INTRODUCTION

Carbon monoxide is responsible for more than half of all fatal poisonings worldwide ***(Raub et al., 2000)*** and may be the leading cause of poisoning mortality in the United States. Carbon monoxide (CO) is an odorless, tasteless, colorless, nonirritating gas formed by hydrocarbon combustion. The atmospheric concentration of CO is generally below 0.001 percent, but it may be higher in urban areas or enclosed environments ***(Olsen, 2005)***. CO binds to hemoglobin with much greater affinity than oxygen (This is because carbon monoxide binds to red blood cells about 240 times more strongly than oxygen), forming carboxyhemoglobin COHb and resulting in impaired oxygen transport and utilization. Carbon monoxide can also precipitate an inflammatory cascade that results in CNS lipid peroxidation and delayed neurologic sequelae ***(Tomaszewski, 2006)***.

AIM OF THE WORK

The aim of this work is to:

- Assess a potential role of S100B protein versus other parameters (carboxyhemoglobin level [COHb], blood sugar level [B.S], and blood pH) as prognostic biochemical parameter of brain injury in carbon monoxide poisoning. This may help for better prediction of the outcome and selection of proper treatment.

- Assess a potential role of APACHE IV in predicting the severity and mortality in patients with acute carbon monoxide poisoning and to determine whether APACHE IV system for measurement of severity of illness is able to provide an accurate risk *parameter* of hospital death in patients with acute CO poisoning.

CARBON MONOXIDE POISONING

Epidemiology and sources:

Carbon monoxide poisoning accounts for an estimated 40,000 annual emergency department visits the United States. The Centers for Disease Control and Prevention reported that from 1968 to 1998, non–fire-related CO poisoning caused or contributed to 116,703 deaths. 70.6% of which were due to motor vehicle exhaust, and 29% of which were unintentional. An estimated 5000 to 6000 people die in the United States each year as a result of CO exposure. The rate of accidental deaths seems to have declined from 1513 per year in 1979 to approximately 500 to 600 per year in the 1990s, likely owing to improved motor vehicle emissions policies and the use of catalytic converters. Unintentional poisoning demonstrates both seasonal and regional variation, and it is most common during the winter months in cold climates as heating systems are being used and windows are closed ***(Mott et al., 2002).***

The Poisoning Control Center of Ain Shams University Hospitals CAIRO received 412 cases of acute carbon monoxide poisoning in 2007, 24 patients was sever and necessitate ICU admission and 5 patients died. Also in 2008 they received 632 cases of acute carbon monoxide poisoning, 22 patients was sever and necessitate ICU admission and 7 patients died.

Environmental CO exposure typically is less than 0.001%, or 10 parts per million (ppm) but may be higher in urban areas. Before catalytic converters, closed environment exposure to car exhaust could produce death within 30 minutes. Exposure to 70 ppm may lead to carboxyhemoglobin COHb levels of 10% at equilibrium (approximately 4 hours) ***(Abelsohn et al., 2002)***, and exposure to 350 ppm may lead to COHb levels of 40% at equilibrium ***(Raub and Benignus, 2002).*** After cooking with a gas stove, indoor air concentrations of CO may reach 100 ppm ***(Tomaszewski, 2006)***. Sources of CO could be exogenous or endogenous as shown in ***table (I)***.

(A) Exogenous sources:

