INTRODUCTION

Carbon monoxide (CO) poisoning is one of the most common fatal poisonings worldwide .It causes tissue hypoxia producing various neurological and cardiological complications. CO-induced hypoxic brain injury can occur at varying degrees leading to vegetative state, development of neuropsychiatric sequelae (NS) or death ***(Hanafy et al., 2013; Akdemir et al., 2014).***

It is estimated that the cost for the care of brain-damaged survivors runs in the billions of dollars each year. Therefore, identification of CO intoxicated patients who will require prolonged intensive care unit (ICU) stay or who may be suitable for intermediate care may help with the optimal use of limited resources. Acute physiology and chronic health evaluation (APACHE) II is used for objective assessment of patients in ICU to predict their chances of survival ***(Ibrahim et al., 2011).***

Poison Severity Score (PSS) has shown to be effective in determining the severity of cases of various intoxications ***(Akdur, 2010).***

Hyperbaric oxygen therapy (HBOT) remains the treatment of choice of CO poisoning. Although there are specific indications for HBOT, its necessity remains controversial. Its effectiveness in preventing neurologic damage

from CO is still questionable especially that there is still no completely reliable method of predicting patients that will have a poor outcome. In addition to the cost and transport risks if the primary facility lacks a chamber ***(Tomaszewski, 2015).***

For many years, computed tomographic (CT) brain imaging has been performed in CO poisoned patients. Although hypodense lesions in the globus pallidus, caudate and putamen lobes are characteristic CT findings of CO poisoning, they may not be apparent especially on early CT scan. Magnetic Resonance Imaging (MRI) brain appears to be superior than CT brain, however, it is usually not readily available on an emergency basis, image acquisition time is long and critical care supportive devices are often incompatible with MRI scanning machines. Therefore, neuro-imaging is not the definitive tool at this time for determining prognosis or need for HBOT ***(Nikkanen and Skolnik, 2011)***.

For all above reasons, objective biochemical markers demonstrating severity and outcome of CO- induced brain damage and helping in patient selection for HBOT is needed. S-100 protein B (S100B), Neuron specific enolase (NSE) and Glial fibrillary acidic protein (GFAP) have been used as biochemical markers of several neurological diseases and due to commercial availability; they have attained a growing attraction in clinical research.

AIM OF THE WORK

This work aims to:

- Assess the role of brain injury biomarkers: S100B, NSE and GFAP protein in early detection and evaluation of acute CO-induced brain injury and its consequences among acutely CO-intoxicated patients in Poison Control Center Ain Shams University Hospitals (PCC-ASUH).
- Evaluate and compare the accuracy of APACHE II versus PSS in predicting the mortality outcome of acute CO-intoxicated patients.
- Suggest criteria for selection of patients candidate for HBOT.

CARBON MONOXIDE GAS

Carbon monoxide (CO) is an odorless, colorless, tasteless, non-irritating gas results from incomplete combustion of organic compounds. It has a molecular weight of 28.01 dalton and a density of 0.968. The specific gravity of CO is almost identical to that of air so that it can disperse easily ***(Penney et al., 2010).***

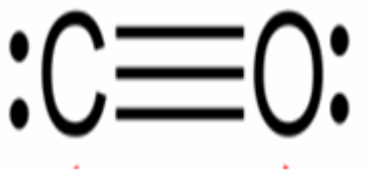

Figure (1): Chemical structure of carbon monoxide molecule ***(Kao and Nañagas, 2004)***.

The molecular structure of CO is formed of one carbon atom joined to one oxygen atom by a triple bond which is extremely stable ***(Kao and Nañagas, 2004)*** **(figure 1).**

Sources of carbon monoxide gas:

(a) Endogenous sources:

Endogenous production of CO occurs during heme catabolism by heme oxygenase enzyme producing carboxyhemoglobin (COHb) levels not more than 1% in the liver **(figure 2)**. The spleen and erythropoeitic system are also important catabolic generators of CO that can increase COHb up to 3%-4% as in hemolytic anemia ***(Gawlikowski et al., 2013)***. Also, severe sepsis has been shown to elevate

endogenous CO production possibly due to upregulation of expression of the heme oxygenase in various tissues by proinflammatory cytokines, endotoxin and oxidative stress ***(Kao and Nañagas, 2006; Loboda et al., 2008).***

