Carbon Monoxide Poisoning: Pathogenesis, Management, and Future Directions of Therapy

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Abstract

Carbon monoxide (CO) poisoning affects 50,000 people a year in the United States. The clinical presentation runs a spectrum, ranging from headache and dizziness to coma and death, with a mortality rate ranging from 1 to 3%. A significant number of patients who survive CO poisoning suffer from long-term neurological and affective sequelae. The neurologic deficits do not necessarily correlate with blood CO levels but likely result from the pleiotropic effects of CO on cellular mitochondrial respiration, cellular energy utilization, inflammation, and free radical generation, especially in the brain and heart. Long-term neurocognitive deficits occur in 15–40% of patients, whereas approximately one-third of moderate to severely poisoned patients exhibit cardiac dysfunction, including arrhythmia, left ventricular systolic dysfunction, and myocardial infarction. Imaging studies reveal cerebral white matter hyperintensities, with delayed posthypoxic leukoencephalopathy or diffuse brain atrophy. Management of these patients requires the identification of accompanying drug ingestions, especially in the setting of intentional poisoning, fire-related toxic gas exposures, and inhalational injuries. Conventional therapy is limited to normobaric and hyperbaric oxygen, with no available antidotal therapy. Although hyperbaric oxygen significantly reduces the permanent neurological and affective effects of CO poisoning, a portion of survivors still have substantial morbidity. There has been some early success in therapies targeting the downstream inflammatory and oxidative effects of CO poisoning. New methods to directly target the toxic effect of CO, such as CO scavenging agents, are currently under development.

Keywords: carbon monoxide poisoning; carbon monoxide; mitochondria

Prevalence of Carbon Monoxide Poisoning

The best available estimates of the yearly incidence of carbon monoxide (CO) poisoning in the United States, based on emergency department visits, are 50,000 (16.0 cases per 100,000 population). Recent studies show declining numbers of CO death, most recently found to be 1,319 in 2014, from estimates of 2,700 in the mid-2000s (1–4). There are approximately 15,000 intentional CO poisonings annually, accounting for over two-thirds of reported deaths (4–6).

Inhalational injury occurs in greater than two-thirds of fire-related deaths (7). In over 25,000 residential fire-related injuries treated in emergency departments in 2001, more than 50% had a diagnosis of anoxia, suggesting CO poisoning from smoke inhalation (8). In a group of burn victims, three-quarters had carboxyhemoglobin (COHb) levels high enough to cause death or harm (9). In these patients, it is difficult to attribute CO poisoning alone as a cause of death, regardless of COHb level, due to concomitant severe burn and inhalational injuries.

Etiology and Pathogenesis

CO is a colorless, tasteless, odorless gas. CO formation is generally caused by incomplete combustion of carbon compounds; common sources include fire, engine exhaust, and faulty furnaces. CO binds to hemoglobin (Hb) in the blood with high affinity, forming COHb. Exposure to levels as low as 10 ppm of CO can lead to detectable COHb levels of approximately 2% (10). The World Health Organization suggests that levels greater than 6 ppm are potentially toxic over a longer period of time (11). COHb levels of 2% or greater in nonsmokers and 10% or greater in smokers are considered abnormal and may produce symptoms (11, 12).

Hb-Specific Effects

CO binds with high affinity to many ferrous heme-containing proteins. Hb has a 250-fold greater affinity for CO than for oxygen (13).

(Received in original form June 25, 2016; accepted in final form October 14, 2016)

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Am J Respir Crit Care Med Vol 195, Iss 5, pp 596–606, Mar 1, 2017
Copyright © 2017 by the American Thoracic Society
Originally Published in Press as DOI: 10.1164/rccm.201606-1275CI on October 18, 2016
Internet address: www.atsjournals.org

CO competes with oxygen for binding to Hb and, by displacement of oxygen, reduces oxygen carrying capacity. CO binding to Hb also stabilizes the relaxed, high-affinity quaternary state of Hb (known as R-state), increasing the affinity for oxygen of other sites within the Hb tetramer, and further reducing oxygen release and delivery. Neither the clinical severity nor the clinical improvement of CO-poisoned patients directly correlates with the blood COHb level or COHb clearance (14, 15). In canine studies, the toxicity of CO gas administered by inhalation is greater than transfusion of a similar concentration of CO-exposed erythrocytes (16). This suggests that the toxic effects of CO result from the global impact of CO inhibition on oxygen delivery as well as on the binding to cellular heme-containing proteins. In addition to Hb, CO binds to other heme-containing proteins, including myoglobin in heart and skeletal muscle, mitochondrial cytochrome c oxidase (COX; complex IV), and others (Figure 1).

