

Carbon Monoxide Intoxication

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Abstract

There is sufficient evidence to suggest that significant numbers of our population are being poisoned by low concentrations of carbon monoxide (CO). In otherwise healthy people, occult indoor exposure may result in commonplace symptoms such as headache, dizziness, weakness, and difficulty in concentrating. In people with pre-existing disease, pollution alone may result in increased morbidity and mortality. Variable symptoms and signs make the poisoning difficult to detect and lead to serious outcomes. Multiple laboratory and image study can help us to detect and diagnose CO poisoning. Although the use of hyperbaric oxygen (HBO) therapy is still controversial after many well-designed studies, many authors recommend the HBO in specific group. The other treatments, such as glucagon or steroid warrant further investigation. ED physicians have to learn to early detect the poisoning and to lower the morbidities and mortalities by appropriate management. (*Ann Disaster Med.* 2005; 4 Suppl 1:S8-S17)

Key words: Carbon monoxide Poisoning; HBO; Resuscitation

Epidemiology

CO is a colorless, odorless, and tasteless gas produced primarily as a result of any carbonaceous fossil fuel. Poisoning of CO remains the leading cause of poisoning mortality in the United States.¹ It accounts for an estimated 40000 annual ED visits and 5000-6000 accidental deaths, most of them were due to motor vehicle exhaust and house fire. About 30% of CO poisoning patients were unintentional.² The death rate from unintentional CO poisoning has declined over the past 3 decades, attributed in large part to prevention of motor vehicles exhaust exposures by stricter emissions control and public education programs.³ However, un-

intentional CO poisoning from some sources remained common. One of these is exposure to CO produced by portable electrical generators, powered by fossil fuels such as gasoline or propane and typically operated when normal electrical service is disrupted by a storm or in remote locations.⁴ The US Consumer Product Safety Commission summarized the 180 unintentional consumer product-related, non-fire-related CO deaths in 1998 as being associated with indoor heating system (71%), stoves and other appliances (10%), charcoal grills (9%), camp stoves (6%), and water heater (4%).⁵

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Table 1. Common symptoms caused by carbon monoxide poisoning

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- Headache
 - Dizziness
 - Weakness
 - Vomiting and diarrhoea
 - Loss of consciousness (without lateralising signs)
 - Seizure
 - Confusion
 - Angina
 - Breathlessness
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Pathophysiology

CO binds to hemoglobin with an affinity more than 220 to 240 times that of oxygen, replaces oxyhemoglobin by Hb-CO, and produces a relative anemia.⁶ It also causes a leftward shift in the oxygen-hemoglobin dissociation curve, decreases tissue oxygen delivery, and leads to tissue hypoxia. However, CO poisoning is much more complex than initially presumed and has mechanism of toxicity beyond the formation of Hb-CO. Some studies revealed that clinical morbidity and mortality due to CO poisoning independent of Hb-CO level or hypoxia. The current understanding of the pathophysiology of CO poisoning relates its clinical effect to the combination of direct CO toxicity and Hb-CO induced tissue hypoxia.^{7,8}

CO may bind to many heme-containing proteins other than hemoglobin, like myoglobin, cytochromes, and guanylyl cyclase and would induced specific toxicity. Myocardial ischemia or arrhythmia would be developed when CO binding to myoglobin. Rhabdomyolysis may coexist.⁹ Binding to cytochrome would lead to generation of free radicals due to disrupt the oxidative metabolism via cytochrome oxidase.

The inactivation of mitochondrial enzyme may also lead to oxygen radicals formation.¹⁰ CO also stimulates guanylyl cyclase, which increases cyclic guanosine monophosphate resulting in cerebral vasodilatation and leads to loss of consciousness.¹¹

The role of nitric oxide (NO) and other free radicals has been researched and mentioned broadly in the setting of CO poisoning. Increased NO level was noted in patients who suffered from CO poisoning with loss of consciousness in many studies. Syncope may be related to NO-mediated cerebral vessel relaxation and dilatation. NO is a peripheral vasodilator which may lead to systemic hypotension and predispose to the severity of cerebral lesion.¹² The delayed neurologic syndrome (DNS) is also related to NO via the oxidative damage and brain lipid peroxidation after CO poisoning.

