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Carbon Monoxide induced toxicity: A literature Review of The Challenges in Early Diagnosis of Cardiotoxicity and Neurotoxicity

Alaa A.Marie, Ola G.Hagag, Asmaa Y.Hussein and Ibrahim A.Mostafa
Forensic Medicine and Toxicology Dept., Faculty of Medicine, Benha University
Email: adralaaahmed@gmail.com

Abstract

Background: Carbon monoxide (CO) is known as silent killer; since it is a colorless, odorless and non-irritating but highly toxic gas. It results from incomplete combustion of carbonaceous substances. The current method for CO poisoning begins with clinical suspicion and a review of the patient's medical history. It is then confirmed by detecting elevated CO-Hb levels (greater than 10%), which can be measured through invasive blood gas analysis or non-invasive techniques like multi-wave pulse oximetry. **Objective:** we summarize recent advances in understanding challenges in early diagnosis of CO induced cardiotoxicity and neurotoxicity. Traditional diagnostic markers such as cardiac enzymes, ECG, and brain CT scans remain essential for diagnosing CO-induced cardiotoxicity and neurotoxicity. Emerging biomarkers like heart-type fatty acid-binding protein (H-FABP) and neurogranin show potential for earlier and more accurate detection of CO poisoning-related organ damage. **Conclusions**: Recent markers are needed for early detection of acute in CO induced cardiotoxicity and neurotoxicity other than traditional markers.

Keywords: Carbon monoxide, H-FABP, Neurogranin, Cardiotoxicity, Neurotoxicity.

1. Introduction:

Various poisons, including natural toxins and synthetic chemicals, exist in our environment and can harm living organisms in numerous ways [1]. Carbon monoxide (CO) is an environmental toxin often called the “silent killer” due to its colorless, odorless, and non-irritating nature [2].

Carbon monoxide poisoning (COP) is the primary factor leading to fatalities among fire victims. About 30% to 40% of individuals affected by CO poisoning do not survive until they reach the hospital. Among those hospitalized, around 2% result in fatalities, 10% achieve partial recovery, and 23% to 47% experience delayed neurological sequelae [1].

The current estimates for the worldwide cumulative incidence and fatality rates of COP are 137 cases and 4.6 deaths per million, respectively. Over the previous quarter of a century, the worldwide incidence has stayed unchanged, although the death rates and the proportion of patients who have passed away have both fallen by 36 percent and forty percent, respectively [3].

2. Methods

A systematic literature review was conducted using primary databases such as PubMed and Medscape Online, along with supplementary sources like Google Scholar and Baidu Scholar. Relevant articles were identified through a search using specific keywords such as "CO," "exposure sources," "toxicity mechanisms," "diagnostic measures," "CO-induced cardiotoxicity," and "CO-induced neurotoxicity." Inclusion criteria were as follows: only original research articles were included, and articles published in English within the last 10 years were considered. Studies focusing on CO-induced toxicity (cardiotoxicity and neurotoxicity) and diagnostic methods were prioritized. Articles that were not directly related to the topic of CO-induced toxicity or were not original research were excluded.

A total of 80 articles were reviewed, with topics distributed as follows: 71 articles on diagnostic methods, 9 articles on clinical guidelines. Filters applied during the search included focusing on original research studies, limiting results to English-language publications, and considering only articles published in the last 10 years. This approach ensured that the review was comprehensive and up-to-date, addressing current knowledge and advances in the diagnosis and pathophysiology of CO poisoning.

3. Results and discussion

3.1. Sources of CO Exposure

Certain industrial activities, as well as the combustion of fossil fuels and biomass, are primary human-induced sources of CO. Scientists estimate that the total annual CO production from both human and natural sources ranges between two and five gigatons. Natural sources of CO include forest fire smoke, gases from coal mines, and even lightning [4]. CO is also present in mainstream cigarette smoke, comprising about 3–4%, leading to an increase in blood carboxyhemoglobin (CO-Hb) levels by approximately 10–15% in heavy smokers [5]. Additionally, methylene chloride, a solvent commonly used in paint or varnish removers, is metabolized into CO in the body. Severe CO poisoning, with CO-Hb saturation reaching up to 50%, has been documented following exposure to methylene chloride [6].

