Carbonmonoxide Poisoning and Hyperbaric Oxygen Treatment

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ABSTRACT

Carbon monoxide (CO) is a colorless, odorless and tasteless gas produced by the incomplete combustion of carbon-based compounds. Carbon monoxide poisoning is the leading cause of death due to poisoning worldwide. CO binds to the hemoglobin, as well as to other heme containing molecules such as myoglobin, cytochrome oxidase of the electron transport chain, platelets and causes hypoxia, perivascular injury and excitotoxicity.

The severity of clinical features in CO poisoning depends on the concentration of CO and the duration of CO exposure. Symptoms associated with mild intoxication such as malaise, nausea and vomiting are frequently misdiagnosed as flu-like symptoms. Headache, which is the most frequent symptom of CO poisoning, is commonly mistaken for migraine and suprasternal pain for acute coronary syndrome. Maintaining a high-index of suspicion for CO poisoning in the emergency department is crucial for early diagnosis and prompt management. The central nervous system is particularly sensitive to the toxic effects of CO poisoning. While petechial hemorrhage associated with severe CO poisoning may cause death in the acute phase, brain edema accounts for the majority of CO related deaths in the sub-acute phase. The most common clinical scenario affecting the central nervous system in CO poisoning, however, is delayed neurologic sequelae (DNS). CO poisoning may cause demyelination of the nerves or may lead to necrosis of the globus pallidus, susbstantia nigra, thalamus or putamen, namely the basal ganglia.

A detailed anamnesis should include the cause, estimated exposure duration and history of loss of consciousness, if any. Increased blood carboxyhemoglobin level only confirms the diagnosis and does not correlate with clinical severity. The cornerstone of treatment is oxygen and it should be started as early as during the transport of the patient to the hospital. Oxygen concentration should be between 12-15 L/min for adult patients and oxygen should be delivered through an oxygen mask, preferably by a non-re-breather face mask. The half-life of carboxyhemoglobin is almost 15 times shorter with hyperbaric oxygen (HBO) treatment at 3 atm abs. HBO treatment should preferably be administered in the acute phase, within 6 hours, but may also be delivered in the sub-acute phase. HBO therapy should be administered to patients with severe CO poisoning, who have a history of loss of consciousness, who present with abnormal neurologic sings and/or cardiologic dysfunction and who suffer severe acidosis.

As was concluded on the HFM-192 report on hyperbaric oxygen therapy (HBO) in military medical setting, CO poisoning requires (often) urgent, comprehensive (multidisciplinary) hyperbaric treatment to ensure a maximal efficiency.

1.0 INTRODUCTION

Carbon monoxide (CO) is a colorless, odorless and tasteless gas produced by the incomplete combustion of carbon-based compounds. While the heme catabolism is an endogenous source of CO, most frequent exogenous sources are:

a. *House fire*
b. *Heaters*
    i. *Water heater*
    ii. *Portable heater*
c. *Furnace*
d. *Chimney*
e. *Gas–powered electrical generators*
f. *Automobile, Boat exhaust*
g. *Cigarette smoke*

Several occupational groups such as fire fighters and miners tend to be most at risk for CO poisoning. Some age groups and particular conditions such as the elderly, unborn babies, infants, children and pregnant women are also more susceptible to poisoning (1, 2). Additionally, individuals with chronic heart disease or respiratory insufficiency and patients with decreased oxygen-carrying capacity (i.e., anemia, blood cancer) are more prone to suffer severe poisoning.

2.0 PATHOPHYSIOLOGY

There are 3 main pathways implicated with carbon monoxide poisoning:

i. *Hypoxia*
ii. *Perivascular injury*
iii. *Excitotoxicity*

2.1 Hypoxia

CO rapidly binds to hemoglobin and forms carboxyhemoglobin (CO-Hb). Compared with oxygen, CO binds to hemoglobin with a 200 fold higher affinity. As the level of CO-Hb increases the oxygen hemoglobin dissociation curve shifts to the left and increases its affinity for oxygen ultimately causing tissue hypoxia.

