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HYPOXIC MECHANISMS IN THE CARBON MONOXIDE -INDUCED INJURY TO CARDIAC & OTHER TISSUES IN ACUTE POISONING : A NOTE ON THE ROLE

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ABSTRACT

In this paper, the role played by hypoxic mechanisms in Carbon Monoxide (CO) induced injury to cardiac and other tissues in acute poisoning has been discussed. Acute poisoning is mainly due to tissue hypoxia. Signs and symptoms of acute CO poisoning can be present at Carboxyhaemoglobin (COHb) levels ranging between 3 to 24%. Exposures resulting in COHb levels greater than 50% are frequently fatal. Formation of COHb is the principal hypoxic mechanism that decreases oxygen carrying capacity of the blood and also impairs the release of oxygen from Hb for its utilization in tissues. Through hypoxic mechanisms, CO may affect any tissue, particularly tissues with high oxygen utilization requirements like brain, liver, kidney and heart.

Keywords: Carbon Monoxide, Hypoxic mechanisms, Poisoning, Carboxyhaemoglobin, Toxicity.

INTRODUCTION

The toxic gas, Carbon Monoxide (CO), which is colorless and odorless, is produced as a byproduct of incomplete combustion of carbon-based fuels and substances. Human beings are exposed to carbon monoxide usually through inhalation. Information on its absorption or toxicity resulting from oral or dermal exposures is not known to common public. Carbon monoxide affects cell metabolism through both hypoxic and non-hypoxic mechanisms. The effects produced by both mechanisms, are largely due to the ability of carbon monoxide to bind to heme and alter the metabolism and/or function of heme proteins.

Carbon monoxide exposure at levels producing hypoxia through hypoxic mechanisms is expected to affect any tissue, particularly tissues with high oxygen (O_2) utilization requirements

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like heart, liver, kidney, and brain. The brain and the heart, are the organs most susceptible to CO toxicity, because of their high metabolic rates. The degree of injury directly associates with the duration and the severity of the exposure. Formation of Carboxyhemoglobin (COHb) is the principal hypoxic mechanism. This formation decreases the O_2 carrying capacity of the blood and also impairs the release of O_2 from Hb for its utilization in tissues. Carbon monoxide decreases O_2 storage in muscle cells through similar mechanisms by binding to myoglobin and displacing O_2 from it. Blood COHb levels have not been shown to be a reliable predictor of severity of acute toxicity, although binding of carbon monoxide to Hb is the primary component of the hypoxic mode of action of carbon monoxide. This can be due to the time elapsed between the removal of the subject from exposure to CO to COHb measurement; and can also be due to the effects of emergency medical treatment with oxygen.

Acute carbon monoxide poisoning is mainly due to tissue hypoxia. In general, signs and symptoms of acute carbon monoxide poisoning can be present at COHb levels ranging from 3 to 24%. [1] More severe signs of carbon monoxide poisoning are poorly correlated with blood COHb levels, with loss of consciousness occurring at a mean level of 24.3% (range: 2–70%);and fatality at a mean level of 32.1% (range: 3.0–60%)[1]. Exposures resulting in COHb levels >50% are frequently fatal.[2] Persistent neurologic sequelae, delayed in onset, can also occur. Although severe carbon monoxide toxicity primarily derive from hypoxia, the relationship between blood COHb levels and signs indicative of life-threatening toxicity is highly uncertain (eg., convulsions, coma, and cardiopulmonary depression).

In subjects with compromised cardiovascular function (e.g., coronary artery disease), adverse cardiovascular effects are associated with the carbon monoxide exposures that result in blood COHb levels ≥2.4%, with effects occurring at the lowest levels. And blood COHb levels between 2.4 and 5.9% exacerbates the underlying cardiovascular disease, including enhancing myocardial ischemia and increasing cardiac arrhythmias. Continuous exposure of healthy subjects, to carbon monoxide resulting in blood COHb levels of 2.4 and 5.1% produced many P-wave deviations under resting conditions.[3] Under conditions of cardiac ischemia, tissue hypoxia secondary to the elevated COHb levels is thought to be a contributing factor to the cardiac effects in patients with coronary artery disease. However, direct cellular effects of carbon monoxide on cardiac muscle are also important. These include modulation of coronary arteriole calcium-activated potassium channels. They are inhibited under hypoxic/ischemic conditions.[4] CO also binds with myoglobin which is another heme protein. It has an affinity approximately 60 times greater than that of oxygen. This binding is enhanced under hypoxic conditions. This binding may partially explain the myocardial impairment that occurs with low-level exposures in patients with ischemic heart disease.[5]

