetypical example of toxicity to myocardial cells.

CO has 200 - 250 times stronger affinity for hemoglobin than oxygen. This situation results in decreased blood oxygen and tissue hypoxia associated with COHb levels. High concentrations of CO induce NO mediated cellular apoptosis. Low levels of CO activate soluble guanylate cyclase which in turn exerts beneficial effects such as vasodilatation and inhibition of platelet aggregation (7). In the current study, hs-cTnT levels were higher in patients with severe CO toxicity compared to the ones with mild CO intoxication.

Although ultramicroscopic changes are reported in cases of CO toxicity, its relative effects need to be documented (17). COHb binding to heme proteins may diminish tissue O_2 usage and cytotoxicity may occur. A direct toxic effect of COHb is discussed as a consequence of experimental studies on cytochrome oxidase (17).

CO binds with cardiac myoglobin causes a rapid decrease in myocardial oxygen reserves (18). When the energy source is blocked, then the function of the myoglobin is diminished (19, 20). CO exposure may also increase oxidative stress in the patients (21).

Myocardial fiber necrosis and other changes observed with electron microscopy are associated with impaired energy metabolism (22, 23). However, cardiac troponins are released without electron microscopic changes (24, 25).

In this study CK-MB levels did not differ between the three groups and did not correlate with COHb. Patients with detectable troponin, but no CK-MB, in the blood may exhibit microscopic zones of myocardial necrosis (microinfarction) (13). Aslan et al. (26) showed that in CO poisoning, patients without known underlying significant coronary artery disease with COHb levels of up to 60% do not develop myocardial damage but they used only cardiac biomarkers CK-MB and cTnT. Similar to study by Aslan et al. the current study did not find any significant elevation in CK-MB levels, but in contrast a significant increase in hs-cTnT levels was found, which might be because of the microscopic myo-

cardial necrosis (26). Myocardial injury, documented with elevations in cardiac biomarkers, could be present in about one-third of the patients with serious CO poisoning and it was associated with mortality (7). The severity of myocardial injury depended on the duration and amount of CO exposure (27). Moreover, the level of CO in the tissues may have an equal or greater impact on the clinical status of the patient than does the blood level of CO (28).

The primary limitation of the current small study group was the method of data collection. There was no information on the length of CO exposure and the timing of the blood COHb levels in relation to the CO exposures. Further studies are necessary in this regard. Another limitation was the retrospective nature of the study. The data were reviewed by one researcher who avoided the selection bias; however, misclassification, may still exist, which cannot be verified or validated. These results apply only to the Elecsys hs-cTnT and CK-MB (Roche Diagnostics) assays, and may not be generalized to other high sensitivity assays by other manufacturers.

Finally, the study design was based on the data available in one hospital, and the obtained results may not necessarily be generalized.

5.1. Conclusion

In conclusion, in patients without clear signs of myocardial infarction, even mild CO poisoning is associated with quantifiable circulating levels of hs-cTnT when TnT is measured using a highly sensitive assay and cardiac complications should be considered in such patients. Plasma levels of the hs-TnT and CK-MB assays were not correlated with the COHb levels.

Footnote

Authors' Contribution: Study concept and design: Kagan Huysal, Yasemin Ustundag Budak, Hakan Demirci and Mehmet Karada; acquisition of data: Kagan Huysal, Yasemin Ustundag Budak, Ufuk Aydin and Hakan Demirci; analysis and interpretation of data: Kagan Huysal, Yasemin Ustundag Budak, Ufuk Aydin, Hakan Demirci, Tamer Turk and Mehmet Karadag; drafting of the manuscript: Kagan Huysal, Yasemin Ustundag Budak, Ufuk Aydin and Hakan Demirci; critical revision of the manuscript for important intellectual content: Kagan Huysal, Yasemin Ustundag Budak, Ufuk Aydin, Hakan Demirci, Tamer Turk and Mehmet Karadag; statistical analysis: Yasemin Ustundag Budak; administrative, technical, and material support: Kagan Huysal, Hakan Demirci, Tamer Turk and Mehmet Karadag; study supervision: Kagan Huysal, Yasemin Ustundag Budak, Ufuk Aydin, Hakan Demirci, Tamer Turk and Mehmet Karadag.