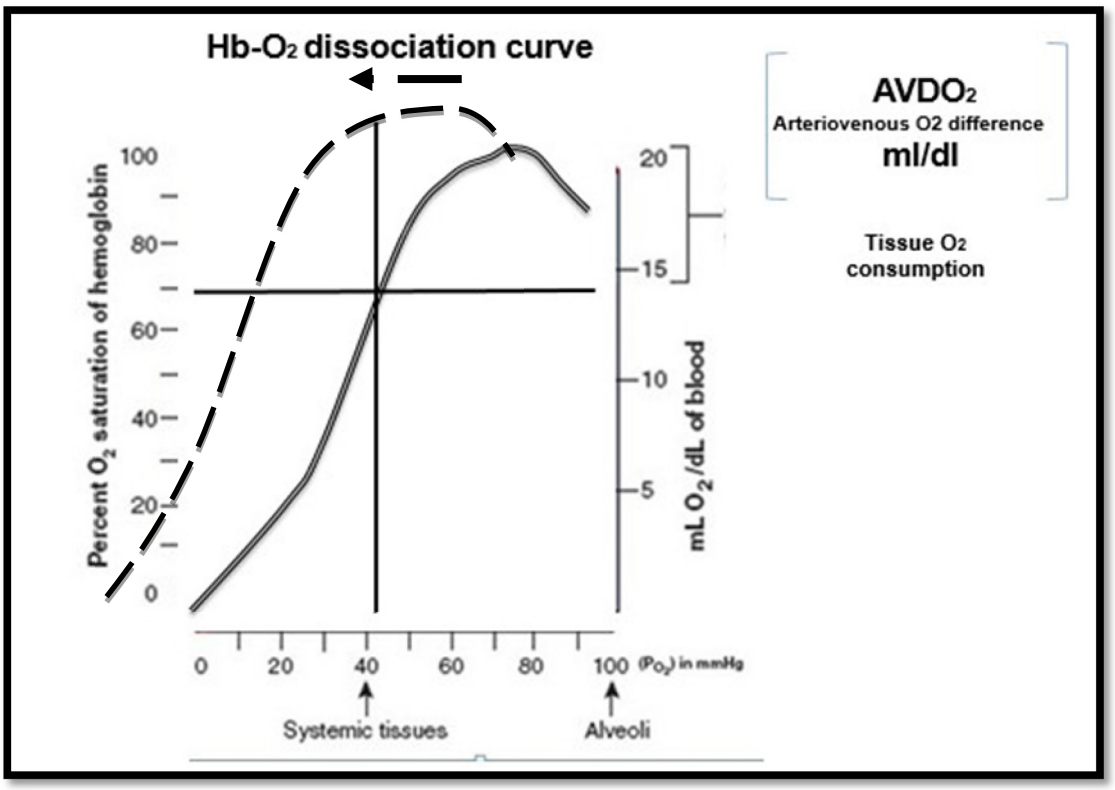


Figure 1: Hemoglobin oxygen dissociation curve. Note the leftward shift (dashed curve). While initial percent oxygen saturation at 40 mmHg was around 75%, it increased to around 90% following leftward shift due to the formation of CO-Hb.

CO causes hypoxia through several mechanisms:

2.1.1 Anemic hypoxia

Anemic hypoxia is the earliest and most frequent consequence of CO poisoning. Following the binding of CO, hemoglobins are almost nonfunctional and can neither bind nor release oxygen. Although this condition is termed as anemic hypoxia, it significantly differs in that in carbon monoxide poisoning, in contrast to anemia, the oxygen dissociation curve displays a leftward shift and therefore the affinity of hemoglobin for oxygen is increased, further limiting oxygen delivery to the tissues. As may be seen from figure 2, the affinity for oxygen is higher in patients with CO poisoning than in patients with anemia, although both causes a 50% decrease in oxygen concentration (Figure 2).