Fatalities are reported with recreational boaters swimming underneath the swim platform near the boat exhaust and campers using gas-powered stoves in outdoor tents. Also winter snow may obstruct vehicular exhaust systems resulting in CO poisoning ***(Fisher, 2001)***. Another source is Methylene chloride (dichloromethane) which is an industrial solvent and a component of paint remover. Inhaled or ingested methylene chloride is metabolized to CO by the liver, causing CO toxicity in the absence of ambient CO. The US Occupational Safety and Health Administration lowered the workplace exposure limit for methylene chloride from 500 to 25 parts per million (ppm) based on concerns of the chronic effects of carboxyhemoglobinemia and permissible exposure limit for CO exposure in workers is 50 ppm averaged over an 8-hour workday ***(Amsel et al., 2001).*** In

addition to the previous sources, CO poisoning has been reported in children riding in the back of pickup trucks, recreational boaters, and persons in an ice skating rink using propane-powered resurfacing machines ***(Pelham et al., 2002).*** Although most accidental deaths are due to house fires and automobile exhaust, consumer products contribute to approximately 180 to 200 annual deaths. The United State Consumer Product Safety Commission summarized the 180 unintentional consumer product related CO deaths in 1998 as being associated with indoor heating systems (71%), stoves and other appliances (10%), charcoal grills (9%), camp stoves (6%), and water heaters (4%) ***(Thomassen et al., 2004).***

(B) Endogenous sources:

Severe sepsis has been shown to elevate endogenous CO production ***(Zegdi et al., 2002).*** Endogenous production of CO occurs during heme catabolism by heme oxygenase but should not produce COHb levels greater than 1%; however, in hemolytic anemia, COHb may increase to 3% to 4% ***(Naik et al., 2003).***

Table (I): Show sources of carbon monoxide

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 (solvent found primarily in paint remover) endogenously converted to carbon monoxide after exposure
Endogenous
Normal heme catabolism by heme oxygenase
Increased in hemolytic anemia, sepsis

(Louise and Kristine, 2004)

Kinetics:

Carbon monoxide (CO) is rapidly absorbed across the pulmonary endothelium. Elimination depends upon the degree of oxygenation and, to a lesser extent, minute ventilation. Carbon monoxide (CO) is removed almost exclusively via the pulmonary circulation through competitive binding of hemoglobin by oxygen ***(Lindell et al., 2003).*** 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 percent hyperbaric oxygen is approximately 30 minutes ***(Peter and Scott, 2006).***

Pathophysiology:

Since not all the signs and symptoms of CO poisoning can be explained only by the formation of carboxyhemoglobin.

So CO toxicity is estimated to be the result of a combination of tissue hypoxia and direct CO-mediated damage at a cellular level. Mitochondria, specially the electron transport chain, seem to be the target for CO at a subcellular level. However, the direct effect of CO in individual complexes of the human mitochondrial respiratory chain has not been completely elucidated ***(Alonso et al., 2003).***

1) Hemoglobin binding

Carbon monoxide (CO) diffuses rapidly across the pulmonary capillary membrane and binds to the iron moiety of heme and other porphyrins with approximately 240 times the affinity of oxygen and causes a leftward shift in the oxygen-hemoglobin dissociation curve, decreasing oxygen delivery to the tissues and resulting in tissue hypoxia. The degree of carboxyhemoglobinemia is a function of the relative amounts of CO and oxygen in the environment, duration of exposure and minute ventilation ***(Louise and Kristine, 2004).***

Non-smokers may have up to 3 percent carboxyhemoglobin at baseline and smokers may have levels of 10 to 15 percent. Severe chronic obstructive pulmonary disease can cause a modest but significant elevation in carboxyhemoglobin levels. The mechanism of this finding is unclear ***(Yasuda et al., 2005).***

2) Direct cellular toxicity

Carbon monoxide poisoning is much more complex than initially presumed and has mechanisms of toxicity beyond the formation of COHb. Several studies have corroborated the

findings of morbidity and mortality due to CO poisoning independent of hypoxia or COHb formation ***(Mendelman et al., 2002).*** Approximately 10 to 15 percent of CO is extravascular and bound to molecules such as myoglobin, cytochromes, and NADPH reductase, resulting in impairment of oxidative phosphorylation at the mitochondrial level. The half-life of CO bound to these molecules is longer than that of COHb a finding which may explain why COHb levels do not correlate with the severity of clinical effects. Cellular energy metabolism is inhibited even after normalization of COHb levels which may explain prolonged clinical effects after COHb levels decrease. Binding to myoglobin may reduce myocardial oxygenation leading to arrhythmias and cardiac dysfunction as well as direct skeletal muscle toxicity and rhabdomyolysis ***(Richardson et al., 2002).***