Clinical Presentations

The clinical presentations of CO poisoning are variable and non-specific, which would be easily confused with other disease. Initial symptoms of CO poisoning include headache, dizziness,

confusion, fatigue, nausea, vomiting, difficulty concentrating, loss of consciousness, and coma (Table 1).¹³ The severity of symptoms is proportional to the exposed amount. The brain and the heart are the most oxygen-dependent organs and the most vulnerable to CO toxicity. Early neurologic manifestations included dizziness and headache. Increasing exposure may produce disturbance of consciousness, confusion, syncope, seizure, acute stroke-like syndromes, and coma. Mechanisms of brain injury following CO poisoning include hypoxia, excitotoxicity, binding to intracellular proteins and disrupting cellular metabolism, interference of intracellular enzyme function including P450, lipid peroxidation leading to oxidative injury, deposition of peroxynitrate (which damages blood vessel endothelium), apoptosis or programmed cell death, cerebral edema leading to secondary vascular effects, lactic acidosis, and oxidative stress from intracellular iron deposition.^{10,11}

Early cardiovascular effects of CO poisoning are manifested as a response to hypoxia. More significant exposure results in hypotension, dysrhythmia, ischemia, infarction, and in extreme cases, cardiac arrest. Early deaths after CO exposure may be due to cardiac dysrhythmia. CO poisoning also exacerbates underlying cardiovascular disorders. In patients with undiagnosed underlying coronary artery disease, CO exposure may act as a stress test similar to anemia. Even in healthy volunteers, CO exposure has been found to result in non-specific ECG changes.¹⁴ Myocardial infarction has been reported in CO poisoning in the absence of underlying coronary artery disease.¹⁵ QT dispersion (QTd) of the ECG, which was defined as the difference between the greatest and the

least QT intervals in any of the 12 leads, is an indirect measure of heterogeneity of ventricular repolarization, which may contribute to ventricular arrhythmias. Gurkan et al documented that QT dispersion increased in patients with CO poisoning in a 16 intoxicated patients series. Increased QTd in the absence of QT interval prolongation may have a lowered arrhythmogenic potential of CO poisoning.¹⁶

CO poisoning also may result in rhabdomyolysis and acute renal failure, potentially as a direct toxic effect of CO on skeletal muscle. Cutaneous blister and non-cardiogenic pulmonary edema have been reported in patients with severe CO poisoning.

CO binds more tightly to fetal hemoglobin than adult one, making infants particularly vulnerable to the toxicity. Symptoms in pediatric patients are often non-specific, such as nausea and vomiting. Misdiagnosis of having viral infection is not uncommon in CO poisoning.¹⁷ CO exposure in pregnancy is an uncommon event, but failing to recognize maternal CO intoxication can have a detrimental effect on the fetus. CO crosses the placenta readily. Animal studies have shown that, with maternal CO exposure, fetal Hb-CO levels reach a higher peak and eliminate more slowly than maternal Hb-CO. Adverse outcomes, such as malformations, stillbirth and neurologic disability, are related to more severe maternal exposure.¹⁸ However, the level of maternal CO haemoglobin is a poor indicator of fetal toxicity. Despite maternal wellbeing, fetal morbidity or mortality can still occur. Postpartum hemorrhage is a serious and potentially catastrophic obstetric complication. There was no previously reported case of postpartum hemorrhage caused by acute CO poisoning. Patrick et al reported

a 41-year-old woman presented with postpartum hemorrhage and altered mental status with elevated serum Hb-CO level.¹⁹

In patients with acute poisoning, 30% or more may experience delayed onset of neuropsychiatric symptoms (DNS).²⁰ Symptoms include cognitive and personality changes, dementia, psychosis, parkinsonism, amnesia, depression, ataxia, hallucination, mutism, cortical blindness, and incontinence. Parkinsonism is also one of the features of delayed CO encephalopathy, and has been reported to occur in 9.5% of CO poisoning patients.²¹ There is also good evidence that apparently minor low level acute and chronic exposure causes varying degrees of neuropsychological impairment.²² In general, patients who present with a more symptomatic initial clinical picture are the most likely to develop persistent sequelae or DNS. DNS occurs most frequently in patients who present unconsciousness, older patients and patients with a prolonged exposure.