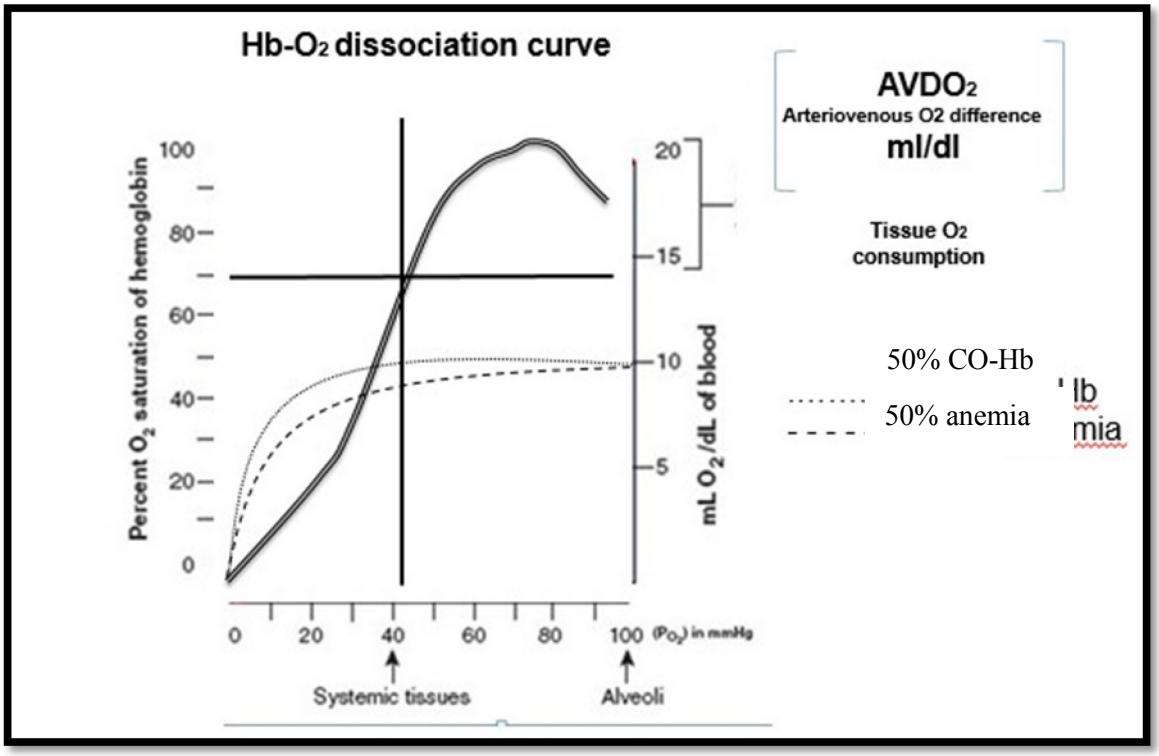


Figure 2: Oxygen affinity for hemoglobin in patients with anemia and CO poisoning, both causing a 50% decrease in oxygen concentration. Note the higher affinity of oxygen in patients with CO poisoning.

2.1.2 Histotoxic hypoxia

Carbon monoxide does not merely bind to hemoglobin but also to a critical enzyme functioning normally in the electron transport chain, i.e. cytochrome a,a3 enzyme. This binding incapacitates oxidative phosphorylation and thereby deprives body systems of their energy source.

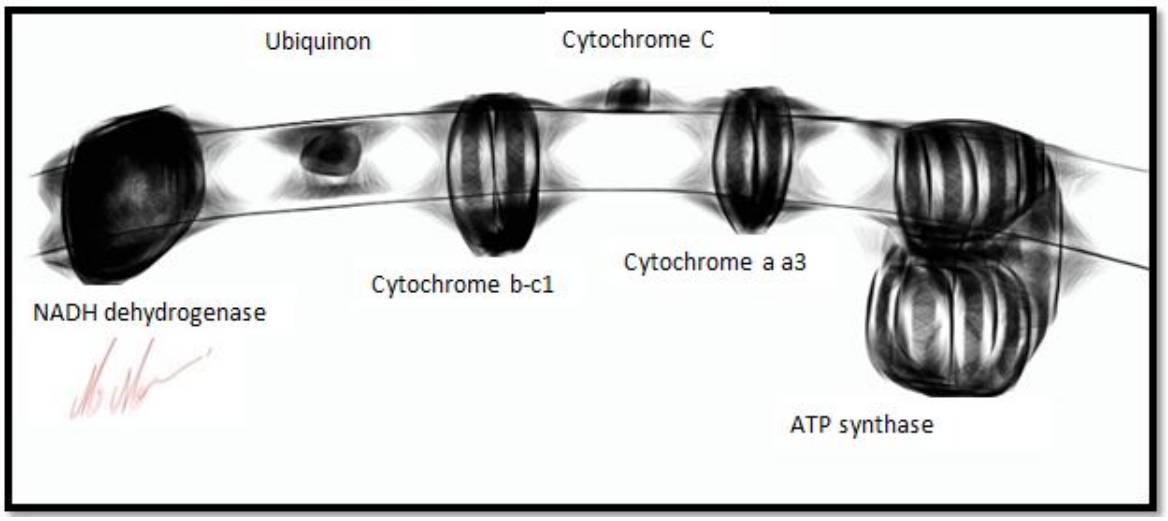


Figure 3: Electron transport chain and the cytochrome oxidase (Cytochrome a a3) enzyme.

2.1.3 Oligemic hypoxia

Occurs due to the binding of carbon monoxide to myoglobin. The resulting nonfunctioning compound is termed as carboxymyoglobin (Mb-CO). Mb-CO is, in great part, responsible for carbon monoxide induced cardiotoxicity. Severe poisoning with Mb-CO may cause ischemic myocardial damage and impair cardiac output thereby leading to oligemic hypoxia. Additionally arrhythmias are frequently observed in patients with Mb-CO induced cardiotoxicity.

2.2 Perivascular injury

CO binds to the heme proteins in platelets. This binding activates platelets, which release nitric oxide (NO) to plasma (3). NO reacts with neutrophil derived superoxide and form the peroxynitrite ($ONOO^-$) molecule, which is a potent nitrating and oxidizing agent. Peroxynitrite activates platelet adhesion molecules and causes platelet-neutrophil aggregation (4). Neutrophil interaction with platelets or with the endothelium is a strong stimulus for degranulation. While primary granules of neutrophils comprise several deleterious enzymes such as elastase, myeloperoxidase (MPO) and lipase, secondary or tertiary granules involve metalloproteinases and ß2 integrins. MPO release promotes endothelial oxidative stress and induces the synthesis of adhesion molecules for neutrophils, which lead to additional neutrophil aggregation (Figure 3). Neutrophil-derived proteases react with xanthine dehydrogenase (XDH) to form xanthine oxidase (XO), which is the major source of reactive oxygen species (ROS), particularly superoxide, in the sub-acute phase (Figure 4).

