

State-of-the-Art: Hyperbaric Medicine for the Treatment of Carbon Monoxide Poisoning: Examining the Issues

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My assignment for this "State of the Art" discussion was to review the most recent basic science advances dealing with the theoretical benefits of hyperbaric oxygen (HBO₂) in carbon monoxide (CO) poisoning.

Scope of the problem: Carbon monoxide is one of many ubiquitous contaminants of our environment that requires prevention and control measures to insure adequate protection of the public health. The incidence of CO-related mortality and morbidity is similar worldwide, and CO may be responsible for over half of all fatal poisonings¹⁻⁴. Carbon monoxide poisoning has been estimated to cause 40,000 persons per year to seeking medical attention at emergency departments in the United States^{5,6}.

Primary mechanism of toxicity: The toxicity of CO is based on its propensity for forming stable complexes with transition metals. The affinity of CO for hemoglobin is more than 200-fold greater than that of O₂ and formation of carboxyhemoglobin (COHb) is a recognized effect of CO exposure⁷.

CO Pathophysiology: Hypoxia, ischemia, and more...: CO enters the body via the lungs and pulmonary cells may be injured by direct interactions, without need for delivery of CO by blood-borne hemoglobin. Elsewhere in the body, CO will be delivered by hemoglobin and concentrations found in perivascular and extravascular sites are estimated using calculations first described by Coburn⁸. The symptoms, signs and prognosis of acute CO poisoning correlate poorly with the level of COHb measured at the time of arrival at the hospital^{4,9-13}. These observations have created two concerns. The first is that investigators must be extremely careful when attempting to study patient populations because determination of the severity of poisonings and, therefore, the efficacy of treatment, will be difficult. The second concern is that these clinical observations raise questions regarding the mechanisms of toxicity and suggest that it extends beyond the classical perspective regarding hemoglobin binding by CO.

Hypoxic stress: An elevated COHb can precipitate tissue hypoxia, and this stress appears to be responsible for fatalities, cardiac injuries, and the acute neurological abnormalities which develop, according to most studies, in approximately 14 % of survivors from serious CO poisoning¹⁴⁻¹⁶. However, both clinical and animal studies have failed to establish a correlation between elevated COHb levels and delayed neurological injuries, which is the most frequent form of CO-associated morbidity^{4,9-13,17}. Recent studies indicate that between 23 and 47% of patients with CO poisoning develop impairments of concentration and learning, dementia, cog wheel rigidity, amnesia and/or depression, between 6 days and 3 weeks after poisoning^{12,18-20}. These events occur despite rapid and appropriate emergency care followed by careful neuropsychological evaluations. CO poisonings that appear to be relatively mild also may cause subtle neurological dysfunction, which indicates that the clinical assessment of the severity of poisoning is unreliable^{12,21-23}. The mechanism for delayed neurological injuries is unknown.

More on basic mechanisms- new information: Mysteries persist regarding the chemical interactions that have bearing on CO pathophysiology. Whereas physiological stresses of CO are classically related to competition between CO and O₂ for hemoproteins, recent attention has focused on interactions between CO and another small gaseous ligand produced *in vivo*, the free radical nitric oxide (*NO). Under virtually all circumstances, the affinity of *NO for hemoproteins is vastly greater than that of either CO or O₂. Despite this fact, there are situations where CO will disturb the association between *NO and hemoproteins. CO increases the steady state concentration of *NO in, and around, both platelets and endothelial cells²⁴⁻²⁶. Electron paramagnetic resonance spectroscopy has provided direct evidence that exposure to CO increases the concentration of *NO in lung and brain^{27,28}. CO does not increase activity of nitric oxide synthase (NOS) in platelets or endothelial

cells, nor does CO increase NOS protein concentration in CO-exposed cells and tissues at a time when they exhibit elevated *NO levels^{24,26,28-30}. In fact, CO partially inhibits NOS activity in rats exposed to 3000 ppm who have COHb levels of approximately 45 %²⁴. It appears that CO increases the steady state level of unbound *NO because it competes for intracellular sites that normally would bind *NO. Toxic effects on cells occur because the liberated *NO is available to undergo reactions with superoxide anion (O₂⁻) which yield the potent oxidizing and nitrating agent, peroxynitrite. These events are a component to CO-mediated brain injury in some animal models^{27,31-33}, and they may relate to a growing body of evidence suggesting that CO functions as a cell signaling messenger analogous to *NO^{34,35}. The point is that when ever CO is generated *in vivo* by heme oxygenase, if *NO is also produced in the vicinity, the CO may act to increase the effective steady state concentration of *NO.

