

Neurologic and Pregnancy Effects of Carbon Monoxide Exposure

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Abstract

Carbon monoxide exposure remains a public health concern worldwide. Despite the burden that carbon monoxide exerts, significant controversy exists regarding optimal treatment of exposed persons. Particular controversy exists around neurologic effects of carbon monoxide exposure, how best to evaluate for neurocognitive dysfunction, and effects on the fetus of pregnant women. This review focuses on the mechanism of injury from carbon monoxide, and summarizes the data regarding neurocognitive dysfunction and fetal effects of exposure.

Keywords: Carbon monoxide; Hyperbaric oxygen; Neurocognitive dysfunction; Pregnancy; Neuropsychiatric testing

Introduction

Carbon monoxide (CO) exposure is the leading cause of poisoning deaths in the North America. It is an odorless and non-irritating gas. Because of these properties and because it lacks a unique clinical signature, CO poisoning is difficult to appreciate and is often misconstrued as “the flu”. It is possible then, that the true incidence of CO poisoning is currently unknown and that many cases of exposure and poisoning may go unrecognized and therefore underreported.

Carbon monoxide is a by-product of the incomplete combustion of hydrocarbons. Common sources include motor vehicle exhaust; heating units and generators; improperly functioning chimneys; and indoor vehicles operation such as propane-fueled forklifts and Zambonis [1,2]. At least in North America, during times of severe inclement weather when loss of power occurs, increased use of propane heaters in poorly vented rooms has led to a number of large outbreaks of CO poisoning [3]. Less commonly, acute CO poisoning is also associated with structural fires. Legislation mandating CO detectors in public and private buildings has led to a decrease in the number of CO poisoning cases [4].

Carbon monoxide is also produced endogenously, during heme degradation and likely serves as an intracellular messenger [5]. Constitutive and inducible isoforms (HO⁻¹, HO⁻²) of the enzyme are known. This CO serves as a signaling molecule involved in numerous cellular functions, such as inflammation, proliferation, and apoptosis [6].

Biochemistry, Physiopathology and Pathology

Carbon monoxide binds rapidly and avidly to hemoglobin (Hb), leading to the formation of carboxyhemoglobin (COHb). The affinity of hemoglobin for CO is 210 times its affinity for O₂ [7]. The oxygen carrying capacity of blood therefore decreases, leading to tissue hypoxia. CO is taken up by Hb so avidly that the partial pressure of CO in capillary blood remains very low, leading to diffusion-limited transfer of CO. Carbon monoxide readily displaces oxygen from hemoglobin while COHb liberates CO exceedingly slowly. In the

presence of COHb, the oxygen dissociation curve shifts to the left, leading to even less oxygen released at the tissue level [8]. The amount of COHb formed depends on the duration of exposure to CO, the concentration of CO in the inspired air and the alveolar ventilation. Carbon monoxide binds to myoglobin in the myocardium, thereby limiting oxygen availability in myocardial mitochondria. This leads to a decrease in oxidative phosphorylation and ultimately the energy source of myocardium [9].

Patients with recognized or unrecognized underlying cardiac pathology may be at risk for death from arrhythmias or myocardial infarction. Chest pain can also occur without underlying coronary artery disease. For example, 2 weeks after accidental exposure to CO, 34% of a group of Swiss soldiers had chest pain [10]. Henry et al. studied mortality risk in patients with moderate to severe CO poisoning. In patients felt to be at low risk for coronary artery disease, 37% suffered myocardial injury and 38% were dead within roughly 7.5 years. This mortality rate was three times higher than expected after controlling for age and gender [11].