Chronic, low-level CO exposure, such as may be seen in a workplace, also has been linked to various symptoms, such as dizziness, headache, anorexia, apathy, insomnia, and perhaps personality change. Chronic exposure may accelerate atherosclerosis. Polycythemia and cardiomegaly have been reported in chronic exposure patients due to chronic hypoxia.²³

Diagnosis

A high index of suspicion is essential to make the diagnosis of occult CO poisoning. In prospective observational studies, patients presenting to the ED with winter flu-like syndrome may have Hb-CO levels ranging from 3% to 24%.²⁴ Histological factors that are important to elicit include the use of gas stoves for heat

and cohabitants with similar symptoms. In addition, patients whose symptoms are associated with particular environments (i.e, workplace), activities (i.e, boating), or use of appliances (i.e, stove, fireplace) may suffer from CO exposure.²⁵

Pulse oximetry may be falsely elevated in the setting of significant CO poisoning because Hb-CO is difficult to distinguish from oxyhemoglobin by wavelength. The pulse oximetry gap, defined as the difference between the measured pulse oximetry by finger probe and the true pulse oximetry obtained spectrophotometrically via co-oximeter, has been found to approximate the Hb-CO level. As the Hb-CO level elevates, the degree of pulse oximetry overestimation increases.^{26,27}

Serum Hb-CO level should be obtained from patients suspected of CO exposure. Endogenous production of CO occurs during heme catabolism by heme oxygenase but should not produce Hb-CO level greater than 1%. The Hb-CO level may increase to 3~4% in hemolytic anemia or severe sepsis.²⁸ Whereas the Hb-CO level of smokers may reach 10%. Low Hb-CO level often correlated with mild symptoms, such as dizziness, headache and nausea. The level greater than 60~70% may rapidly fatal. Several studies revealed a wide overlap between serum Hb-CO level and clinical symptoms underscores the difficulty in using level alone to determine the severity of exposure. So the clinical treatment strategies cannot solely based on the Hb-CO level.²⁹ The severity of clinical symptoms is related not only to the environmental CO concentration, but also to the duration of exposure. Sometimes, because Hb-CO level declines with time and with oxygen therapy, an initial Hb-CO level may not

reflect accurately the magnitude of a patient's exposure if it is drawn at a time that is remote from the exposure of after oxygen therapy has been instituted. In some settings, exhaled CO levels measured by using a Breathalyzer-type device can help to confirm the diagnosis, whether in the pre-hospital or ED settings.³⁰ Blood Hb-CO concentrations are described in reviews and textbooks, to exhibit a single exponential (i.e., linear on a semilogarithmic scale) decrease during the elimination process. However, a few reports have described a biphasic decrease in Hb-CO concentrations with a shorter half-life during the early phase of elimination after a short exposure to CO.³¹

Takeshi et al have shown in a preliminary report that blood Hb-CO shows a biphasic decrease after short-term (3–8 minutes) exposure, which was compatible with a two-compartment model and that the biphasic nature of the elimination curve was not altered by various factors that might affect the half-life of blood Hb-CO such as peak Hb-CO level, mode of exposure to CO, or concentration of oxygen used during the CO elimination phase.³² Routine blood gas analyzers without co-oximeters calculate rather than measure oxyhemoglobin saturation and do not recognize the contribution of abnormal hemoglobins. Arterial sampling is not necessary because prospective comparison of arterial and venous Hb-CO levels in poisoning patients has shown a high degree of correlation.³³