The mechanism behind the apparent ability of CO to increase steady state concentration of *NO is under investigation. The following discussion is our current hypothesis. It is based on an assessment of potential competition between ligands using published values for the association and dissociation constants for myoglobin, which we use as a 'model' intracellular hemoprotein (Table 1)³⁶.

TABLE 1. RATE CONSTANTS FOR DIFFERENT LIGANDS WITH MYOGLOBIN

GAS	ASSOCIATION RATE CONSTANT (M⁻¹sec⁻¹)	DISSOCIATION RATE CONSTANT (sec⁻¹)
O₂	14 x 10⁶	12
*NO	17 x 10⁶	1.2 x 10⁻⁵
CO	0.5 x 10⁶	1.9 x 10⁻²

The calculated affinity binding constant favors *NO over CO by a factor of 10⁵ when steady state concentrations of CO and *NO are equal (e.g. for *NO $1.7 \times 10^7 / 1.2 \times 10^{-5} = 1.4 \times 10^{12}$; for CO $0.5 \times 10^6 / 1.9 \times 10^{-2} = 2.6 \times 10^7$). It is unlikely, however, for both ligands to have equal concentrations *in vivo*. Coburn (1970) demonstrated that a predictable relationship exists between the tissue concentration of CO and blood COHb up to a level of 50%. For example, at a COHb of 7 % the extravascular fluid CO concentration should be approximately $22 \times 10^{-9} \text{ M}$ ^{8,37}. Because CO is freely soluble, a similar concentration is expected to occur inside cells. The rate of *NO production by endothelial cells (which we have taken as an example because these cells are physically close to delivered CO from the blood) has been estimated to be $1.1 \times 10^{-18} \text{ M / cell / min}$ ³⁸. Therefore, even in a situation where there is a relatively low COHb, the CO concentration may be as much as 10⁹ greater than the concentration of *NO. Therefore, competition is feasible even when considering equilibrium kinetics.

The potential for effective competition is even more favorable for CO when considering simple competition kinetics. It is more appropriate to make an assessment of competition using the association rate constants for these ligands, rather than the affinity constants. The physiological and clinical settings where this relationship may have bearing is early during a CO exposure from exogenous sources, when ever there is a change in CO production *in vivo* or when a reduction in local *NO production occurs. Since the association constant for CO and *NO differ by a factor of only 34, even a small increase in CO concentration relative to that of *NO will have an impact favoring CO competition with *NO for myoglobin. Adverse effects on endothelial cells *in vitro* that are mediated by *NO-derived oxidants can be demonstrated with exposure to a CO concentration of only $11 \times 10^{-9} \text{ M}$ ³⁰. There may also be physiological conditions which allow favorable competition between CO and *NO. Liver parenchyma has been estimated to generate $0.45 \times 10^{-9} \text{ M CO / gram liver / min}$ ³⁹.

Concomitant hypoxia and ischemia: Severe CO poisoning causes mitochondrial dysfunction and oxidative stress in the central nervous system. In experimental CO poisoning, mild manifestations occur when cerebral perfusion is maintained, whereas mortality and morbidity are profoundly enhanced when exposures to high CO concentrations occur in the presence of reduced cerebral perfusion⁴⁰. The concomitant impairment of cerebral blood flow can be triggered by cardiac dysfunction due to CO or to fixed cerebral vascular lesions⁴⁰⁻⁴³.

In the face of concomitant hypoperfusion, Coburn demonstrated that 20 to 45 % of CO present in circulating blood shifts into skeletal muscle and other tissues⁴⁴. CO will impair mitochondrial electron transport when cells sustain a reduction in O₂ delivery, as will occur when an elevated COHb level occurs concurrent with restricted perfusion^{42,43}. In the setting of hypoperfusion and high CO concentrations, CO binds to cytochrome c oxidase which will inhibit ATP synthesis and cause generation of hydroxyl-like radicals^{42,45}. Energy production and mitochondrial function are restored after COHb levels decrease⁴². These observations have not explained the two historical characteristics of clinical poisoning that are correlated with a high risk for delayed morbidity: (1) A prolonged exposure to CO, called a "soaking", and (2) Syncope or temporary unconsciousness^{17,46-50}. It is unclear whether the transient changes observed during CO poisoning precipitate delayed neuronal dysfunction or death⁵¹. Moreover, in some models with neuronal injuries, it has been difficult to document evidence of impaired mitochondrial function or a cellular hypoxic stress⁴³.