This has led to a search for morphological changes that could be attributed to CO, especially because the myocardium binds more CO than skeletal muscle [12]. Ultramicroscopic lesions have been reported but the relative roles of general tissue hypoxia and specific CO toxicity are unknown [13]. In addition to COHb, the binding of CO to various cytochromes is also significant and is thought to be responsible for cytotoxicity. The marked decrease in cytochrome oxidase in experimental studies suggests a direct toxic effect [14]. Myocardial injury with ischemic ECG changes and elevated cardiac biomarkers were found in 37% of 230 patients with moderate to severe CO poisoning with 5% in-hospital mortality [11]. Therefore, patients admitted to the hospital with CO poisoning should have a baseline ECG and serial cardiac biomarkers. Electron microscopy of left ventricular biopsies of a 25-year-old woman with functional evidence of cardiac failure after acute CO poisoning and otherwise normal myocardial perfusion showed slight ultrastructural changes in the myocytes, large glycogen deposits and swollen mitochondria [13]. The above changes have been thought to be signs of impaired energy metabolism of the myocardial cells. Human patients with CO poisoning have also been shown to have reduced ejection fractions after the exposure, similar to a Takotsubo-like pattern [15]. In rat

heart, CO causes vasodilatation and increased coronary flow that are not mediated by simple hypoxia [16]. CO exposure in the fetal period in rats causes myocyte hyperplasia and cardiomegaly. This cellular response is sustained through the early neonatal period in animals exposed to CO both in utero and in the post-partum [17]. Although hemorrhages and areas of necrosis in the heart, mostly in the septum and the papillary muscles were described with CO poisoning as early as 1865 [18], few human cases of acute, fatal CO intoxication, with small foci of coagulation necrosis have been reported [19].

Recent investigations suggest other mechanisms of CO-mediated toxicity. One hypothesis is that CO-induced tissue hypoxia may be followed by reoxygenation injury to the CNS. Hyperoxygenation facilitates the production of partially reduced oxygen species, which in turn can oxidize essential proteins and nucleic acids, resulting in typical reperfusion injury [20]. However, other experimental models have found the CO-liberating molecules are protective against reperfusion injury [21]. In addition, CO exposure has been shown to cause lipid peroxidation, (i.e. degradation of unsaturated fatty acids) leading to reversible demyelination of CNS lipids [22]. CO exposure also creates substantial oxidative stress on cells, with production of oxygen radicals resulting from the conversion of xanthine dehydrogenase to xanthine oxidase [23].

Neurologic Effects

Disturbances of brain function predominate in acute CO intoxication and delayed neurological effects also occur [24]. Some brain regions are particularly sensitive to hypoxic damage including the cerebral cortex, particularly its second and third layers; the white matter, the basal nuclei, and Purkinje cells of the cerebellum [25,26].

Attempts have been made to relate this “selective vulnerability” to the cause of the hypoxia, but the nature and distribution of the lesions appear to depend on the severity, suddenness, and duration of the oxygen deprivation, as well as on its mechanism (hypoxemia or ischemia) rather than on its cause. Regions with relatively poor vascularization and “watershed” areas between two sources of blood supply, such as the globus pallidus, may be more vulnerable, especially during periods of hypotension [27]. The effects of hypoxia on the brain, therefore, do not reflect the cause and neither the character of the lesions nor the areas affected are regarded as pathognomonic for CO [28].

The neuropathology of CO toxicity has been well described in postmortem studies [26] and includes, in acute cases, petechial hemorrhages of the white matter involving the corpus callosum; in cases surviving more than 48 h there is often multifocal necrosis involving globus pallidus; hippocampus; pars reticularis of the substantia nigra; laminar necrosis of the cortex; loss of Purkinje cells in the cerebellum; and with white matter lesions. CO intoxication usually spares the hypothalamus, walls of the third ventricle, thalamus, striatum, and brainstem [26,29].

Myelin damage is constant and ranges from discrete, perivascular foci in the corpus callosum, the internal-external capsule and the optic tracts usually seen in comatose patients who died within 1 week, to extensive periventricular demyelination and axonal destruction observed in comatose subjects with longer survival, sometimes leading to formation of plaques of demyelination [30]. A distinct constellation of brain and MRI abnormalities appears premortem and in those surviving an exposure. It includes globus pallidus lesions, white matter

changes, and diffuse low-density lesions throughout the brain [31,32]. In general, CT and MRI neuroimaging findings reflect the neuropathologic changes described by Lapresle and Fardeau [26].