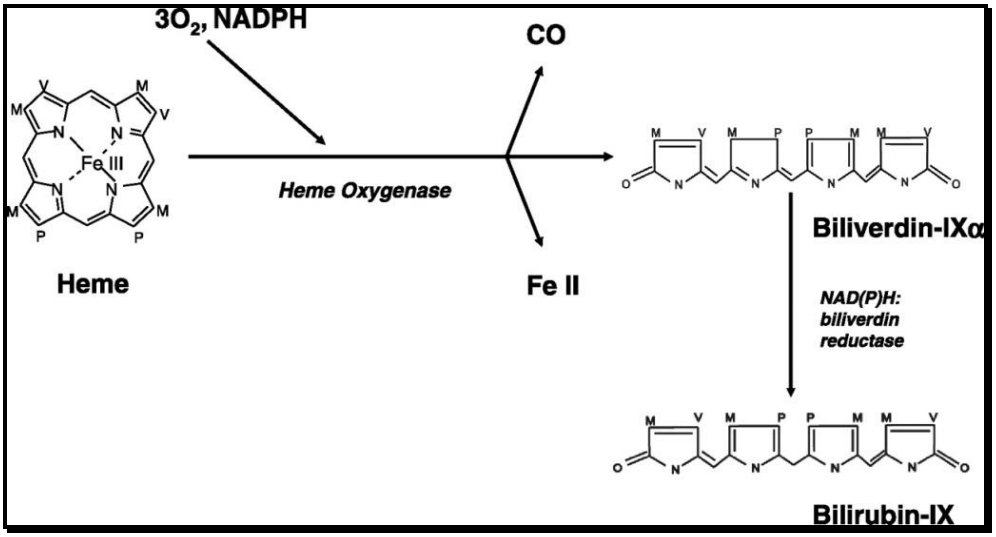

Figure (2): Heme degradation, endogenous CO production **(*Siow et al., 1999).***

Other hemoprotein degradation such as myoglobin, catalase and cytochrome oxidase contribute to the total amount of CO generated. In physiologic amounts, endogenous CO functions as a neurotransmitter ***(Piantadosi, 2008)***.

(b) Exogenous sources:

The combustion of any carbonaceous fuel, such as gasoline, natural gas, kerosene or oil in enclosed or semi-enclosed spaces can produce CO gas. Automobile exhaust is responsible for over half of unintentional deaths. This number may be decreasing as older vehicles without catalytic

converters, which reduce CO emissions, are being disposed ***(Satran et al., 2005).***

Smoke inhalation survivors are subjected to the deleterious effects of CO as well as hydrogen cyanide toxicity, another common fire intoxicant, resulting in higher morbidity and mortality than CO alone. However, up to 80% of the deaths due to smoke inhalation were attributable to CO poisoning ***(Mandel, 2012).***

Cigarette smoking represents a significant source of CO exposure in the general population. The amount of absorbed CO following the use of cigarette depends on certain factors as the frequency and the intensity of inhalation. The CO concentration is about 4.5 % in cigarette smoke and will result in COHb levels varying from 3 to 8 % ***(Lippa, 2005).***

Methylene chloride (dichloromethane) is an industrial solvent and a component of paint remover. Inhalation or ingestion of methylene chloride can cause CO poisoning as it is metabolized to CO in the liver ***(Olson and Smollin, 2010).***

Table (1): Sources of Carbon Monoxide ***(Kao and Nañagas, 2006)***.

Exogenous
Incomplete combustion of carbonaceous fossil fuel
House fires
Automobile exhaust
Propane-powered vehicles (forklifts, ice skating rink resurfacers)
Gas-powered furnaces, ovens, fireplaces
Heaters
Indoor grills
Camp stoves
Boat exhaust
Cigarette smoke
Methylene chloride
Endogenous
Normal heme catabolism by heme oxygenase
Increased in hemolytic anemia, sepsis

CARBON MONOXIDE POISONING

History of carbon monoxide poisoning:

Human beings have been poisoned by CO since they first discovered hydrocarbon fuels. Napoleon surgeon, Larrey, noticed soldiers with CO toxicity when billeted in huts heated by wood burning stoves ***(Walker and Hay, 1999)***.