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. It also inactivates cytochrome oxidase enzyme leading to decrease peripheral oxygen utilization by a mechanism similar to but less sever than cyanide. CO and cyanide poisoning can occur simultaneously in patients following smoke inhalation, and their combined effects on oxygen transport and utilization appear to be synergistic ***(Alcorta, 2004).***

3) Nitric oxide

Many studies suggest that the syncope due to CO poisoning may be related to NO-mediated cerebral vessel relaxation and low blood flow. Nitric oxide also is a peripheral vasodilator and may result in systemic hypotension which may contribute to the severity of cerebral lesions ***(Landry and Oliver, 2001).*** Following severe intoxication, central nervous system (CNS) pathology was detected including white matter demyelination with edema and focal areas of necrosis of the globus pallidus and tissues with relatively low oxygen demand, suggesting elements of hypoperfusion and hypoxia. Recent studies have demonstrated release of nitric oxide (NO) free radical from platelet and vascular endothelium following exposure to CO. The release of nitric oxide forms the free radical peroxynitrite which inactivate mitochondrial enzymes and damage the cerebral vascular endothelium. Nitric oxide may increase the adherence of neutrophils to the endothelium, by potentiating the function of neutrophil adhesion molecules such as B2-integrin. Neutrophil adherence to the microvasculature seems to activate xanthine oxidase with oxidative radical formation, oxidative damage, and ultimately brain lipid peroxidation, which is thought to be responsible for delayed neuropsychiatric sequelae (DNS) ***(Thom and Zhang, 2004).***

Malonylaldehyde (a reactive product of lipid peroxidation) causes adduct formation with myelin basic protein (MBP) which constitutes 30% of myelin protein of

CNS, resulting in altered antibody recognition of MBP leading to Immunohistochemical degradation of MBP over days, along with influx of macrophages and CD-4 lymphocytes. Lymphocytes subsequently exhibit an auto-reactive proliferative response to MBP, and there is a significant increase in the number of activated microglia in brain. A mechanism which may explain the delayed CO- mediated neuropathology. ***(Thom et al., 2004)***. Recent studies have demonstrated release of nitric oxide (NO) free radical from platelet and vascular endothelium following exposure to CO due to mitochondrial dysfunction after binding to cytochrome oxidase with resultant oxidative stress ***(Guy and Michael, 2007). Figure (1)*** show summary of pathophysiology of carbon monoxide poisoning.