Evaluation of Persons Exposed to CO

The gold-standard test to evaluate for the presence of CO is a venous or arterial carboxyhemoglobin concentration (COHb) performed on a co-oximeter. A handheld pulse co-oximeter capable of determining SpCO much like a typical pulse oximeter does is available (Massimo Corporation, Irvine, CA, USA). There is some debate as to the absolute accuracy of this device, leading most facilities use this handheld oximeter as a screening tool – if an elevated COHb is found, then traditional carboxyhemoglobin determination by co-oximetry is ordered [33].

Because CO is formed endogenously, COHb is present in normal concentrations of roughly 1.5% or less. Numerous studies have sought to determine a “normal” range of COHb in smokers, patients with chronic lung disease, and other groups of individuals. Heaving smokers can have COHb concentrations of over 15% [24]. Second-hand smoke can also lead to an increase in COHb concentrations, with expired CO doubling after passive cigarette smoke exposure [34].

Investigators have sought to correlate COHb concentrations with severity of acute symptoms and neurologic sequelae - however, no such correlation has been found [35]. This likely due to the significant heterogeneity among the studies: primarily the differences in time of removal from CO source to COHb determination; the provision of oxygen during that time period; a lack of detail in published case reports; and a lack of accurate data due to the retrospective nature of most of these studies. Some authors have attempted to estimate COHb concentrations by extrapolating from ambient CO concentrations [36]. Such methods are not often utilized and they have not been externally validated.

Severity of Poisoning

There exists considerable debate over how to access or assign a level of severity to a case of CO poisoning. Some authors have assigned an increasing severity of poisoning based upon symptoms Table 1 [37]. Other authors have stratified poisoning according to blood COHb concentrations. Sadovnikoff et al. defined less severe poisoning as a COHb concentration of less than or equal to 10% [38]. Chambers et al. defined severe poisoning as a COHb concentration greater than 15% or a loss of consciousness [39], thereby, by definition; a less severe poisoning would be a case in which the COHb concentration is less than 15%.

Carbon Monoxide Exposure in Pregnancy

During pregnancy, the minute ventilation increases up 30-40% [40]. This is due to several factors, includes a central respiratory stimulation, increased sensitivity of peripheral chemoreceptors, and increased oxygen consumption during pregnancy. It has been hypothesized, therefore, that pregnant women are at increased risk of CO poisoning [41]. However, in an elegant and thorough study of volunteers exposed to ambient CO of different concentrations for various lengths of time while sedentary and while exercising, Peterson and Stewart for no difference in COHb concentrations with exercise [42].

Grade of severity of maternal CO exposure	
Grade 1	Alert and oriented, but headache, dizziness and nausea
Grade 2	Alterations of mental state
Grade 3	Not alert, disorientation, loss of recent memory, muscle weakness, or incoordination
Grade 4	Disoriented, depressed sensorium, limited and inappropriate response to simple commands
Grade 5	Comatose

Table 1: Severity of CO Exposure used by Koren et al. [37].

Carbon monoxide does cross the placenta, probably by both passive and facilitated diffusion [43]. The effects of the placenta, the presence of hemoglobin F in the fetus, and the leftward shift in the hemoglobin-oxygen dissociation curves in the fetus have led to confusion and uncertainty regarding the actual fetal COHb that occurs at a given maternal COHb concentration. There are very limited human case reports documenting a fetal COHb concentration concurrently with a maternal level in a case of CO poisoning. In a case series of 20 pregnant women with CO poisoning (with COHb measured in 10 of the cases), Curtis et al. [44] reported that in 3 of the cases where the mother died, there was no COHb found in the fetus, and that in 2 of the cases the fetal COHb was one-third or less of the maternal value.

Concomitant COHb data do exist in mother-baby pairs for cigarette smokers and non-smokers, and provide some interesting insight. Haddon et al. [45] examined the COHb concentrations of 50 smoking and non-smoking women, and the COHb of 26 paired mother-fetus blood samples obtained at birth. In all cases, the umbilical cord and maternal COHb concentration were approximately equal. These data are also consistent with the findings of Friberg et al., who administered CO to women prior to elective abortions [46]. Other investigators have found that the fetal COHb is more than twice as high as maternal COHb in mothers who smoked during pregnancy and during labor Bureau et al. [47] concluded that “extrapolation from our results would lead one to believe that in most fetuses the HbCO [fetal] level would vary from 7.6% to 12.6% throughout the intrauterine life when mothers smoke one pack of cigarettes per day.” Lastly, Cole et al. [48] found that in women who smoked throughout pregnancy and labor, the fetal: maternal COHb concentration ratio was 1.8:1. So, the majority of evidence suggests that with chronic exposure to CO, fetal COHb is higher than maternal COHb. However, no data regarding the rate of decline of fetal/neonate COHb exist.