Large clinical surveys have reported a correlation between neurological morbidity and the occurrence of an interval of unconsciousness during CO exposure^{17,47,48}. However, such an overt insult is not always necessary for neurological injuries to occur in humans^{12,21-23}. Many neuroimaging techniques suggest that CO causes perivascular injuries in the CNS. Bianco⁵² and Silverman⁵³ have hypothesized that the initial site of injury by CO may be the vasculature, based on detection of hemosiderin deposits. These deposits are thought to result from focal hemorrhages. Recently, more sophisticated neuroimaging techniques have been used to detect abnormalities in patients who, in some cases, exhibited only subtle neurological impairments. Abnormalities in resting cerebral blood flow^{54,55} and abnormalities in cerebral vasoactivity to carbon dioxide⁵⁶ have been detected by single-photon emission computed tomography (SPECT). Changes have also been detected which suggest that CO causes a disturbance in coupling between neuronal O₂ demand and blood flow. DeReuck, et al.⁵⁷, examined 7 patients between 5 and 7 days after CO poisoning using positron emission tomography (PET) with ¹⁵O₂. They found a global increase in cerebral O₂ extraction along with regional areas of diminished blood flow, especially in the frontal and temporal lobes. Although these observations serve to underscore the vascular nature of CO-mediated neuropathology, they do not assist with clinical assessments of patients. To date, no objective parameters have been identified which prospectively assess the severity of poisoning. Some recent findings with state-of-the-art neuroimaging techniques have exhibited correlations with the clinical improvement in case reports, whereas others may show abnormalities when no clinical changes are noted⁵⁸⁻⁶⁰. In experimental studies, blood levels of glutathione, oxidized proteins and products of lipid peroxidation offer insight into CO-mediated pathology⁶¹. However, additional work is necessary to establish if these or some other survey may be useful to stage the severity of clinical poisonings.

Vascular injuries due to CO: The level of CO in tissues may have an equal or greater impact on the clinical status of patients and development of pathology than does the blood level of CO. This phenomenon is most clearly demonstrated with regard to CO-mediated vascular injuries. When human beings or experimental animals have been exposed to relatively low CO concentrations for extended periods of time, capillary leakage of macromolecules from the lung and systemic vasculature has been documented^{28,29,62-65}. In contrast, when an hypoxic stress was established in animals by exposing them for 8 to 45 minutes to extremely high CO concentrations, sufficient to cause COHb levels of 60 to 90 %, capillary leakage was not detected⁶⁶⁻⁶⁸. A proposed pathological mechanism of CO which is independent of hypoxic stress has been demonstrated in experimental studies to be due to elevations in the steady state concentration of the free radical, nitric oxide (*NO)^{28,29}.

Cascade of pathology – vascular injury and more...: The findings outlined above for vascular injuries have provided further insight into CO-induced neuropathology because endothelial *NO-mediated changes are a prerequisite for neutrophil adherence to the cerebral microvasculature of CO poisoned animals^{27,32,33}. However, *NO-mediated vascular stress is not sufficient by itself to cause neutrophil sequestration in this model of CO-mediated brain injury. During the latter portion of the exposure when rats breathe 3000 ppm CO and become unconsciousness, they invariably sustain a period of hypotension that is presumably mediated by cardiac decompensation^{31,43,69}. Cerebral blood flow, which initially is approximately 150 % above normal due to *NO-mediated vasodilation, decreases to about 50 % below normal for a period of 4 to 6 minutes when rats lose consciousness^{43,69}. With regard to mechanisms of brain injury, it is important to emphasize that unlike typical ischemic/hypoxic injury, there is never a time when cerebral blood flow is nil, and the interval of hypoperfusion is less than six minutes^{43,69}. The sudden alteration in microvascular flow, coupled with the *NO-mediated oxidative changes to endothelium, cause neutrophils to adhere to endothelium.