2.3 Excitotoxicity

CO poisoning causes neutrophil diapedesis and brain lipid peroxidation by activating neutrophils (5). Endogenous protective mechanisms against oxidative stress are impaired due to XO activation and lipid peroxidation occurs within the brain tissue. Lipid peroxidation products such as malondialdehyde interact with myelin basic protein (MBP) and change its three-dimensional structure and stimulate lymphatic immune reaction, which in turn induces microglia expression and activation, eventually starting an inflammatory process (Figure 3). Lipid peroxidation products cause injury to neural membranes and are believed to be responsible for neurologic symptoms and sequela.

Glutamate is an important neurotransmitter implicated with neural toxicity (6). Glutamate induces N-methyl D aspartate (NMDA) activation and Ca^{+2} influx into the cell cytoplasm. Ca^{+2} activates several deleterious enzymes such as protease, phospholipase and endonuclease, which together cause cellular membrane damage and DNA injury (Figure 5).

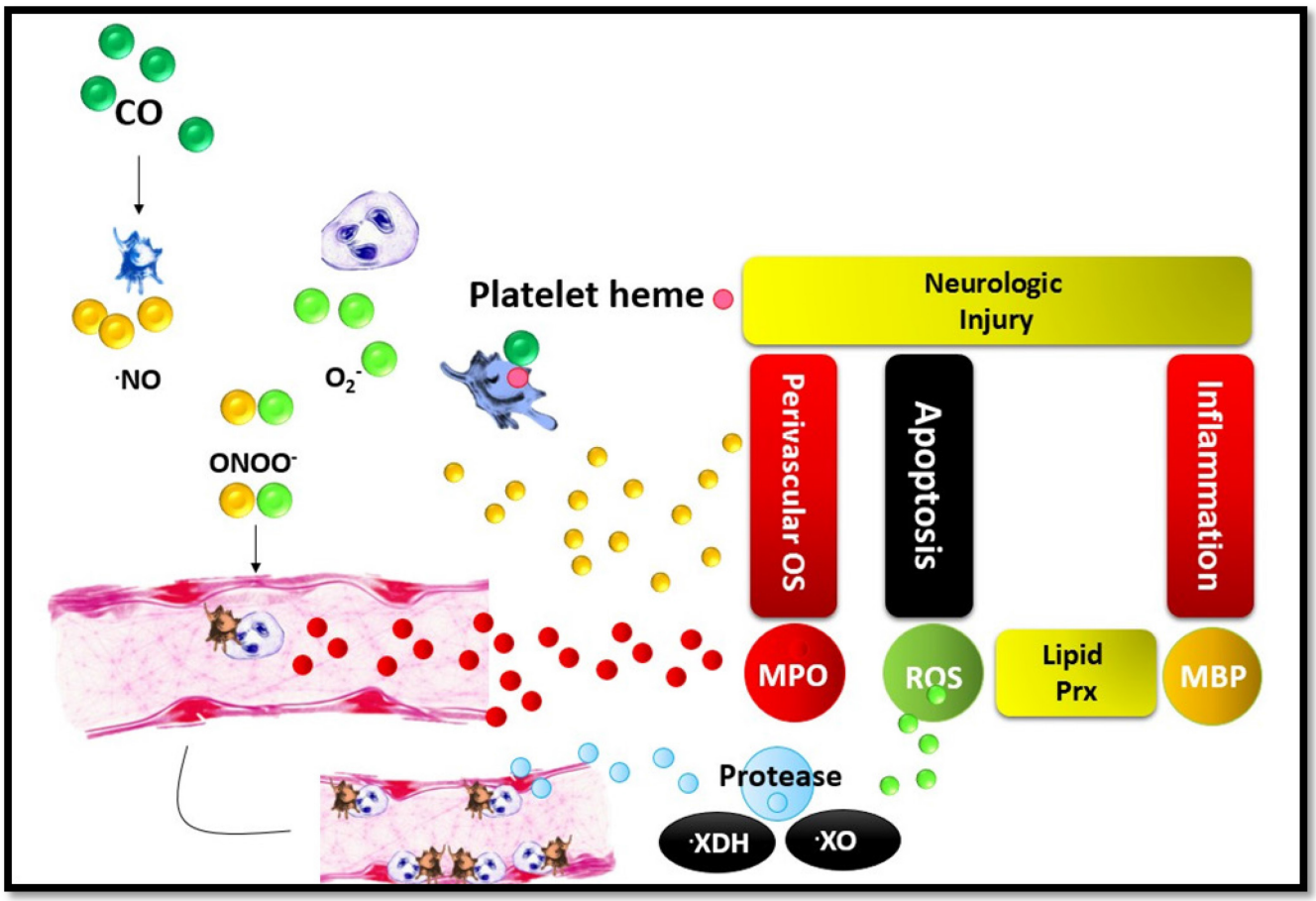


Figure 3: Pathway leading to CO induced perivascular oxidative stress and injury.