Animal Models of Maternal-Fetal CO Poisoning

In order to generate data regarding mother-fetal COHb in acute and chronic CO poisoning, Longo et al. developed and utilized a pregnant ewe model of CO poisoning. In one study, Longo and Hill subjected pregnant ewes to CO concentrations of 30-100 ppm for a duration of 24 to 48 h [49]. At 100 ppm CO, maternal sheep COHb exceed that of the fetal sheep for the first 6 h of exposure; after that, the fetal COHb exceeded the maternal value. The time required for fetal COHb to rise above maternal concentrations was also related to the ambient CO concentration; at 68 ppm of CO it took approximately 14 h to occur. Thus, in this sheep model it appears that during acute CO exposure (that is as few as 6 h and as many as 14 h), fetal COHb does not reach the level of maternal COHb.

Longo’s group used data from the pregnant ewe studies to mathematically model the maternal and fetal COHb as functions of time during and after exposure of the mother sheep to various inspired CO concentrations [50]. They found that following a change in the inspired CO concentration, the fetal COHb lags behind maternal COHb by several hours. During prolonged CO uptake, fetal COHb eventually overtakes maternal COHb, and approaches an equilibrium value approximately 10% higher than the mother’s. The model further predicted that the fetal COHb concentrations decrease slower than the mother’s, with a fetal HgCO half-life of roughly twice as a long. Unfortunately, this mathematical model was derived from sheep data and validated only with other data from sheep, yet this manuscript has been cited frequently as providing evidence that the COHb of a human fetus decreases slower than the COHb of a human mother. Delvau recently performed a systematic review and meta analysis of published Haldane constants in adult and fetal blood. While there is considerable heterogeneity amongst the research data, the investigators conclude that the Haldane (M) constant for adult hemoglobin is 209 and that for fetal hemoglobin is 178 [51]. However, until data of serial human fetal COHb concentrations are collected, to state that human fetal COHb concentrations decrease much slower than maternal COHb concentrations is speculative.

Further critical analysis of Longo’s sheep studies reveal inconsistencies with human experience that are difficult to reconcile. For instance, 57% of fetal sheep died during experimentation when the fetal COHb reached concentrations of 15% for a period of 30 minutes [49]. This high degree of fetal demise is not seen in human case series, thus making the ability to draw meaningful conclusions from Longo’s sheep data suspect.

Human Fetal Exposure to CO

There is remarkably little human data of human fetal effects due to carbon monoxide exposure. Isolated case reports exist, but there are tremendous variations in the clinical scenarios that make drawing any meaningful conclusions difficult at best.

Koren’s ‘Motherisk’ group in Toronto published the only prospective multicenter study of CO exposure in pregnant women [37]. They found that pregnancy outcome was adversely affected in 3 of 5 pregnancies in which there was severe toxicity; two stillbirths and one child with cerebral palsy. All 31 babies with mild or moderate in utero exposure to CO exhibited normal physical and neurobehavioral development. Severe maternal CO toxicity was associated with statistically significant more adverse fetal outcomes when compared to mild maternal toxicity. They concluded that while severe CO poisoning

poses serious fetal risk, mild accidental exposure is likely to result in normal child outcome.

Neurocognitive and Psychiatric Effects of CO Exposure

There is consensus that CO poisoning can lead to adverse neurocognitive and psychiatric sequelae. Risk factors for such adverse outcomes, how to define these adverse outcomes, how to objectively measure neurocognitive and psychological effects after CO exposure, and what percentage of patients develops these outcomes is the subject of considerable debate.

A limited number of studies have looked at the psychiatric effects of CO exposure. Case series most commonly identify depression and anxiety, but other psychiatric effects such “personality changes” have been described [52-55]. These studies are also of limited size and suffer from a lack of consistent methodologies, do not always control for malingering or effort, have significant selection bias, and non-uniform follow-up. Overall, reported prevalence of depression and anxiety after CO poisoning ranges between 33% and 100% [54,56-58].