The primary sources of CO found in poisoning cases are home fires (the air near a house fire can contain up to 5% CO, incomplete fuel combustion (charcoal, briquettes, fuel gas, petroleum), insufficiently ventilated or poorly maintained heating or cooling equipment, exhaust gas from internal combustion engine-powered vehicles, and industrial accidents (like those at chemical plants or iron foundries) [7].

3.2. Routes of Exposure:

Poisoning occurs when a relatively high quantity of carbon monoxide gas is inhaled. This is because carbon monoxide enters the circulation via the lungs, which in turn limits the amount of oxygen that is delivered to the organs and tissues of the body. Individuals who suffer from cardiovascular disorders, such as angina pectoris, are the ones who are most at risk for adverse health effects when exposed to lower amounts of carbon monoxide. It is possible for carbon monoxide to be poisonous at dramatically high levels of exposure, and even those who are in excellent health may be vulnerable to harmful effects [5].

3.3. Mechanisms of carbon monoxide poisoning

Despite the robust bond between CO and hemoglobin, this bond can be disrupted, resulting in the gradual displacement of CO by oxygen. As well, CO binds to myoglobin in the myocardium and skeletal muscle, resulting in dysfunctional tissue oxygen transport. In the myocardium, this leads to cardiac dysfunction [8]. In acute CO poisoning, the primary toxic effect is functional anemia, which is caused by the formation of CO-Hb. This results in insufficient oxygenation at the tissue level, as the oxygen transport capacity is reduced.

A shift to the left occurs in the oxygen-hemoglobin dissociation curve as a result of the binding of CO to a hemoglobin subunit. This occurs because CO enhances the oxygen affinity at the other binding sites. Because of this shift, oxygen release is inhibited in regions with low oxygen levels, which makes tissue hypoxia severity worse [9]. CO is also capable of directly inhibiting enzymes such as cytochrome c oxidase, which may have a negative impact on the activities of the heart and the nervous system [10].

By increasing vascular permeability, tissue hypoxia brought on by exposure to CO causes an increase in the buildup of interstitial fluid and a reduction in the amount of blood that is circulating (hemoconcentration), which impacts a number of organs. Edema of the brain, which may cause neurological symptoms and a change in consciousness, pulmonary edema, which can lead to respiratory failure, decreased myocardial contractility, arrhythmias, heart failure, and renal failure are all potential outcomes of this condition [11].

3.4. Clinical presentation of Acute CO Poisoning

When CO-Hb levels are below 10%, there are no notable symptoms observed. Neurological symptoms such as nausea, headache, and dizziness manifest when CO-Hb exceeds 10%. CO-Hb levels ranging from 30% to 50% lead to heightened respiratory and heart rates, loss of consciousness, motor paralysis, and confusion. CO-Hb levels exceeding 50% pose a significant threat to life and are crucial for diagnosing CO poisoning [12].

Table 1: Carboxyhemoglobin (CO-Hb) saturation levels % and symptoms of acute carbon monoxide poisoning [13]

CO-Hb (%)	Clinical symptom
< 1	**Normal range (due to endogenous production)**
< 10	**Smoker's blood (no symptom)**
10–20	**Headache, fatigue, ear ringing**
20–30	**Headache, weakness, nausea, vomiting**
30–40	**Severe headache, dizziness, nausea, vomiting**
40–50	**Syncope, confusion, increased respiration and heart rate**
50-60	**Coma, convulsions, depressed respiration**
60–70	**Coma, convulsions, cardiopulmonary depression, often fatal**
70 <	**Respiratory failure, death**

Images and Markers for Early Diagnosis of CO Induced Organ Injuries:

Many researchers have focused on identifying biomarkers to predict complications and severity after COP. Biomarkers such as creatine kinase (CK), creatine kinase-MB, troponins, natriuretic peptides (NT-proANP, NT-proBNP), and S100B have been used to assess the toxicity of CO on the brain and heart [14].

3.5. Laboratory investigation for diagnosis of CO poisoning

A. Measurement of carboxyhemoglobin level in blood

Measuring elevated CO-Hb levels in the blood is essential for confirming a diagnosis of suspected exposure [15]. CO-Hb levels, on the other hand, can be deceiving in patients who smoke heavily or who suffer from conditions such as chronic obstructive pulmonary disease and high blood pressure. A further point of contention is the dependability of non-invasive methods. Injuries have been observed even at CO-Hb levels of 5–10%, and sudden death from severe arteriosclerotic heart disease has been reported at CO-Hb levels of 20–30%. The principal targets of carbon monoxide are the brain and the heart [16, 17].