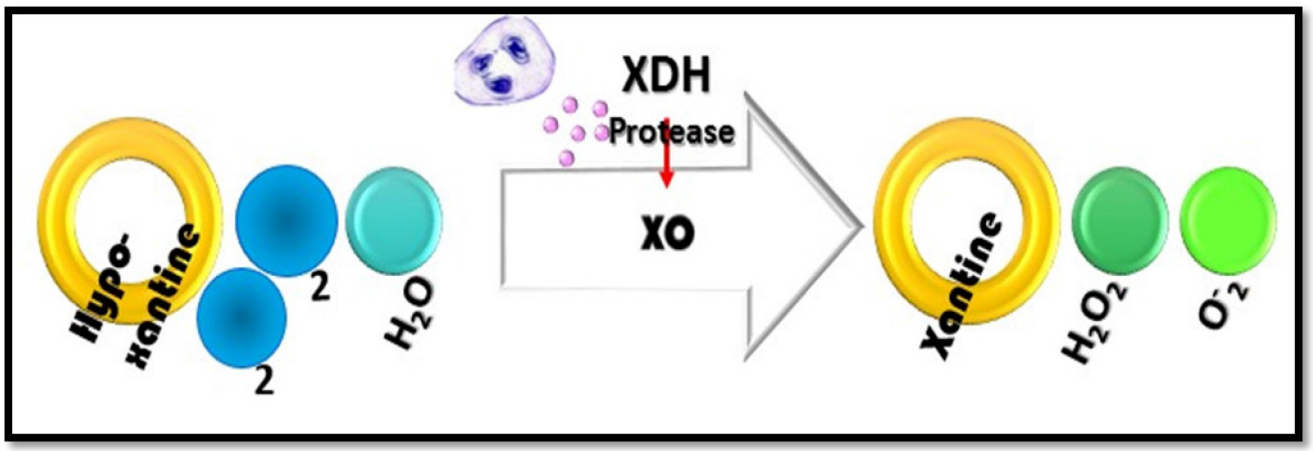


Figure 4: Neutrophil-derived proteases react with XDH to form XO, which is the major source of reactive oxygen species (ROS), particularly superoxide, in the sub-acute phase.

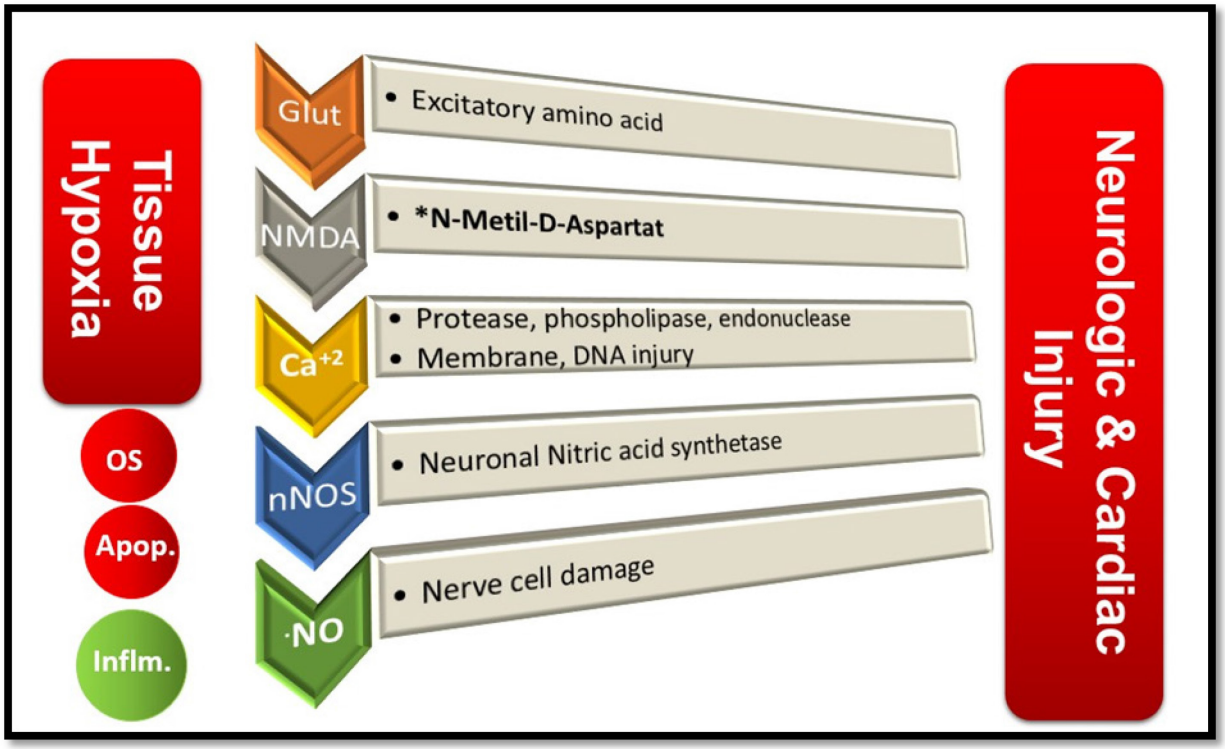


Figure 5: Pathway to neural and cardiac injury through excitotoxicity. OS (oxidative stress), Apop. (Apoptosis), İnflm. (inflammation), Glut (Glutathione), nNOS (neuronal nitric oxide synthase).