Mitochondrial Inhibition and Free Radical Generation

CO inhibits mitochondrial respiration by binding the ferrous heme a_3 in the active site of COX, effectively shutting down oxidative phosphorylation, similar to the effects of cyanide and nitric oxide (NO) (16–21). COX has only a threefold preference for CO compared to O_2 (22, 23). Thus, due to competitive binding of O_2 and CO to COX, CO-mediated mitochondrial inhibition is greatest under hypoxic conditions (22, 23). With COX inhibited, oxidative phosphorylation slows down, decreasing ATP production in tissues, such as the brain or heart. Other complexes in the electron transport chain continue to shuttle electrons, generating superoxide, leading to further damage of cells and tissues (24) (Figure 1).

Platelet and Inflammatory Effects

Excess CO activates platelets by displacement of NO from platelet surface hemoproteins (25). Displaced free NO can react with superoxide to produce peroxynitrite, further inhibiting mitochondrial function and increasing platelet activation (25–29). Activated platelets can stimulate neutrophils (26, 30) to degranulate and release myeloperoxidase (MPO) (27). MPO amplifies the inflammatory effects by triggering more neutrophil activation, adhesion, and degranulation (27) (Figure 2). Proteases from the neutrophils have been proposed to oxidize endothelial cell xanthine dehydrogenase to xanthine oxidase, generating reactive oxygen species (ROS) (27). MPO and ROS will catalyze lipid peroxidation, forming adducts with myelin basic protein that trigger lymphocyte response and microglia activation (28, 31). Indeed, a study of cerebrospinal fluid of CO-poisoned patients who suffered delayed neurological sequelae demonstrated increased levels of myelin basic protein than those without severe symptoms 1 month after initial poisoning (32). These inflammatory effects are ongoing long after the initial CO poisoning, and are possibly independent of COHb level (27, 32). The