B. Pulse oximetry:

The delay in the administration of hyperbaric oxygen (HBO) to patients has been demonstrated to be reduced by pulse CO oximetry, which offers fingertip

measurement at the site of the injury. Regrettably, the accuracy of pulse CO oximetry alone in comparison to CO-Hb measured by spectrophotometry from a laboratory CO oximeter is still uncertain. Consequently, it is necessary to confirm pulse CO oximetry levels with laboratory measurements. Furthermore, conventional pulse oximetry is unable to differentiate between oxy-Hb and CO-Hb, which can result in the omission of significant CO-Hb levels and profound hypoxia [18].

C. Images and Markers for Early Diagnosis of CO Induced Organ Injuries:

Many researchers have investigated biomarkers that can predict complications and severity following COP. Specific biomarkers like CK, CK-MB, troponins, natriuretic peptides (NT-proANP, NT-proBNP), and S100B have been used to predict the harmful effects of carbon monoxide on the cardiovascular system and the brain[14].

3.6. Diagnosis of CO induced cardiotoxicity:

3.5.1. Cardiac Enzymes:

In the majority of cases, the enzymes that are utilized are CK-MB and Troponin I (TnI). Troponin I and CK-MB levels were found to be elevated in patients with chronic obstructive pulmonary disease [19]. Myocardial damage causes an increase in the levels of three cardiac proteins: creatine kinase-myocardial band (CK-MB), TnI, and brain natriuretic peptide (BNP). These proteins are expressed in the heart muscle.

According to reports, CO-induced cardiomyopathy can be reliably diagnosed on echocardiography by elevated concentrations of CK-MB and high-sensitivity troponin I (hsTnI). Screening for myocardial dysfunction in patients with CO poisoning may be made possible by cardiac enzymes (excluding BNP) [20, 21]. Patients at high risk for CO-induced cardiomyopathy may be identified by higher hsTnI or CK-MB levels upon admission to the emergency department (ED). Because of this, these biomarkers may be useful for screening patients for acute CO poisoning to decide if they need to have transthoracic echocardiography [22].

3.5.2. Electrocardiogram (ECG):

The most prevalent ECG findings are sinus tachycardia and ST-T depressions, despite the absence of a distinct "CO" ECG pattern. Myocardial infarction can be precipitated by even a minute amount of exposure to CO, particularly in patients with coronary artery disease. Patients who present to the emergency department with chest pain and ECG changes may be suspected of having CO poisoning. Patients who have CO poisoning must undergo a thorough evaluation for cardiovascular disease [23].

3.5.3. Human fatty acid-binding protein Biomarkers (heart type) in early Diagnosis of CO induced cardiac injury

Fatty acid-binding proteins (FABPs) are a subfamily of intracellular lipid-binding proteins that carry out the reversible binding and trafficking of hydrophobic ligands within cells to various organelles and regions, including the nucleus, endoplasmic reticulum, mitochondria, and peroxisomes [24]. Myocytes contain heart-type fatty acid-binding protein (H-FABP), which is released from damaged myocardium [19].

- **Heart-type fatty acid-binding protein (H-FABP):**

A variety of tissues, including the heart, skeletal muscle, brain, kidney, lung, testis, aorta, adrenal gland, mammary gland, placenta, ovary, and brown adipose tissue, have yielded H-FABP, additionally known as FABP3 [25].

When cardiomyocytes sustain damage, they quickly release H-FABP into the bloodstream, despite the protein's abundance in the myocardium. As a sensitive indicator for detecting and assessing myocardial damage in patients with heart failure, the serum concentration of H-FABP has been proposed as an early biochemical marker for acute myocardial infarction [26].

❖ **Prognostic value of H-FABP:**

The prognostic significance of H-FABP for the early prediction of unfavorable clinical outcomes in patients with suspected ACS has only recently been explored. Despite the limited number of studies conducted, the findings are encouraging, as heightened plasma concentrations of H-FABP in patients with ACS are significantly associated with elevated rates of cardiac events and cardiac mortality [27].