References

1. Chiew AL, Buckley NA. Carbon monoxide poisoning in the 21st century. *Crit Care*. 2014;**18**(2):221.
2. Icme F, Kozaci N, Ay MO, Avci A, Gumusay U, Yilmaz M, et al. The relationship between blood lactate, carboxy-hemoglobin and clinical status in CO poisoning. *Eur Rev Med Pharmacol Sci*. 2014;**18**(3):393–7. [PubMed: 24563440]
3. Guzman JA. Carbon monoxide poisoning. *Crit Care Clin*. 2012;**28**(4):537–48. doi: 10.1016/j.ccc.2012.07.007. [PubMed: 22998990]
4. Ku CH, Hung HM, Leong WC, Chen HH, Lin JL, Huang WH, et al. Outcome of patients with carbon monoxide poisoning at a far-east poison center. *PLoS One*. 2015;**10**(3):e0118995. doi: 10.1371/journal.pone.0118995. [PubMed: 25745854]
5. Kara H. Author's reply: cerebrovascular ischaemia after carbon monoxide intoxication. *Singapore Med J*. 2015;**56**(3):175. [PubMed: 25820856]
6. Atescelik M, Bozdemir MN, Yildiz M, Gurbuz S, Ayranci M, Goktekin MC, et al. QT dispersion in carbon monoxide poisoning. *Eur Rev Med Pharmacol Sci*. 2012;**16 Suppl 1**:25–9. [PubMed: 22582480]
7. Lippi G, Rastelli G, Meschi T, Borghi L, Cervellin G. Pathophysiology, clinics, diagnosis and treatment of heart involvement in carbon monoxide poisoning. *Clin Biochem*. 2012;**45**(16-17):1278–85. doi: 10.1016/j.clinbiochem.2012.06.004. [PubMed: 22705450]
8. Roderique JD, Josef CS, Feldman MJ, Spiess BD. A modern literature review of carbon monoxide poisoning theories, therapies, and potential targets for therapy advancement. *Toxicology*. 2015;**334**:45–58. doi: 10.1016/j.tox.2015.05.004. [PubMed: 25997893]
9. Garg J, Krishnamoorthy P, Palaniswamy C, Khera S, Ahmad H, Jain D, et al. Cardiovascular Abnormalities in Carbon Monoxide Poisoning. *Am J Ther*. 2014. doi: 10.1097/MJT.0000000000000016. [PubMed: 24518173]
10. Muthu V, Kozman H, Liu K, Smulyan H, Villarreal D. Cardiac troponins: bench to bedside interpretation in cardiac disease. *Am J Med Sci*. 2014;**347**(4):331–7. doi: 10.1097/MAJ.0b013e31829107ea. [PubMed: 23656921]
11. Zhelev Z, Hyde C, Youngman E, Rogers M, Fleming S, Slade T, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. *BMJ*. 2015;**350**:h15. doi: 10.1136/bmj.h15. [PubMed: 25646632]
12. Koylu R, Cander B, Dundar ZD, Koylu O, Akilli NB, Ivelik K. The Importance of H-FABP in Determining the Severity of Carbon Monoxide Poisoning. *J Clin Med Res*. 2011;**3**(6):296–302. doi: 10.4021/jocmr675w. [PubMed: 22393341]
13. Gualandro DM, Puelacher C, Mueller C. High-sensitivity cardiac troponin in acute conditions. *Curr Opin Crit Care*. 2014;**20**(5):472–7. doi: 10.1097/MCC.0000000000000132. [PubMed: 25159476]
14. Everett BM, Cook NR, Magnone MC, Bobadilla M, Kim E, Rifai N, et al. Sensitive cardiac troponin T assay and the risk of incident cardiovascular disease in women with and without diabetes mellitus: the Women's Health Study. *Circulation*. 2011;**123**(24):2811–8. doi: 10.1161/CIRCULATIONAHA.110.009928. [PubMed: 21632491]
15. Agewall S, Giannitsis E, Jernberg T, Katus H. Troponin elevation in coronary vs. non-coronary disease. *Eur Heart J*. 2011;**32**(4):404–11. doi: 10.1093/eurheartj/ehq456. [PubMed: 21169615]
16. Burtis CA, Ashwood ER, Bruns DE. *Tietz textbook of clinical chemistry and molecular diagnostics*. Elsevier Health Sciences; 2012.
17. Castoldi AF, Coccini T, Randine G, Hernandez-Viadel M, Felipo V, Manzo L. Lymphocyte cytochrome c oxidase, cyclic GMP and cholinergic muscarinic receptors as peripheral indicators of carbon monoxide neurotoxicity after acute and repeated exposure in the rat. *Life Sci*. 2006;**78**(17):1915–24. doi: 10.1016/j.lfs.2005.08.032. [PubMed: 16288783]
18. Chung Y, Huang SJ, Glabe A, Jue T. Implication of CO inactivation on myoglobin function. *Am J Physiol Cell Physiol*. 2006;**290**(6):C1616–24. doi: 10.1152/ajpcell.00360.2005. [PubMed: 16421206]
19. Queiroga CS, Almeida AS, Vieira HL. Carbon monoxide targeting mitochondria. *Biochem Res Int*. 2012;**2012**:749845. doi: 10.1155/2012/749845. [PubMed: 22536507]
20. Brown SD, Piantadosi CA. Reversal of carbon monoxide-cytochrome c oxidase binding by hyperbaric oxygen in vivo. *Adv Exp Med Biol*. 1989;**248**:747–54. [PubMed: 2551142]