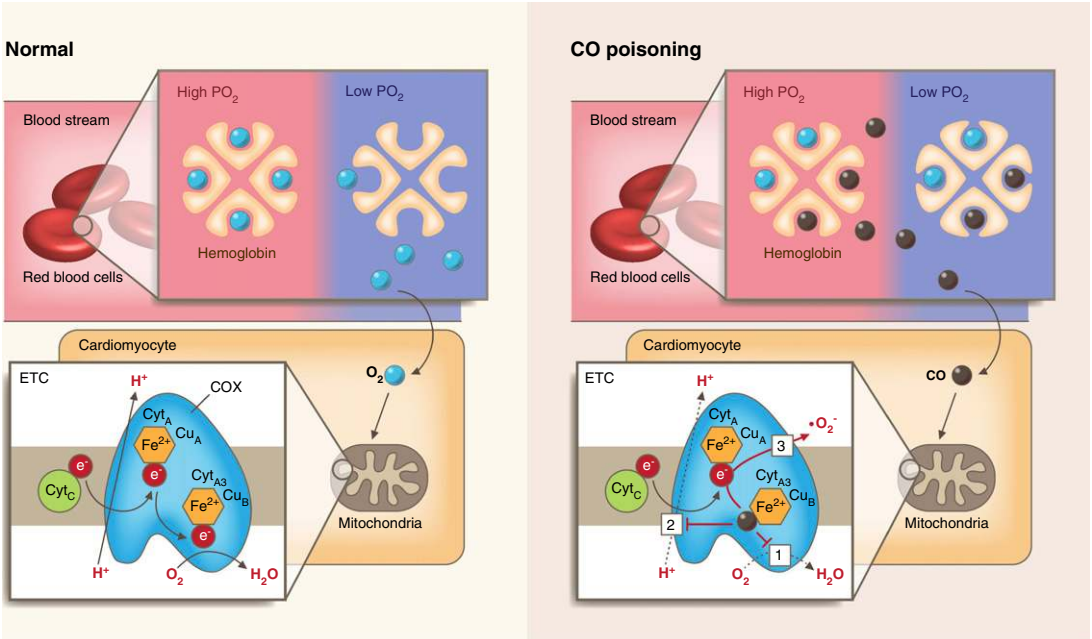

Figure 1. Hemoglobin (Hb) and mitochondrial effects of CO. Normal: Hb binds oxygen and delivers it to peripheral tissue with low PO_2. Reduced cytochrome c (Cyt_c) transfers its electron (e^-) to cytochrome c oxidase (COX) subunit 1 (Cyt_A: binuclear center with heme *a* and copper [Cu_A]). The electron reduces oxygen (O_2) at subunit 2 (Cyt_{A3}: binuclear center with heme *a3* and copper [Cu_B]), forming water and transporting a proton (H^+) through the inner mitochondrial membrane. CO toxicity: CO competitively binds to Hb with O_2, reducing total oxygen carrying capacity by: (*1*) preferentially binding to CO instead of O_2 (anemia-like effect); and (*2*) stabilizing the relaxed quaternary state of Hb, which binds to O_2 with higher affinity and will not release it in low PO_2 environment. CO binds competitively with O_2 at the reduced heme *a3* in subunit 2. This causes: (*1*) inhibition of the reduction of O_2 to water (the end destination of electrons in the electron transport chain); (*2*) cessation of the transfer of H^+ into the intermembrane space, shutting down ATP generation through ATP synthase; and (*3*) accumulation of electrons entering the electron transport chain through complexes I and III, which can produce superoxide, leading to deleterious effects. ETC = electron transport chain.

inflammatory cascade driven by NO and ROS contributes to neurological and cardiac injuries from CO poisoning (Figure 2) (27).

Heme Release and Local Tissue CO Levels

Exogenous CO exposure can also induce CO production in tissues via heme-dependent induction of heme oxygenase (HO)-1. CO exposure rapidly increases brain cytosolic heme levels through three mechanisms: (*1*) alteration in heme synthesis, a process that is regulated by CO; (*2*) release of heme from damaged cellular proteins; and (*3*) disturbance in mitochondrial heme storage by CO (33). Heme-induced stress up-regulates HO-1 within 6–24 hours after CO exposure. Beyond causing increased oxidative stress and cellular inflammation, free heme sustains local CO levels when it is metabolized by HO-1 into biliverdin, iron, and CO (34–36), further contributing to CO production (Figure 2) (33). CO levels in rat brain tissue can remain persistently elevated up to 2 hours after CO exposure, likely from endogenous, HO-1–dependent CO synthesis (33) (Figure 2).

Mechanisms of Brain Ischemia

CO-mediated reductions in oxygen delivery and mitochondrial oxidative phosphorylation produce ischemic and anoxic brain injury, leading to cognitive deficits in survivors (37). Brain injury from ischemia can occur from excitotoxicity, acidosis, ionic imbalance and depolarization, oxidative stress, nitrative stress, inflammation, and apoptosis (38). A large intracellular influx of calcium due to the inactivation of plasma membrane Ca^{2+} ATPase arising from decreased oxidative phosphorylation and reduced ATP synthesis enhances brain injury (38). Decreases in ATP activate intracellular proteases and lipases that cause mitochondrial membrane depolarization, cell death, and neurotransmitter release, specifically glutamate (38, 39). Increased glutamate release and hydroxyl radical generation, responsible for ischemic brain injury, have been observed during and immediately after CO hypoxia in rats (40). Glutamate activates *N*-methyl-D-aspartate receptors, enhancing cellular dysfunction and apoptosis (38). *N*-methyl-D-aspartate antagonists have shown to ameliorate CO-mediated neurodegeneration in mice (41) (Figure 2).

Diagnosis and Clinical Manifestations

CO poisoning is ideally diagnosed by a clinical triad: (*1*) symptoms consistent with CO poisoning; (*2*) history of recent CO exposure; and (*3*) elevated COHb levels (12). These criteria are not strict; caution should be given to not eliminating cases of potential chronic lower-level CO poisoning (11, 42). In ambiguous presentations, ambient CO air levels can be helpful, as can knowledge of potential sources of CO poisoning (faulty furnaces, etc.). Symptoms most commonly include headache, dizziness, fatigue, nausea/vomiting, altered mentation, chest pain, shortness of breath, and loss of consciousness (12). Many patients are found unconscious or severely ill, making history unobtainable. Emergency medical services are capable of measuring environmental CO levels to