In patients with congestive heart failure (CHF), increased plasma concentrations of H-FABP are associated with higher rates of cardiac events. During the initial stages of ACS, H-FABP should be utilized to identify patients at high risk for cardiac events who may benefit from more aggressive treatment strategies [28].

3.6. **Diagnosis of CO induced neurotoxicity**

3.6.1.Brain computerized tomography (CT) scans:

A computerized tomography (CT) scan of the brain is a rapid and readily accessible diagnostic procedure, thus it typically constitutes the initial examination conducted for these patients. Computed tomography (CT) is regarded as the initial diagnostic method for assessing patients suspected of poisoning, especially in instances of altered consciousness. CT scans in the acute phase of COP often show focal, bilateral, and symmetrical hypodensities in the globus pallidus, indicating necrosis in these areas..

The selective damage observed in the globus pallidus during CO poisoning may be related to the hypotensive effects of CO on the inadequate anastomotic vascular supply to these structures, or it may be the result of a direct interaction between CO and the heme iron present in the globus pallidus, which is known to have one of the highest concentrations of iron in the brain [29]. The globus pallidus may be unaffected in extremely rare cases, but the caudate nucleus, putamen, or thalamus may be involved. Because the cerebellum and brainstem are posterior

structures and thus more resistant to hypoxia, their involvement during the acute phase is rare and usually indicative of more severe poisoning.

Involvement of the cortex during the acute phase is uncommon and usually impacts the hippocampus and temporal lobes. As the disease advances, CT scans may show widespread demyelination, which appears as diffuse hypodense areas in the centrum semiovale and bilateral periventricular white matter. The corpus callosum, subcortical white matter, internal and external capsules, and other structures may be involved in more severe cases of this process [30].

3.6.2.Neurogranin as a biomarker for early diagnosis of CO induced brain injuries:

Neurogranin (Ng) is a small, neural-specific postsynaptic protein consisting of 78 amino acids, primarily localized intracellularly, and plays a crucial role in postsynaptic signal transmission. It is concentrated on dendritic spines in areas such as the hippocampus and basal forebrain. Ng interacts with calmodulin (CaM) to regulate calcium influx, with the binding process being phosphorylated by protein kinase C (PKC) and influenced by calcium concentrations. Ng is involved in the regulation of CaM-dependent nitric oxide synthase activity by targeting CaM. Nitric oxide modulates Ng by reducing its ability to bind to CaM or undergo phosphorylation by PKC. This is because Ng is involved in targeting CaM. Ng is found in high concentrations in certain regions of the brain, including the cerebral cortex, hippocampus, amygdala, caudate nucleus, and putamen; however, it is not nearly as common in the cerebellum, brainstem, or spinal cord [31].

Ng is recognized as a substrate of PKC and is crucial in connecting PKC and Ca/CaM signaling, which is pertinent to synaptic plasticity [32]. In animal models, Ng knockdown impairs long-term potentiation (LTP) and cognitive function, whereas upregulation enhances LTP and cognitive performance [33].

Ng concentrations diminish in the hippocampi with advancing age and are associated with central nervous system dysfunction. The brain-specific protein neurogranin was hypothesized to aid in the diagnosis of brain injury. A significant advantage of Ng is its measurability in whole blood samples. Current research partially seeks to assess Ng potential role in mitigating the overutilization of CT scans in mild brain injuries [34].

The expression and localization of Ng appear to be modified in pathological conditions of neuronal tissue. Ng has been identified as being relocated from its intracellular position to the extracellular space, allowing for its detection in blood and cerebrospinal fluid during acute or chronic conditions that result in brain tissue damage, with its quantification reflecting neuronal disintegration [35].

3.7. Evaluation of acute monoxide poisoning severity

The conventional approach to evaluate exposure severity centers on neurological and cardiac manifestations indicative of tissue hypoxia, including loss of consciousness and chest pain. Objective evidence of ischemic injury may present with neurological symptoms; however, the identification of cardiac ischemia necessitates examinations for electrocardiographic (ECG) alterations and elevations in cardiac enzymes, specifically troponin and CK-MB. Myocardial injury is prevalent, especially among individuals experiencing loss of consciousness or possessing underlying vascular disease, or both [5].