3.0 CLINICAL PRESENTATION

The severity of clinical features in CO poisoning is dependent on the concentration and duration of CO exposure. This relationship is demonstrated in Figure 6.

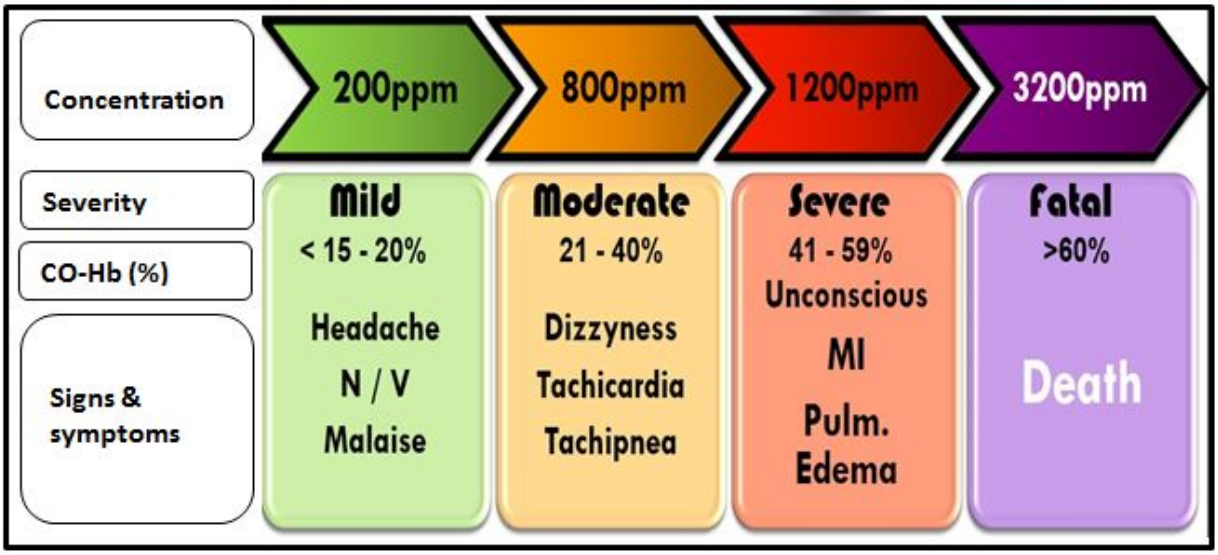


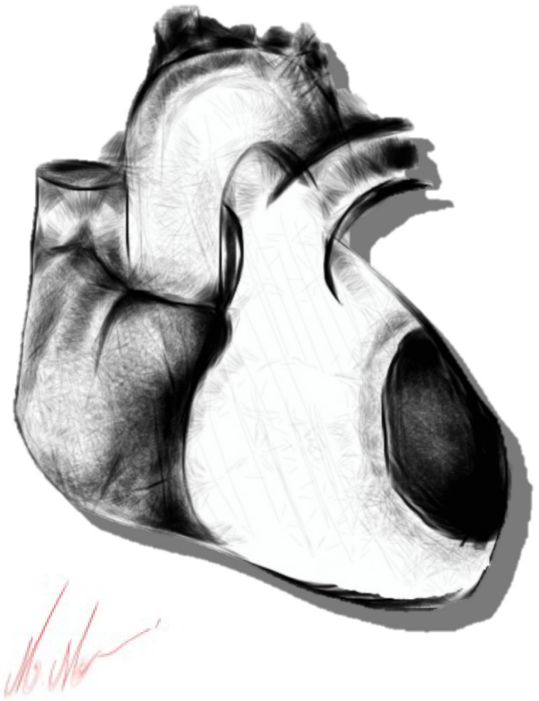
Figure 6: The relationship between CO concentration and the clinical picture.

CO-Hb level is not always consistent with clinical severity and may not be used to predict delayed neurological sequelae. It is rather used as a reliable tool to confirm the clinical diagnosis. Symptoms associated with mild intoxication such as malaise, nausea and vomiting are frequently misdiagnosed as flu like disorders (7) Headache, which is the most frequent symptom accompanying CO poisoning, similarly is commonly mistaken for migraine and suprasternal pain for acute coronary syndrome. Maintaining a high-index of suspicion for CO poisoning in the emergency department is critical for early diagnosis and prompt management (8). Another particular condition in CO poisoning is that since the arterial blood partial oxygen pressure remains within the normal range, the carotid and aortic chemoreceptors are not stimulated and therefore there is no or little stimulation of respiration.