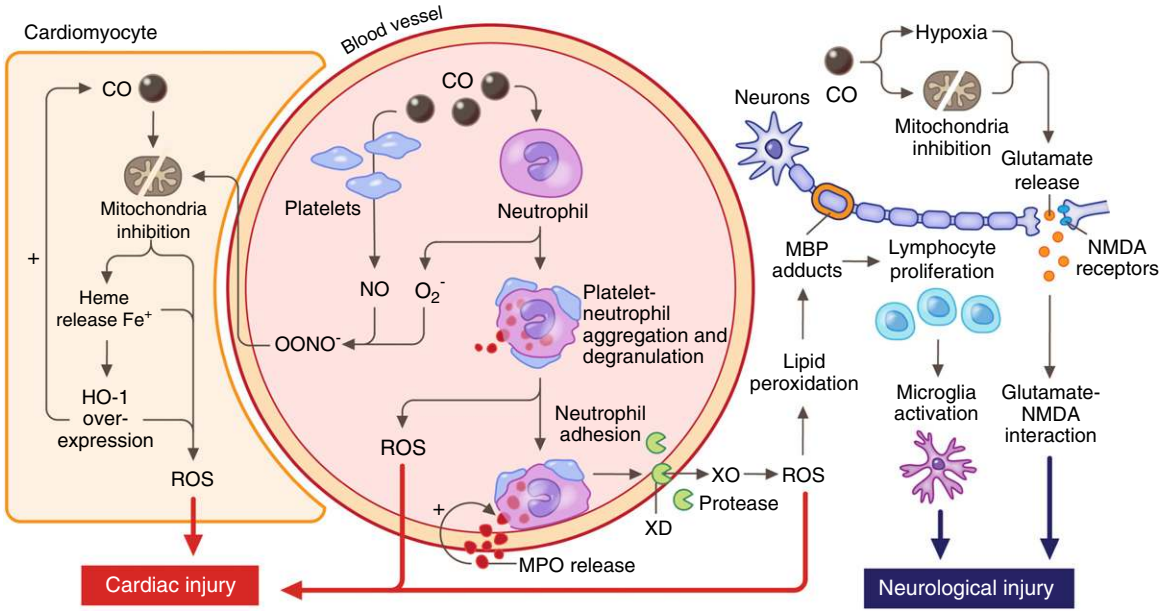

Figure 2. Inflammatory mechanisms of CO toxicity. CO activates platelets by displacing platelet nitric oxide (NO) from surface hemoproteins. NO reacts with oxygen free radicals (O_2^-) to produce peroxynitrite ($ONOO^-$), which inhibits mitochondrial function and activates platelets and neutrophils itself. Inhibition of mitochondria leads to further production of reactive oxygen species (ROS) and causes release of free heme and ensuing increase of heme oxygenase (HO)-1, further causing oxidative stress. HO-1 metabolizes free heme to produce more endogenous CO, creating a positive-feedback loop locally. Activated neutrophils will degranulate and release myeloperoxidase (MPO), causing more neutrophil activation, as well as adhesion. Proteases released from neutrophils can oxidize endothelial cell xanthine dehydrogenase (XD) to xanthine oxidase (XO), generating ROS, causing cellular damage as well as lipid peroxidation, specifically on myelin basic protein (MBP). When peroxidated, MBP forms adducts that cause lymphocyte proliferation, microglia activation, and, ultimately, neurologic injury. The general effects of hypoxia and the effect of CO toxicity directly on mitochondria cause glutamate release, which activates *N*-methyl-D-aspartate (NMDA) receptors, further leading to neurologic injury.

provide evidence of exposure. Measurement of elevated COHb levels in blood should serve as a confirmation of diagnosis due to suspected exposure (12). Although the diagnosis is more difficult, chronic lower-level CO exposure is associated with decreased cognitive function and neurological issues (11, 42, 43). More unique symptoms of chronic CO exposure include chronic fatigue, vertigo, paraesthesias, polycythemia, abdominal pain, diarrhea, and recurrent infections (29, 42).

Conventional pulse oximetry cannot distinguish between COHb and oxyHb, and, as such, can miss significant COHb levels and profound hypoxia (44). Pulse CO oximetry, available since 2005, can measure multiple species of Hb (COHb and methemoglobin) by using readings at eight wavelengths of light instead of the two wavelengths used by standard oximetry, which can measure only deoxyHb and oxyHb. Pulse CO oximetry provides fingertip measurement on the scene of injury (45) that has been shown to reduce the delay of patients receiving hyperbaric oxygen (HBO_2) (46). Unfortunately, it is still unclear if the accuracy of pulse CO oximetry alone compared with COHb measured by spectrophotometry from laboratory CO oximeter is adequate, and thus, pulse CO oximetry levels should be confirmed with laboratory measurements (12, 46) (47). A prospective study on the performance of pulse CO oximetry showed that normal COHb pulse CO oximetry values cannot rule out CO poisoning (47).