Conclusions:

This paper concludes that carbon monoxide (CO) poisoning remains a significant global health concern due to its high morbidity and mortality rates. Cardiac and neuronal toxicity from CO exposure often result in severe health complications. While traditional biomarkers such as CK-MB, troponins, NT-proBNP, and Brain CT scans have demonstrated utility in diagnosing CO-induced cardiotoxicity and neurotoxicity, there is an ongoing need for earlier and more sensitive markers. Identifying such markers could significantly reduce the morbidity and mortality associated with CO poisoning.

Recommendations:

Future research should focus on the validation of emerging biomarkers, such as heart-type fatty acid-binding protein (H-FABP) and neurogranin, for early detection of cardiac and neurotoxic effects of CO poisoning. Clinical studies are needed to assess their sensitivity, specificity, and reliability in real-world settings. Further work is also required to explore the potential of these biomarkers in improving early diagnosis, enabling more timely interventions, and ultimately reducing the long-term consequences of CO exposure.

References

[1] M. Tavassoli, A. Afshari, AL. Arsene, et al. Toxicological profile of Amanita virosa - A narrative review. Toxicol Rep ;vol 6 :pp143-50. 2019.

[2] RW. Byard: Carbon monoxide - the silent killer. Forensic Sci Med Pathol ;vol 15 pp:1-12. 2019.

[3] C. Mattiuzzi, G. Lippi. Worldwide epidemiology of carbon monoxide poisoning. Hum Exp Toxicol ;vol 39:pp 387-92. 2020.

[4] HE. Obanya, NH. Amaeze, O. Togunde, et al. Air pollution monitoring around residential and transportation sector locations in Lagos Mainland. J Health Pollut ;vol 8:pp18-39. 2018.

[5] JJ. Rose, L. Wang, Q. Xu, et al. Carbon monoxide poisoning: pathogenesis, management, and future directions of therapy. Am J Respir Crit Care Med ;vol 195 :pp596-606. 2017.

[6] DR. Hess. Inhaled Carbon Monoxide: From Toxin to Therapy. Respir Care ;vol 62:pp1333-42. 2017.

[7] NJ. Brady, PS. Patel, S. Moayedi, D. Sward. A novel source of carbon monoxide for suicide attempt. Undersea Hyperb Med. 2022 ;vol 49: pp329-31. 2022.

[8] JA. Chenoweth, TE. Albertson, MR. Greer. Carbon monoxide poisoning. Crit Care Clin ;vol 37 :pp 657-72. 2021.

[9] A. Dorey, P. Scheerlinck, H. Nguyen, et al. Acute and Chronic Carbon Monoxide Toxicity from Tobacco Smoking. Mil Med ;vol 185: pp61-7. 2020.

[10] D. Stucki, W. Stahl. Carbon monoxide - beyond toxicity? Toxicol Lett. 2020 ;vol 333:pp251-60. 2020.

[11] N. Dindar Badem, E. Cömertpay, F. Coşkun. How much apoptosis does carbon monoxide poisoning cause? Primary clinical soluble TWEAK protein level study. Hum Exp Toxicol ;vol 38:pp974-82. 2019.

[12] LK. Weaver. Carbon monoxide poisoning. Undersea Hyperb Med ;vol 47:pp151-69.2020.

[13] H. Kinoshita, H .Türkan, S. Vucinic, et al. Carbon monoxide poisoning. Toxicol Rep ;vol 7: pp169-73. 2020.

[14] T. Gawlikowski, M. Golasik, E. Gomółka, et al. Proteins as biomarkers of carbon monoxide neurotoxicity. Inhal Toxicol ;vol 26:pp885-90. 2014.

[15] L. Eichhorn, M. Thudium, B. Jüttner. (2018): The diagnosis and treatment of carbon monoxide poisoning. Dtsch rztebl Int ;vol 115:pp863-77.

[16] K. Tabrizian, J. Shahraki, M. Bazzi, et al. Neuro-protective effects of resveratrol on carbon monoxide-induced toxicity in male rats. Phytother Res ;vol 31:pp10-5. 2017.