21. M. Ismail M. Some Biomarkers in Carbon Monoxide-Induced Cardiotoxicity. *J Environ Analytic Toxicol.* 2013;**03**(04). doi: 10.4172/2161-0525.1000176.
22. Kumazawa T, Watanabe-Suzuki K, Seno H, Ishii A, Suzuki O. A curious autopsy case of accidental carbon monoxide poisoning in a motor vehicle. *Leg Med (Tokyo).* 2000;**2**(3):181–5. [PubMed: 12935724]
23. Tritapepe L, Macchiarelli G, Rocco M, Scopinaro F, Schillaci O, Martuscelli E, et al. Functional and ultrastructural evidence of myocardial stunning after acute carbon monoxide poisoning. *Crit Care Med.* 1998;**26**(4):797–801. [PubMed: 9559621]
24. Sabatine MS, Morrow DA, de Lemos JA, Jarolim P, Braunwald E. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. *Eur Heart J.* 2009;**30**(2):162–9. doi: 10.1093/eurheartj/ehn504. [PubMed: 18997177]
25. Jaffe AS, Wu AH. Troponin release--reversible or irreversible injury? Should we care? *Clin Chem.* 2012;**58**(1):148–50. doi: 10.1373/clinchem.2011.173070. [PubMed: 22039010]
26. Aslan S, Erol MK, Karcioglu O, Meral M, Cakir Z, Katirci Y. [The investigation of ischemic myocardial damage in patients with carbon monoxide poisoning]. *Anadolu Kardiyol Derg.* 2005;**5**(3):189–93. [PubMed: 16140649]
27. Kalay N, Ozdogru I, Cetinkaya Y, Eryol NK, Dogan A, Gul I, et al. Cardiovascular effects of carbon monoxide poisoning. *Am J Cardiol.* 2007;**99**(3):322–4. doi: 10.1016/j.amjcard.2006.08.030. [PubMed: 17261390]
28. Nikkanen H, Skolnik A. Diagnosis and management of carbon monoxide poisoning in the emergency department. *Emerg Med Pract.* 2011;**13**(2):1–14. [PubMed: 22164402]