The first scientific studies of the hypoxic effects of CO were described by Claude Bernard around 1846 ***(Mitchell et al., 2007)*.**

It has been almost 100 years since Drs. Douglas and Haldane first published their study detailing the hemoglobin dissociation curves for both oxygen and CO ***(Douglas et al., 1912).*** Those findings combined with a series of additional experiments involving the interplay among oxygen, CO, and hemoglobin (in vitro and in vivo) represented the first truly scientific explanation and evidence based treatment for CO poisoning (***Haldane, 1895, 1919, 1917).***

Pineas in 1924 described the classic CO induced bilateral lesions of the globus pallidus and the diffuse subcortical demyelination. He also correlated it with the akinesia after CO poisoning while Grinker in 1925 correlated them with the occurence of parkinsonism after CO poisoning. The effectiveness of HBOT in experimental CO poisoning in dogs and guinea pigs was demonstrated in 1942 ***(Jain, 2014)***.

Magnitude of carbon monoxide poisoning:

Carbon monoxide poisoning is common in modern society resulting in significant morbidity and is one of the leading causes of deaths due to poisoning. Exact statistics for CO poisoning are difficult to ascertain, mainly due to incomplete reporting and misdiagnosis ***(Lai et al., 2006).***

In Egypt:

In Cairo, PCC-ASUH is the first established and largest national Poison control center in Egypt receiving large number of poisoned patients yearly. In 2007, the PCC-ASUH received 412 cases of acute CO poisoning of which 24 patients were severe and necessitated ICU admission and 5 patients died. Also in 2008, 632 cases of acutely CO poisoned patients were presented to PCC-ASUH, 22 patients were severe and necessitated ICU admission and 7 patients died ***(PCC-ASUH records)***. More recent figures were presented by PCC-ASUH annual reports as shown in table 2.

In Menoufiya poisoning control center, a dramatic increase in CO poisoned patients was observed from 3.37% in 2001-2002 to 11.11% in 2003-2004 ***(Moustafa, 2004).***

The total reported poisoning cases in Benha University Hospital Poison Center from May 1st 2006 to May 1st 2007 were 54 out of total 646 cases and CO represented 96.4% of gas poisoning in the same year ***(Azab et al., 2008).***

Table (2): Magnitude of carbon monoxide poisoning as demonstrated in last three annual reports of PCC-ASUH

Annual reports	Total No	CO exposure	Total deaths	Deaths by CO	
2011 Annual report	21550	323	61	4	(6.6%)
2012 Annual report	19744	450	78	9	(11.5%)
2013 Annual report	20474	419	74	4	(5.4%)

In other countries:

Data from the American Association of Poison Control Centers Toxic Exposure Surveillance System in 2005 reported 16,449 exposures, with 66 deaths ***(Lai et al., 2006).***

The Center for Disease Control and Prevention (CDC) reports paint a much broader picture, that each year, more than 500 Americans die from unintentional CO poisoning, and more than 2,000 die from intentional CO poisoning. Regarding Morbidity, which is primarily related to occurrence of NS represents up to 40 % of CO poisoned victims ***(Perry et al., 2014).***

More recent figures stated that non-fire related CO poisoning is responsible for up to 50,000 emergency department (ED) visits and 1200 deaths per year, making it one

of the leading causes of poisoning death in the United States ***(Clardy et al., 2018).***

In Far East Asia such as Taiwan, CO Poisoning caused 526 ED visits with 55 deaths during 2009–2013. In Republic of China, 1.35 billion population in ED visits and 55 deaths during 2009–2013 ***(Zou et al., 2014)***.

In Europe as Italy, estimated incidence is about 6.000 cases per year resulting in more than 350 deaths/ year. In the United Kingdom; about 50 people annually die because of CO-poisoning ***(Pepe et al., 2011).***

Manner of carbon monoxide poisoning:

Acute exposure: Accidental poisoning occurs when fumes of the combustion of any carbonaceous fuel accumulate with conditions of restricted oxygen. Poisoning is considered to be a seasonal condition with the winter months being a particular risk, when people switch on their heating systems in enclosed or semi-enclosed spaces ***(Satran et al., 2005).*** Suicide has been a preferred method of suicide due to its high risk of success mostly motor vehicle ***(Kudo et al., 2014).***

Chronic exposure: Occupational exposure is a particular risk for occupations that release CO during combustion processes leading to chronic exposure of low levels of CO gas. Occupations with the highest risk include acetylene workers, boiler room workers, carbon black makers, coke oven workers,

customs workers, diesel engine operators, dockworkers, garage mechanics, metal oxide reducers, miners, organic chemical synthesizers, petroleum refinery workers, pulp and paper workers ***(Pulster and Hillman, 2015).***