[17] K. Tabrizian, H. Khodayari, R. Rezaee, et al. Magnesium sulfate protects the heart against carbon monoxide-induced cardiotoxicity in rats. Res Pharm Sci ;vol 13: pp 65-75. 2018.

[18] PC. Ng, B. Long, A. Koyfman. Clinical chameleons: an emergency medicine focused review of carbon monoxide poisoning. Intern Emerg Med ;vol 13:pp223-9.2018.

[19] AK. Erenler, T. Yardan, A. Baydin, et al. Heart-type fatty acid-binding protein as a potential biomarker of acute carbon monoxide poisoning. Am J Emerg Med ;vol 31:pp1165-9. 2013.

[20] M. Atescelik, M. Bozdemir, M. Yildiz, et al. QT dispersion in carbon monoxide poisoning. Eur Rev Med Pharmacol Sci; vol16:pp25-9. 2012.

[21] H. Koga, H. Tashiro, K. Mukasa, et al. Can indicators of myocardial damage predict carbon monoxide poisoning outcomes? BMC Emergency Medicine ;vol 21:pp 7-15. 2021.

[22] J-S. Kim, BS. Ko, CH. Sohn, et al. High-Sensitivity Troponin I and Creatinine Kinase-Myocardial Band in Screening for Myocardial Injury in Patients with Carbon Monoxide Poisoning. Diagnostics ;vol 10:pp242-7. 2020.

[23] Ü. Kaldirim, M. Erkencigil, SK. Tuncer, et al. Electrocardiographic findings of carbon monoxide intoxication; two cases. African Journal of Emergency Medicine ;vol 3:pp17-30 2013.

[24] RL. Smathers, DR. Petersen. The human fatty acid-binding protein family: Evolutionary divergences and functions. Human Genomics ;vol 5:pp170-80. 2011.

[25] A. Chmurzyńska. The multigene family of fatty acid-binding proteins (FABPs): function, structure and polymorphism. J Appl Genet ;vol 47:pp39-48. 2006.

[26] K. Setsuta, Y. Seino, T. Ogawa, et al. Use of cytosolic and myofibril markers in the detection of ongoing myocardial damage in patients with chronic heart failure. Am J Med ;vol 113:pp717-22. 2002.

[27] Y. Chen, LB. Agellon. Distinct Alteration of Gene Expression Programs in the Small Intestine of Male and Female Mice in Response to Ablation of Intestinal Fabp Genes. Genes (Basel) ;vol 11:pp56-78. 2020.

[28] H. Goel, J. Melot, MD. Krinock, et al. Heart-type fatty acid-binding protein: an overlooked cardiac biomarker. Ann Med ;vol 52:pp 444-61. 2020.

[29] T. Beppu. The role of MR imaging in assessment of brain damage from carbon monoxide poisoning: a review of the literature. AJNR Am J Neuroradiol ;vol 35:pp 625-31. 2014.

[30] M. Varrassi, A. Di Sibio, C. Gianneramo, et al. Advanced neuroimaging of carbon monoxide poisoning. Neuroradiol J. 2017 ;vol 30:pp461-9. 2017.

[31] A. Petersen, NZ. Gerges. Neurogranin regulates CaM dynamics at dendritic spines. Sci Rep ;vol 5:pp111-35. 2015

[32] MF. Rey-Burusco, M. Ibánez-Shimabukuro, M. Gabrielsen, et al. Diversity in the structures and ligand-binding sites of nematode fatty acid and retinol-binding proteins revealed by Na-FAR-1 from Necator americanus. Biochemical Journal ;vol 471:pp 403-14, 2015.

[33] KB. Casaletto, FM. Elahi, BM. Bettcher, et al. Neurogranin, a synaptic protein, is associated with memory independent of Alzheimer biomarkers. Neurology. 2017 ;vol 89: pp1782-8. 2017.

[34] N. Pankratova, M. Jović, ME. Pfeifer. Electrochemical sensing of blood proteins for mild traumatic brain injury (mTBI) diagnostics and prognostics: Towards a point-of-care application. RSC advances ;vol 11:pp301-19. 2021.

[35] MA Lam, SJ. Hemley, E. Najafi, et al. The ultrastructure of spinal cord perivascular spaces: Implications for the circulation of cerebrospinal fluid. Scientific Reports; vol 7:pp12-39. 2017.