High levels of carbon monoxide after acute exposure produce symptoms of central nervous system toxicity. Though mechanisms of acute and delayed adverse nervous system effects are not established conclusively, tissue hypoxia secondary to COHb formation may be a contributing factor, particularly in association with high levels of blood COHb (>60%)[3]. The hypoxic state also triggers release of nitric acid from platelets and endothelial cells, leading to the formation of the free radical peroxynitrate. This causes mitochondrial dysfunction with a marked decrease in cytochrome oxidase, capillary leakage and apoptotic cell death. Direct

cellular effects of carbon monoxide like ATP depletion, excitotoxicity, oxidative stress and postischemic reperfusion injury also contribute to neurotoxicity. Cerebrovascular vasodilation and increased cardiac output occur as compensatory mechanisms to maintain O_2 delivery to the brain, under conditions of hypoxia induced by COHb formation.[6]

Exposure to carbon monoxide at levels producing hypoxia would be expected to affect any tissue, in particular those tissues with high O_2 utilization requirements. The kidney is the greatest contributor to basal metabolic rate next only to the brain because of the use of ATP-dependent active transport processes. Carbon monoxide-induced hypoxia decreases the availability of oxygen to produce ATP in renal mitochondria, which produces adverse effects to the kidneys. Acute renal failure secondary to rhabdomyolysis has been observed in cases of acute carbon monoxide poisoning.[7] Visual field deficits, retinal hemorrhage & optic atrophy have been associated with severe CO poisoning in humans. The fetus is particularly vulnerable to maternal carbon monoxide exposure. Carbon monoxide in the maternal system distributes to fetal tissues. Measurements of fetal COHb concentrations in fetal and maternal blood of nonsmoking women have found fetal COHb concentrations to be approximately 10–15% higher than maternal blood[8].

Hematological effects of carbon monoxide include compensatory responses to tissue hypoxia resulting from the binding of carbon monoxide to Hb. Because carbon monoxide has a much higher affinity for Hb than O_2, greater than 200 times that of O_2, with relatively low partial pressures of carbon monoxide, O_2 is displaced from Hb. Binding of carbon monoxide to Hb has two effects:(a) the amount of O_2 that can be stored on Hb for delivery to tissues, decreases; and (b) it impairs the release of O_2 from Hb for its diffusion into tissues. CO thus causes a leftward shift of the oxyhemoglobin dissociation curve.[5] At sufficient levels of COHb, the combined effect results in tissue hypoxia, the principal mechanism of many adverse effects of carbon monoxide exposure. To maintain O_2 delivery to tissues under conditions of hypoxia, compensatory hematological responses like increased blood volume, erythrocyte count, hematocrit, and Hb occur.

Targets of carbon monoxide through non-hypoxic mechanisms include components of many physiological regulatory systems, such as brain and muscle oxygen storage and utilization (neuroglobin, myoglobin); prostaglandin cell signaling pathway (cyclooxygenase, prostaglandin H synthase); nitric oxide cell signaling pathway (e.g., nitric oxide synthase); steroid and drug metabolism (cytochrome P450), energy metabolism and mitochondrial respiration (cytochrome c oxidase, NADPH oxidase); and Reactive Oxygen Species(ROS) (catalase, peroxidases); and various transcription factors. Most of these non-hypoxic mechanisms have been attributed to the binding of Carbon Monoxide to heme proteins other than Haemoglobin (Hb)[3].

The current understanding of principal mechanisms underlying the hypoxic mechanism of carbon monoxide is the higher affinity of carbon monoxide for Hb than O_2 and the increased binding affinity for O_2 from COHb. Binding of O_2 and carbon monoxide to the four heme moieties of Hb is actually cooperative.[9] With successive additions of carbon monoxide or O_2, the associative reaction rate becomes faster, impairing the release of O_2 from Hb for utilization in tissues.[10] Although the blood COHb level reflects the current carbon monoxide body burden, measurement of blood COHb has not been shown to be a reliable predictor of severity of acute

toxicity.[1] Cardiac enzyme markers are associated with elevated risk for long-term cardiac mortality following carbon monoxide poisoning; And the biochemical markers for brain injury, such as neuron-specific enolase and S-100 beta protein, have not been found to reliably correlate with severity of poisoning[11]. Although hypoxic mechanisms of action of carbon monoxide are well established (i.e., those related to formation of COHb), further research is needed in the area of biomarker profiles for carbon monoxide poisoning to optimally treat patients who were exposed to this toxic gas.

Conflict of Interest: None

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