In an attempt to determine which patients may benefit from hyperbaric oxygen (HBO), Weaver et al. [59] studied 163 patients with CO poisoning who did not receive HBO as part of a larger study [60]. Although their outcome was limited to cognitive sequelae at 6 weeks post-poisoning, they found that 42% of patients exhibited neurologic sequelae. From several analyses, they stated that risk factors were loss of consciousness, age of 36 years or more, time interval of exposure greater than or equal to 24 hours, and carboxyhemoglobin concentrations greater than or equal to 25%.

In the largest study attempting to determine the prevalence of depression and anxiety after CO poisoning, Jasper et al. found that depression and anxiety was present in 45% of patients 6 weeks after CO poisoning and in 42% at 12 months [52]. However, 33% of the patients reported a history of affective disorder prior to the episode of CO poisoning (and nearly 77% of the suicidal-attempt subgroup had a history of a mood disorder). Interestingly, Jasper et al. found that accidentally-poisoned people were just as likely to have depression and anxiety at 6 and 12 months post-poisoning as were people who had attempted suicide with CO.

Adding further complications to this issue is the fact that neurocognitive testing is subject to subjective as well as conscious and unconscious biases. For instance, when professionals administered neurocognitive testing to people after CO exposure, the results of the tests were reported as more abnormal when the tester knew that the subject had been exposed to CO than when no such history was provided [61]. Furthermore, it is established that when financial or other incentives are present that patients may exhibit what has been termed Malingered Neurocognitive Dysfunction (MND) [62,63]. Testing mechanisms to detect MND exist, but are rarely performed and virtually never reported in medical literature.

Treatment

Management of CO-exposed patients first consists of removing the patient from the CO exposure source and administering 100% oxygen to accelerate the elimination of CO. Under normobaric conditions and breathing room air, the half-life of HgCO is approximately 320 minutes [64], when administering normobaric 100% oxygen, the half-like is approximate 80 minutes [65]. When 100% oxygen is administered under greater than atmospheric pressure (i.e.: hyperbaric oxygen), the

half-life decreases even further, to roughly 20 minutes. In case of normobaric oxygen therapy, the ideal duration of oxygen administration is unknown, but it is generally recommended to continue oxygen treatment until the HbCO is negligible [66] Due to the aforementioned animal data regarding fetal HgCO, it is recommended that if HBO is not used, that pregnant women breathe 100% oxygen for 5 times longer than it takes for their own HbCO to become negligible [66].

While no firm recommendations for the use of hyperbaric oxygen are universally agreed upon, when available and if the patient is sick enough, HBO is generally recommended. Proposed indications for HBO are provided in Table 2. It is important to realize, however, that not all studies demonstrate the superiority of HBO over normobaric oxygen. Scheinkestel found no difference in neurocognitive outcomes between patients treated with HBO compared to patients treated with normobaric oxygen [67]. Furthermore, there is considerable variability in which patients are treated with HBO. Some HBO centers do not treat patients poisoned with CO. It is therefore advisable that clinicians consult with a medical toxicologist and HBO centers in their area if there is any question about the use of HBO for a specific patient.

Indications for hyperbaric oxygen treatment
Any loss of consciousness during carbon monoxide exposure
Any abnormal neurologic finding on examination
Severe metabolic acidosis on presentation
Myocardial ischemia on presentation
COHb concentration of >25% at presentation
COHb concentration of >10% if pregnant at presentation

Table 2: Proposed indications for hyperbaric oxygen treatment.

Conclusion

Carbon monoxide poisoning continues to be a cause of significant morbidity and mortality worldwide. Currently there is insufficient scientific evidence to effectively or accurately determine the risk of exposure to a fetus other than mild maternal toxicity is likely to have little or no fetal toxicity. Moreover, long-term effects on survivors of carbon monoxide poisoning is also difficult to predict, largely due to severe limitations and biases inherent in neurocognitive testing. If performed, neurocognitive testing should be conducted by an exposure-blinded professional experienced in conducting tests to detect malingering.

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