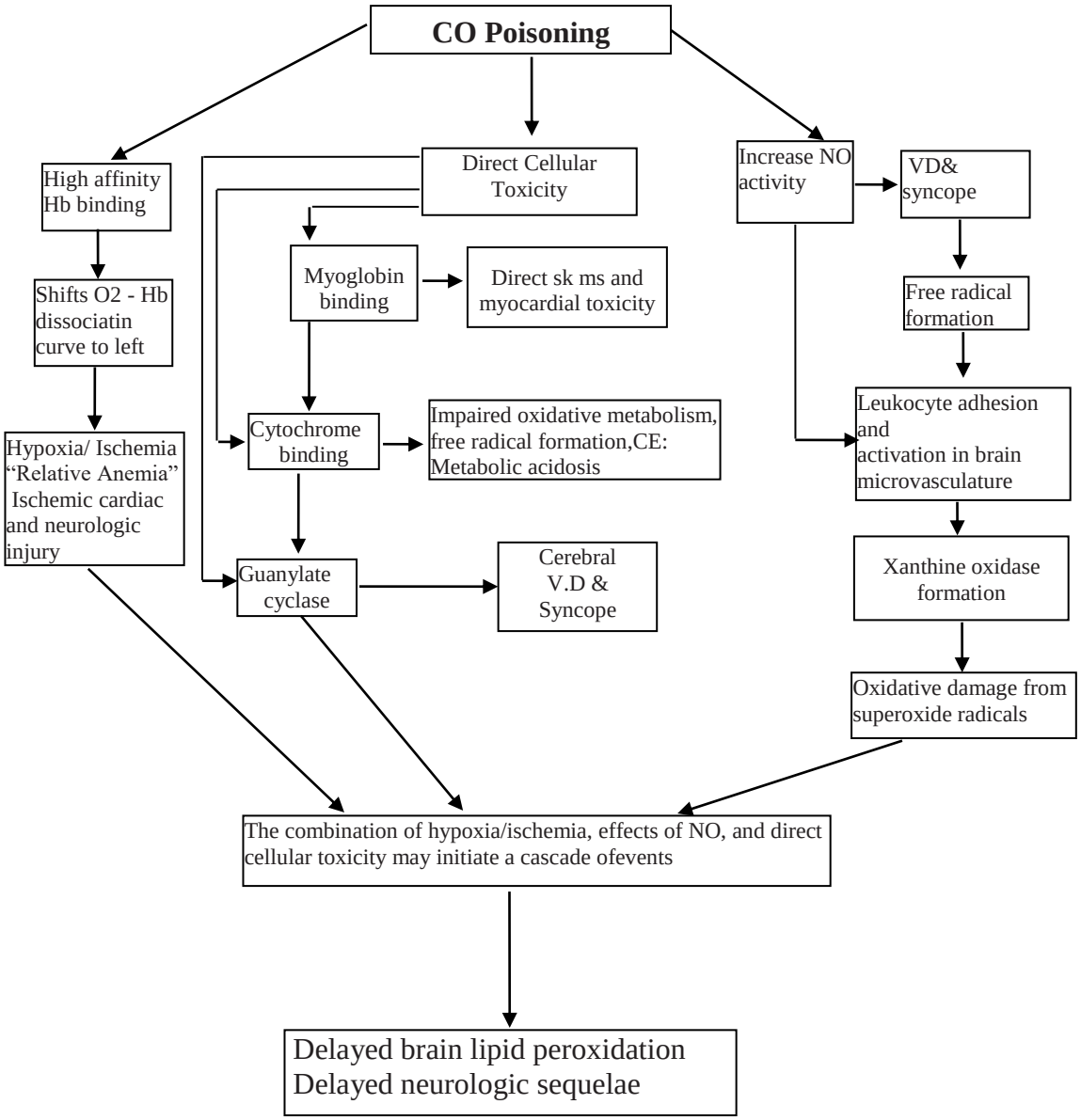

Figure (1): Pathophysiology of carbon monoxide poisoning
(Louis and Kristine, 2004)

CLINICAL PRESENTATION:

The clinical findings of carbon monoxide (CO) poisoning are highly variable and largely nonspecific**.** These are shown in ***table (II)*****.** Mildly or moderately CO-intoxicated patients often present with constitutional symptoms, including headache (the most common presenting symptom), malaise, nausea, vomiting and dizziness, and may be misdiagnosed with acute viral syndromes. In addition to current symptoms, the clinician should specifically inquire (of the patient and/or witnesses) about loss of consciousness. More significant exposures result in hypotension, dysrhythmia, ischemia, infarction, and cardiac arrest in extreme cases. Early deaths after CO exposure may be due to cardiac dysrhythmias ***(Kao and Nanagas, 2004)***.