Other diagnostic testing in the CO poisoning patient depends on the clinical scenario and may include blood gas monitoring, electrolytes, cardiac markers, BUN and creatinine, CPK, chest radiograph, ECG, neuropsychometric testing, and neuroimaging studies. CXR may reveal non-cardiogenic pul-

monary edema. ECG may show non-specific dysrhythmia or myocardial injury change. Cardiac markers and CPK may be elevated. In different studies, performed on animal models, changes in glucose and lactate levels correlate well with the extent and outcome of CO poisoning, but such a correlation has not been shown in humans.³⁴ S100B, a structural protein of astroglial cells, has been shown to be a possible marker of CO poisoning in human. Miran Brvar et al demonstrate that acute carbon monoxide poisoning is associated with elevated S100B levels in a 42 rats model.³⁵

CT of the brain in patients with severe CO exposure may show signs of cerebral infarction secondary to hypoxia, ischemia and hypotension. A well reported finding is bilateral globus pallidus low-density lesions due to local low blood flow, metabolic acidosis and hypotension. Globus pallidus lesions may be delayed several days after initial presentation and may resolve with time. Concomitant white matter lesions also may be seen. MRI in patients with CO exposure may show diffuse, symmetric white matter lesions, predominantly in the periventricular areas. Single-photon CT, EEG and quantitative MRI have been studied as adjuvant diagnostic test in CO poisoning patients but generally are not widely available in the ED. SPECT in particular may correlate better than other neuroimaging findings with the development of delayed neurologic sequelae.³⁶

Treatment

Treatment of the CO poisoning patients should begin with oxygen supplement and aggressive supportive care, including airway management, blood pressure support and stabilization of car-

diovascular status. High-flow oxygen therapy should be administered immediately to treat hypoxia resulting from CO poisoning and to accelerate elimination of CO from the body. HBOT is not universally available and is not risk-free. HBOT may have a role in preventing adverse neurologic sequelae in CO poisoning. HBOT consists of the delivery of 100% oxygen within a pressured chamber resulting in a manifold increase in the dissolved oxygen in the body. HBOT at 3.0 ATA was found in a porcine study to provide enough dissolved oxygen to supply the body's need in the near-absence of hemoglobin.³⁷ The half-life of Hb-CO is 240 to 320 minutes at room air, 40 to 80 minutes at 100% oxygen, and about 20 minutes at 100% HBOT at 2.5 to 3.0 ATA.³⁸

HBOT has been shown in CO poisoning animals not only to reduce CO binding to hemoglobin, but also to reduce CO binding to other heme-containing proteins, such as cytochrome aa3. HBOT also alter neutrophil adhesion to endothelium, decrease free radical-mediated oxidative damage, reduce neurologic deficit and reduced overall mortality.³⁹

Several case series comment on the apparent efficacy of HBOT compared with NBO in reducing adverse neurologic outcome. One series of patient treated with HBOT after CO-induced cardiac arrest yield no survivors. Patients presenting with acidosis or hypoxia or patients receiving HBOT more than 6 hours after exposure tend to show increased morbidity and mortality. Even in this population, late HBOT may result in improved neurologic function.⁴⁰ Another series of 31 patients treated with HBOT and 79 treated with NBO showed a "poor outcome" in 6 of 31 (19.4%) HBOT patients and 35 of 79 (44.3%) NBO patients.⁴¹

Six prospective, randomized controlled trials compared HBOT with NBO for CO poisoning. 4 of these studies showed a benefit of HBOT and 2 of these didn't. The conclusions of these studies are conflicting and highlight the controversy of the utility of HBOT. Therefore, no widespread agreement exists regarding selection of patients for HBOT in the setting of CO poisoning, and a reliable method to identify patients at high risk for neurologic sequelae is not available. Broad criteria for recommending HBOT for CO poisoning have included any history of loss of consciousness, neurologic symptoms, cardiovascular dysfunction, metabolic acidosis, abnormalities on neuropsychometric testing, pregnancy with elevated Hb-CO (>15~20%) level, persistent symptoms despite NBO, and significant high Hb-CO level (>25%).^{42,43}