Activated neutrophils attach to the vascular wall via interactions between β_2 integrin adhesion molecules and endothelial (ICAM) counter-receptors⁷⁰. β_2 integrin adhesion molecules are required for neutrophil adherence and progression of the oxidative stress cascade in CO poisoning^{27,33,71,72}. This occurs 45 minutes after the rats are removed from CO, based on the inhibitory potential of monoclonal antibodies to β_2 integrins^{33,72}. The 45 minute delay between initial adherence and β_2 integrin commitment is unusually long compared with some models of leukocyte-mediated tissue injury. The delay is due to the flux of *NO from platelets²⁴. Nitric oxide will inhibit β_2 integrin function⁷³. Once the animals are in fresh air and CO leaves the body, the *NO flux drops and adherent leukocytes become activated. Activated leukocytes liberate proteases and reactive O₂ species that cause conversion of endothelial xanthine dehydrogenase to xanthine oxidase, and xanthine oxidase activity is required for subsequent brain lipid peroxidation^{27,31-33}. These biochemical events occur within 90 minutes after CO poisoning. Metabolic defects in the basal ganglia and hippocampus appear at 5 days, and evidence of impaired learning plateaus in 3 weeks after poisoning⁷⁴. The cellular and biochemical events which occur during this three week period appear to be related to inflammatory processes and are under active investigation⁷⁵.

HBO₂ and experimental CO poisoning: HBO₂ has been shown to diminish cerebral edema, reduce mortality and improve neurological outcome in various models of acute CO poisoning⁷⁶⁻⁷⁸. The initial motivation for administering HBO₂ was to hasten removal of CO, based on the well known relationship that COHb half life is inversely related to the inspired partial pressure of O₂^{79,80}. Hyperbaric oxygen also hastens dissociation of CO from cytochrome oxidase^{41,42}, and vascular oxidative stress is prevented because HBO₂ inhibits β_2 integrin-dependent leukocyte adhesion^{72,81}. Neutrophils from humans exposed to HBO₂ exhibit the same diminished adherence as those in animal studies⁸².

Additional studies/ more variables: Several investigations have suggested an association between CO-induced neurotoxicity and that caused by excitatory amino acids^{83,84}. Although this issue is currently under investigation, at least in some studies excitotoxicity is linked to elevations of intracellular calcium, *NO and O₂[•]. There are three types of receptors activated by excitatory amino acids: N-methyl-D aspartic acid (NMDA), D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainic acid. Agents that inhibit NMDA receptor activation attenuate CO-mediated delayed neuronal degeneration of pyramidal cells in the hippocampus and cochlear ganglion cells^{85,86}.

Monoamine neurotransmitters such as norepinephrine and dopamine are elevated after CO exposure, and enzymatic breakdown as well as auto-oxidation will generate reactive O₂ species^{87,88}. These agents appear to contribute to oxidative stress after CO poisoning because free radical production in brain can be diminished by inhibiting monoamine oxidase-B, an enzyme located in microglial cell⁸⁹. Nitric oxide will augment pre-synaptic release of monoamine neurotransmitters by activating NMDA receptors^{90,91}. Activated microglia can also mediate neuronal injury by generating *NO-derived oxidants⁹². Microglia can attack oligodendroglia and

have been associated with demyelination processes⁹³. Therefore, once again, *NO-mediated oxidative stress may be a common biochemical link among different pathways of CO poisoning.

Summary: Neuropathology following CO poisoning may include neuronal death in the cortex, hippocampus, substantia nigra and globus pallidus⁹⁴. One of the most common abnormalities is demyelination of cerebral cortex, which occurs in a perivascular distribution along with evidence of a breach in the blood-brain barrier⁹⁴⁻⁹⁶. Blood flow and perivascular abnormalities have been shown using several neuroimaging techniques⁵²⁻⁵⁷. Acute vascular and perivascular changes also have been found in brains of experimental animals^{12,27,97}. Moreover, the variability observed in lesions found in the cerebral white matter and globus pallidus of animals has been correlated with the fall in local blood flow and metabolic acidosis^{16,98}. Clinical and experimental findings suggest that the effects of CO are global and variations in the clinical manifestations of poisoning arise because brain regions respond differently to the stresses. The threat to life and acute neurological compromise from CO poisoning are thought to be due to direct hypoxic stress. The syndrome of delayed neurological sequelae appears to be a consequence of a cascade of events involving oxidative stress and inflammatory responses. HBO₂ inhibits CO-mediated hypoxia and inflammation.

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