Most common signs and symptoms associated with CO poisoning in the acute phase:

i. *Headache*
ii. *Dizziness*
iii. *Nausea/vomiting*
iv. *Lethargy*
v. *Asthenia*
vi. *Confusion*
vii. *Convulsion*
viii. *Disorientation*
ix. *Dyspnea*
x. *Irritability*
xi. *Chest pain*
xii. *Coma*

3.1 Cardiotoxicity



Cardiac and brain tissues are the most vulnerable tissues in CO poisoning (9). Signs and symptoms associated with cardiotoxicity or brain injury are usually observed in the severely poisoned patient. While cardiotoxicity is usually responsible for acute death, brain injury is mostly responsible for delayed signs and symptoms. Pathologies implicated with cardiotoxicity are tissue hypoxia causing cellular damage, CO binding to cytochrome-c oxidase leading to impaired cellular metabolism, ROS mediated lipid peroxidation and cellular death.

CO induced cardiotoxicity causes decreased myocardial function (pump failure) due to myocardial ischemia. Additionally, CO cardiotoxicity may lead to several cardiac rhythm abnormalities (10).

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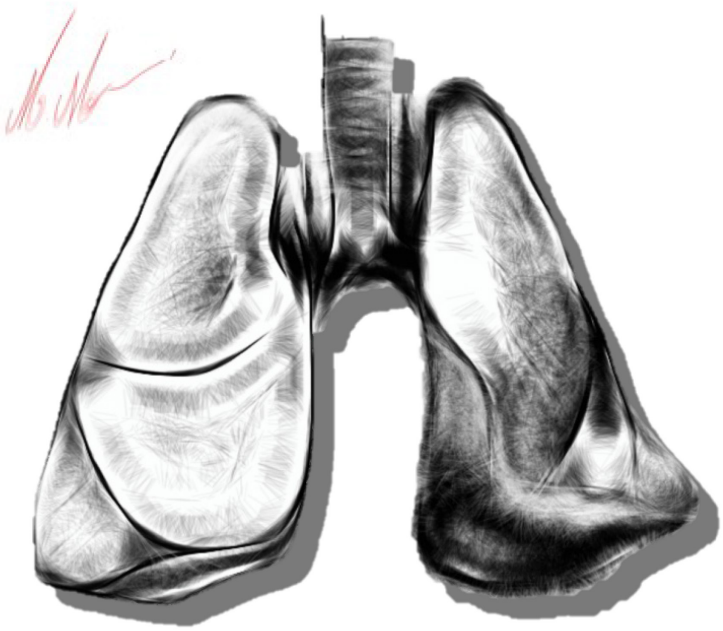
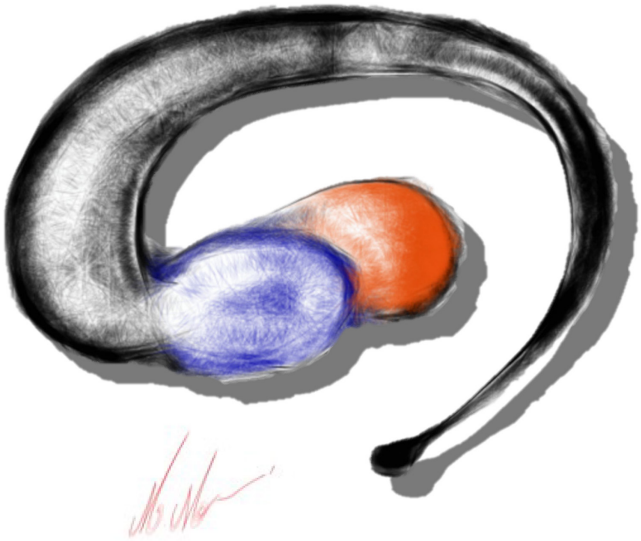


3.2 Pulmonary toxicity

The prevalence of pulmonary edema in CO poisoning is between 10-30%. The cause of pulmonary edema may be either direct toxicity on alveolar membrane or aspiration due to unconsciousness. Plain x-ray of the lungs should be obtained for each patient with a pre-diagnosis of CO poisoning.

3.3 Central nervous system injury



The central nervous system is particularly sensitive to the toxic effects of CO poisoning. While petechial hemorrhage associated with severe CO poisoning may cause death in the acute phase, brain edema accounts for the majority of CO related deaths in the sub-acute phase. The most common clinical scenario affecting the central nervous system in CO poisoning, however, is delayed neurologic sequelae (DNS). CO poisoning may cause demyelination of the nerves and may lead to necrosis of the globus pallidus, susbstantia nigra, thalamus or putamen, namely the basal ganglia (11).

The more severe the acute state the higher the risk of DNS development. Neurological deterioration may occur over a wide span of time, but commonly occurs within 2 to 40 days. The prevalence varies from 1 to 47%. Older people are more susceptible. While complete resolution usually occurs within 2 months in patients with mild CO poisoning, it may take up to one year in patients with severe poisoning (12).