Clinical Manifestations

Critical illness. Some patients are critically ill, and thus, specialized intensive and supportive care is necessary. Severe acute CO poisoning is characterized by cognitive dysfunction that can progress rapidly with progressive brain injury and edema (29). Characteristics associated with high short-term mortality are pH values less than 7.20, fire as a source of CO, loss of consciousness, high COHb level, and need for endotracheal intubation during HBO_2 therapy (14).

Cardiovascular effects. CO poisoning can cause profound cardiovascular effects. Up to one-third of patients with moderate to severe CO poisoning present with myocardial injury, which may be associated with increased long-term mortality (48–50). Higher levels of COHb are associated with both acute and long-term development of myocardial infarction (51). In one study, over half of CO-poisoned patients who were deemed eligible for HBO_2 due to CO poisoning were found with reduced left ventricular function (52).

Numerous mechanisms may play a role in myocardial ischemia and cardiac dysfunction in CO poisoning. In animal studies, decreased systemic oxygen delivery from CO poisoning is initially compensated by increased cardiac output and oxygen extraction, until these compensatory mechanisms are ultimately overwhelmed, leading to cardiovascular collapse (53). The decreased oxygen delivery, increased global O_2 demand, and increased myocardial contractility from CO poisoning, can trigger myocardial infarction in patients with underlying coronary artery disease (48). Environmental air studies have shown that CO and other air pollutants increase the risk for arterial and venous thrombosis (49). Global endothelial dysfunction from CO and increased free radical production has been proposed to increase coronary vasoconstriction (49). CO at toxic levels can increase thrombosis, likely due to CO binding to fibrinogen-bound heme and increased platelet aggregation (48). CO increases inducible NO synthase expression, which mediates NO-induced myocardial damage during ischemia–reperfusion (54) The inhibition of oxidative phosphorylation and the direct binding of CO to myoglobin (which has a 60-fold greater affinity for CO than oxygen) in myocytes causes cardiac dysfunction and myocardial infarction even in the absence of underlying coronary disease (49, 55). CO-induced mitochondrial inhibition could cause a stunned myocardium–like syndrome (with hypokinesia in the setting of unobstructed coronary arteries) (56).

CO poisoning increases risk of developing an arrhythmia (57). Inhibition of oxidative phosphorylation and reduced ATP availability alter calcium gradients, leading to increased calcium sensitivity of myofilaments, increased diastolic intracellular calcium, and a hyperadrenergic state (57). The most common electrophysiology disturbance from CO appears to be disruption of repolarization and prolongation of the QT interval (58, 59). In a study on ventricular myocytes, CO increased the late component of the inward sodium current by increasing NO levels, leading to the S-nitrosylation of the myocardial voltage-gated sodium channel, Nav1.5. The increased late sodium current mediated by CO was proarrhythmic (59). L-NAME, an NO synthase inhibitor, and ranolazine, a Nav1.5 channel inhibitor, blocked these proarrhythmic effects and reduced corrected QT interval prolongation (59).

Neurological and affective sequelae. Survivors of CO poisoning suffer from long-term neurocognitive sequelae related to brain injury (12, 15). Symptoms include impaired memory, cognitive dysfunction, depression, anxiety, and/or vestibular and motor deficits (12, 15). These deficits are evident by 6 weeks, with studies showing a greater than 40% incidence of depression, anxiety, and cognitive dysfunction (15). Although patients can improve over many months, and even up to 1 year, at 6 years after CO poisoning, studies show patients still exhibited a 19% incidence of cognitive deficits and a 37% incidence of neurologic deficits (15, 60, 61). At 33 years after a mining accident involving 156 patients with CO poisoning, intellectual disturbances were found in 68.6% and neurologic symptoms were found in 48.7%, illustrating the irreversible nature of these deficits (62). Risk factors for 6-week cognitive impairment include an age of 36 years or greater and longer duration of CO exposure ($\geq$24 h) (63). The severity of initial symptoms does not necessarily correlate with the development of longer-term neurological issues (64). Low-level, chronic exposure can also lead to neurological and cognitive deficits that do not resolve after removal from the CO source, suggesting neurological damage even at low levels of COHb and environmental CO (11, 42, 43).