ToxicoKinetics of carbon monoxide poisoning:

Carbon monoxide is rapidly absorbed across the alveolar endothelium. CO absorption through the lungs depends on duration of exposure, the concentration of CO in the environment and the alveolar ventilation rate ***(Baek et al., 1999).***

In blood, about 85% of absorbed CO combines with hemoglobin producing COHb while the remainder attaches to myoglobin and other blood proteins ***(Yildirim et al., 2015).***

The half-life of CO, while a patient is breathing room air, is approximately 300 minutes, while breathing high-flow oxygen via a non-rebreathing facemask is about 90 minutes and with 100 % HBOT is approximately 20 minutes ***(Peter and Scott, 2006).***

It is eliminated in the respiratory tract and less than 10% through oxidative metabolism to carbon dioxide ***(HPA, 2007).***

Pathophysiology of carbon monoxide poisoning:

1. Hemoglobin binding:

The most obvious deleterious effect of CO is binding to hemoglobin with affinity 230-270 times greater than oxygen, decreasing its oxygen carrying capacity. Therefore, despite adequate partial pressures of oxygen in blood (PO_2), there is decreased arterial oxygen content and decreased oxygen saturation (SO_2) as well. Further insult occurs because CO causes a leftward shift of the oxyhemoglobin dissociation curve, thus decreasing the offloading of oxygen from hemoglobin to tissue ***(Boztepe et al., 2014).***

2. Myoglobin binding:

Myoglobin, another heme protein acting as an oxygen reservoir passing oxygen from blood to mitochondria, binds CO with an affinity about 60 times greater than oxygen impairing its ability to utilize oxygen ***(Garrabou et al., 2011).***

3. Direct cellular toxicity :

Carbon monoxide interferes with cellular respiration by binding to mitochondrial cytochrome oxidase interfering with aerobic metabolism. The cells respond by switching to anaerobic metabolism causing anoxia, lactic acidosis and eventually cell death.Inactivation of cytochrome oxidase may be only an initial part of the inflammatory cascade that results

in ischemic reperfusion injury to the brain after CO poisoning ***(Tomaszewski, 2015).***

Depending on the dose of CO, activation of hypoxia-inducible factor 1α occurs by means of gene regulation resulting in variable degrees of neurologic and cardiac injury. Moreover, CO exposure is accompanied by activation of caspase-1, a protease implicated in delayed cell death ***(Weaver, 2009).***

Carbon monoxide also stimulates guanyl cyclase, which increases cyclic guanosine monophosphate resulting in cerebral vasodilation which has been associated with loss of consciousness in an animal model of CO poisoning ***(Alcorta, 2004).***

4. **Role of reactive oxygen species and nitric oxide (endothelial derived relaxation factor)**:

The production of reactive oxygen species (ROS) is a major component of CO poisoning that has been recently demonstrated. Studies have shown that CO is capable of inducing the formation of ROS primarily through interaction with the mitochondria. CO exposure has also been shown to directly induce the production of hydrogen peroxide and superoxide. One mechanism involves the conversion of xanthine dehydrogenase into xanthine oxidase causing the formation of peroxide. A second mechanism is through

inhibition of the activity of cytochrome C, leading to a buildup of superoxide within the mitochondrial matrix this leads to a net increase in production of ROS The effects of excess levels of ROS are widespread and include nucleic acid damage, lipid peroxidation, protein oxidation/nitrosylation, programmed cell death and immune system activation ***(Roderique et al., 2015).***

Carbon monoxide poisoning involves NO, a well-characterized gasotransmitter with wide-ranging effects at both the cellular and systemic level. CO displaces NO from heme containing proteins in the platelets and vascular endothelium. At the same time, CO has also been shown to be capable of activating certain forms of nitric oxide synthase, resulting in an overall increased production of NO. NO causes vasodilation that leads to profound hypotension. NO is also a powerful oxidizing agent, the combination of CO and NO can lead to the conversion of NO into peroxynitrite which is a much more potent free radical than NO itself and is resistant to degradation by enzymes like superoxide dismutase ***(Zhang and Ducsay, 2014).***

5. Role of ion channels:

Ion channels are major regulators of many vital processes including myocardial rate/rhythm, renal function, muscle contraction/relaxation, and nerve action potentials. CO interacts with these channels playing a role in the neuronal and cardiac dysfunction ***(Roderique et al., 2015).***