Although the efficacy of one HBOT treatment protocol over another has not been determined, one session of HBOT at 2.5 to 3.0 ATA is recommended initially, with further sessions considered if symptoms persist. Patients not meeting criteria for HBOT should receive 6 to 12 hours of 100% oxygen delivered by tight-fitting facemask.⁴⁴ Infants and children receive the same HBOT protocols as adult. Many authors recommend HBOT for pregnant patients due to the potential benefit to the fetus and mother despite the safety of HBOT in pregnancy have been questioned. A maternal Hb-CO level greater than 15% to 20%, evidence of fetal distress, and other criteria for HBOT in CO poisoning often are cited as indications for HBOT in CO poisoning pregnant patient.⁴⁵

The only absolute contraindication is untreated pneumothorax. Relative contraindications include claustrophobia, oto-

sclerosis or other scarring of middle ear, bowel obstruction, significant COPD particular with bullae formation, and requirement of care beyond what can be provided in a monoplace chamber. Most patients complain about painful barotraumas affecting the ears and sinuses. Less common risks include seizure, pulmonary edema and hemorrhage, oxygen toxicity, decompression sickness including pneumothorax and nitrogen emboli.^{44,46}

Normal physiologic processing of the small amount of CO naturally produced in the body is regulated by at least 2 mechanisms that decrease the affinity of CO for the heme molecule. One pathway involves the amino acid histidine, which, in proximity to the Hb-CO complex, causes dissociation through steric hindrance. The second pathway involves bisphosphoglycerate (BPG), an intermediate product in glycolysis and gluconeogenesis. When BPG binds to heme, the affinity for CO is decreased, shifting the oxygen-dissociation curve to the right. Glucagon contains a distal histidine and increases BPG levels by 2 enzymatic pathways. Treatment of CO poisoning with glucagon is a proposed novel therapeutic approach to rapidly decrease CO blood levels by increasing steric hindrance of the heme-CO association and by production of BPG, which decreases the affinity of heme for CO. However, it didn't reveal significant effect in glucagon group in one animal model.⁴⁷

Other treatments tried for CO poisoning in the past included hyperventilation, hypothermia, osmotherapy, fluid restriction and glucocorticoid, none of which have been found to be effective.

Disposition

Patients with mild exposure and mild symptoms can be treated in an ambulatory setting with high-flow oxygen. Nevertheless, patients with moderate to severe poisoning should be considered to be admitted.⁴⁸ Mild poisoning is defined by some authors as a Hb-CO level less than 25% and mild gastrointestinal symptoms and mild neurologic symptoms. Before discharging a patient from the ED, the source of CO poisoning may require investigation. Admission should be considered for patients with symptoms of moderate to severe CO poisoning, such as altered mental status or persistent neurologic or cardiovascular dysfunction. The accompanied comorbidities, such as cardiac ischemia, burns, or hemodynamic instability should receive specialized care. Besides, not all facilities have the capability to provide the specialized care in addition to HBOT, adequate transfer is also mandatory.

Summary

CO is an insidious poison with a lot of exposure sources. CO poisoning presents with variable signs and symptoms and may mimic some non-specific viral infection. The clinical syndromes are often overlooked because of a range of presentations, obscure symptoms, and a lack of awareness of the problem. Failed to diagnose CO poisoning may result in significant morbidity and mortality. In the ED, a high index of suspicion must be maintained for possible CO poisoning.

ED management of CO poisoning includes aggressive supportive care and oxygen supplement. HBOT accelerates the dissociation of CO from hemoglobin and may prevent DNS. Although the indications for HBOT still was controversial, the general indications which was

accepted by majority of authors include severe neurologic or cardiovascular signs, high serum Hb-CO level (non-pregnancy with Hb-CO level >25% or pregnant patients > 15 to 20%), metabolic acidosis, or persistent symptoms and signs despite 100% oxygen supplement. There was still no ideal HBOT protocol in nowadays. The emergency physicians have to confront and identify the insidious poison, and learn to make a suitable decision and disposition, even to transfer to hospitals with hyperbaric facilities.

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