Symptoms associated with DNS:

i.	*Parkinson-like syndromes*	*ii.*	*Anxiety*
iii.	*Ataxia*	*iv.*	*Depression*
v.	*Bradykinesia*	*vi.*	*Mood disorders*
vii.	*Choreoathethosis*	*viii.*	*Mania*
ix.	*Dyspraxia*	*x.*	*Dementia*
xi.	*Gait and motor disturbances*	*xii.*	*Cognitive impairment*
xiii.	*Intentional tremor*	*xiv.*	*Concentration deficit*
xv.	*Epilepsy*	*xvi.*	*Memory loss*
xvii.	*Myoclonus*	*xviii.*	*Personality changes*
xix.	*Vertigo*	*xx.*	*Psychosis*
xxi.	*EEG abnormalities*	*xxii.*	*Sensorineural hearing loss*
xxiii.	*Urinary incontinence*	*xxiv.*	*Cortical blindness*
xxv.	*Dysphasia*	*xxvi.*	*Peripheral neuropathies*
xxvii.	*Gilles de la Tourette syndrome*	*xxviii.*	*Insomnia*

4.0 DIAGNOSIS

As stated in the previous section, diagnosis of, particularly mild and moderate, carbon monoxide poisoning requires a high index of suspicion. CO-Hb examination, either through blood gas analysis or new generation CO-oximeter, is used to confirm or refute the clinical diagnosis. A detailed anamnesis should include the cause and history of poisoning, estimated exposure duration and history of loss of consciousness, if any. New generation CO-oximeters use non-invasive finger probes similar to that used in pulse oximetry and provide a fast and easy way of diagnosis. Yet their reliability has yet to be determined. Laboratory examination should preferably include the following:

i. *Whole blood : Slight leukocytosis (Hypovolemic)*

ii. *Urinalysis : Myoglobinuria (Rhabdomyolysis)*

iii. *Creatinine Phosphokinase ↑: Myoglobinuria (Rhabdomyolysis)*

iv. *Troponin, creatine kinase-MB : Cardiac pathology*

v. *Serum lactate level: Metabolic acidosis*

vi. *Alanine and aspartate aminotransferase: Multiple organ dysfunction*

vii. *Electroencephalogram: Neural pathology*

viii. *Electrocardiogram , echocardiogram : Cardiac pathology*

Computerized tomography in the acute phase may show cerebral edema and magnetic resonance imaging at the sub-acute phase shows ischemia of the basal ganglions. Fetal diagnosis requires further assessment involving Doppler USG, fetal heart rate monitoring and uterine contraction to evaluate cardiac sounds and activity.

5.0 MANAGEMENT

The management of CO poisoning starts at the scene by turning off the potential source of CO exposure. Next the environment should be promptly ventilated and thereafter professional support should be sought. Basic life support including cardiopulmonary resuscitation, if indicated, should follow these steps. The cornerstone of treatment is oxygen and oxygen treatment should start as early as during the transport of the patient to emergency department. Oxygen concentration should be between 12-15 L/min for adult patients and oxygen should be delivered through an oxygen mask, preferably by a non-re-breather face mask. The duration of oxygen therapy depends on the severity of poisoning but should preferably not be under 4 hours. While the half-life of oxygen is around 320 minutes in room air (21% oxygen), it is approximately 60 minutes while inspiring 100% oxygen from a non-rebreather mask and only about 23 minutes while inspiring 100% oxygen inside a hyperbaric chamber at 3 atm abs.

Indications for HBO treatment in CO poisoning as determined by The Undersea and Hyperbaric Medical Society are as follows:

i. *History of transient or prolonged unconsciousness*

ii. *Abnormal neurologic signs*

iii. *Cardiovascular dysfunction*

iv. *ST depression in ECG*

v. *Severe acidosis*

vi. *Patients who are >36 years of age*

vii. *CO-Hb percentage >25%*

HBO treatment should preferably be administered in the acute phase, within 6 hours, but may also be delivered in the sub-acute phase. Since studies have demonstrated that leukocyte-endothelium interaction is best prevented at 3 atm abs, treatment of CO poisoning in the acute phase may be set at this pressure. Studies have shown that a treatment protocol involving 3 sessions in the first 24 hours, with a minimum of 1 hour oxygen inspiration in each session, decreases the risk of DNS development (12). The total number of HBOT sessions varies depending on the severity of poisoning and on the clinical outcome.

The effects of HBOT on hypoxia associated with CO poisoning is well established. Experimental studies have shown that in addition to resolving tissue hypoxia, HBO treatment restores mitochondrial oxidative metabolism (13) prevents lipid peroxidation (14) and impedes leukocyte-endothelium adhesion (15). The majority of clinical studies with HBOT have demonstrated favorable outcomes as compared to treatment protocols without HBOT.

CO poisoning has been one of the first indication of European Undersea and Baromedical Society and Undersea and Hyperbaric Medical Society. As was concluded on the HFM-192 report on hyperbaric oxygen therapy (HBO) in military medical setting, CO poisoning requires (often) urgent, comprehensive (multidisciplinary) hyperbaric treatment to ensure a maximal efficiency.

6.0 REFERENCES

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