Severe CO toxicity can produce more severe neurologic symptoms such as seizures, syncope, or coma, and also lead to delayed symptoms or long-term adverse effects of carbon monoxide poisoning which can occur days or weeks after poisoning. The delayed symptoms or effects may include memory loss, changes in personality, disorientation, impaired reasoning ability, and behavioral or learning difficulties ***(Olsen, 2005).***

Table (II): Clinical signs and symptoms associated with carbon monoxide poisoning

Severity Signs and symptoms:	
Mild	
Headache	
Nausea	Vomiting
Dizziness	Blurred vision
Moderate	
Confusion	Syncope
Weakness	Chest pain
Dyspnea	Tachycardia
Tachypnea	Rhabdomyolysis
Severe	
Palpitations	Dysrhythmias
Hypotension	Myocardial ischemia
Cardiac arrest	Respiratory arrest
Noncardiogenic Pulmonary edema	
Seizures	Coma

(Tomaszewski, 2006)

Hypotension may result from myocardial injury secondary to ischemia, direct myocardial depressant activity from myoglobin binding or peripheral vasodilation, and may persist even after neurologic and metabolic symptoms have resolved ***(Yanir et al., 2002).*** Acute myocardial injury is common among CO-poisoned patients and is associated with increased long-term mortality (LTM). A retrospective study done by ***Kao and Nanagas (2004)*** revealed that among 230 patients with moderate to sever CO poisoning, one third of

them experienced myocardial ischemia evidenced by ECG changes and cardiac enzyme. By follow up of those patients, it was found that mortality was twice more in those patients with myocardial injury than those without myocardial injury ***(Henry et al., 2006).***

Delayed Neuropsychiatric Syndrome:

Delayed neuropsychiatric syndrome occurs most frequently in patients who present comatose, older patients and patients with a prolonged exposure**.** Neuropsychometric testing abnormalities have been associated with decreased level of consciousness at presentation, particularly if the duration of unconsciousness exceeds 5 minutes ***(Parkinson et al., 2002)***. In up to 40 % percent of patients with significant CO exposure, delayed neuropsychiatric sequelae (DNS) can arise 1-4 weeks after apparent recovery characterized by variable degrees of cognitive deficits, memory loss, personality changes, movement disorders, and focal neurologic deficits, DNS usually occur within 20 days of CO poisoning, and deficits may persist for a year or longer ***(Kwon and Chung, 2004).*** The development of DNS correlates poorly with COHb levels although the majority of cases are associated with loss of consciousness during acute intoxication .The incidence and severity of DNS have become increasingly important clinical end points in studies of treatment for CO poisoning ***(Hampson and Little, 2005).***

DIAGNOSIS:

The diagnosis of CO poisoning is based upon a compatible history and physical examination in conjunction with an elevated carboxyhemoglobin level measured by CO-oximetry of a blood gas sample**.** Pulse oximetry cannot screen for CO exposure, as it does not differentiate carboxyhemoglobin COHb from oxyhemoglobin and its reading represents an inexact summation of oxyhemoglobin and carboxyhemoglobin. In cases of carbon monoxide poisoning or in chronic heavy smokers, a falsely reassuring pulse oximetry reading may mask life-threatening arterial desaturation ***(Lee et al., 2000).***

Arterial sampling is not necessary because prospective comparison of arterial and venous COHb levels in poisoned patients has shown a high degree of correlation. The accuracy was maintained at COHb levels exceeding 60% ***(Lopez et al., 2001).*** Carboxyhemoglobin COHb levels should be measured via a CO-oximeter, which measures total hemoglobin concentration, oxyhemoglobin, and deoxyhemoglobin and concentrations of abnormal hemoglobins, such as COHb and methemoglobin by differentiating wavelength absorbance values ***(Widdop, 2002).*** Blood partial pressure of O2 (PO2) measurements tend to be normal because PO2 reflects O2 dissolved in blood, and CO does not affect this process. In contrast, hemoglobin-bound O2 (which normally comprises 98 percent of arterial O2 content) is profoundly reduced in the presence of COHb ***(Ilene and Manaker, 2006).*** Once the diagnosis of CO intoxication is confirmed, it is recommend to obtain an electrocardiogram