Imaging findings in CO-poisoned patients. As altered mentation is a common presenting symptom of CO poisoning, many patients may receive head computed tomography (CT) or magnetic resonance imaging (MRI). The most common MRI findings are generally white matter hyperintensities (WMHs) and hippocampal atrophy (65, 66). Although the metabolically active, ischemia-sensitive globus pallidus can be involved, it is not the most common site of abnormalities (65, 67). A prospective study of 73 CO-poisoned patients found that 12% of patients had WMHs, particularly in the periventricular area (66). WMHs in the centrum semiovale

were associated with cognitive impairments (66). The thalamus, putamen, and caudate nucleus can also be affected acutely, appearing as asymmetric hyperintense foci in T2-weighted and fluid-attenuated inversion recovery images (68, 69). CT scans can show bilateral symmetric hypoattenuation (68, 69). In very severe cases of CO poisoning, the more ischemia-resistant posterior structures, such as the brainstem and cerebellum, are also affected (68, 69).

Delayed posthypoxic leukoencephalopathy (DPHL) can develop days to weeks after a recovery from prolonged cardiac arrest or severe hemorrhagic shock (70). In the setting of CO poisoning, DPHL is thought to be caused by direct myelinotoxicity from impaired cellular respiration, again secondary to the inhibition of aerobic respiration by CO binding to COX (70). The MRI findings of DPHL show diffuse cerebral WMH, particularly in the centrum semiovale, on T2-weighted images, and are seen in CO poisoning (70).

A late imaging finding is diffuse brain atrophy, due to neuronal necrosis and apoptosis (67). This appears as sulcal widening or increased ventricular size in disproportion to patient age on MRI and CT (71). These changes are found in both patients with and without long-term neurocognitive deficits (71). White matter demyelination is thought to be one cause of delayed neurocognitive deficits, and, in the chronic setting, there is decreased signal on T1-weighted images and increased signal on T2-weighted images, most commonly in the periventricular white matter and centrum semiovale (71). In more severe poisoning, these changes can also occur in the subcortical white matter, corpus callosum, and internal and external capsules (71). In a long-term follow-up study 33 years after a large CO poisoning mining accident, 129 had an MRI in which 72.0% had cerebral atrophy, 37.9% had pallidum lesions, and 52.7% had lacunar infarctions (62).

Management

Current therapy for CO poisoning is 100% normobaric oxygen (NBO_2) or HBO_2 (2.5–3 atmospheres) (72, 73). NBO_2 and HBO_2 remove CO at a faster rate from the blood by increasing the partial pressure of oxygen, which increases the dissociation rate of CO from Hb (12, 74–76). NBO_2 reduces the elimination half-life of CO from 320 minutes in room air to 74 minutes (12, 74, 77) (Figure 3). HBO_2 can reduce the half-life of COHb to 20 minutes (55, 78); however, in actual clinical practice, the half-life may be higher, up to 42 minutes (79). HBO_2 has demonstrated a reversal effect on inflammation and mitochondrial dysfunction induced by CO poisoning (31, 80, 81).

Almost all patients receive NBO_2 upon rescue or arrival to the emergency department. There is often significant delay in delivery of HBO_2 between diagnosis in the field, transportation to a hyperbaric therapy center, and actual treatment (12, 14, 29, 60, 82).

There have been several randomized controlled studies evaluating the benefit of HBO_2 versus NBO_2 (82–89) (Table 1). A metaanalysis of seven randomized control trials, with a total of 1,361 participants (90), did not reveal an overall benefit from HBO_2 (the odds ratio for neurological deficits was 0.78, with a 95% confidence interval of 0.54–1.12); however, these trials were very heterogeneous. The outcome measures are difficult to compare in a metaanalysis study. Three studies used only 2.0 atmospheres for HBO_2, which is not considered adequate for CO poisoning (72, 73). Only one looked at neurocognitive outcomes greater than 1 month after poisoning, despite the observed potential of neurological sequelae to improve over months to 1 year after poisoning (61, 82). The only study to meet all Consolidated Standards of Reporting Trials criteria and measure 1-year outcome was the Weaver and colleagues trial (82, 91). This study did show a significant improvement in long-term neurocognitive dysfunction, and should be weighed most heavily in judging the effectiveness of HBO_2 (82).

Although the American College of Emergency Physicians acknowledges HBO_2 as a therapeutic option for CO poisoning, it does not mandate HBO_2 use (92). Recent practice recommendations by experts in the hyperbaric medicine field, however, do recommend HBO_2 use for CO poisoning (12). HBO_2 should be considered for all cases of serious acute CO poisoning, including loss of consciousness, ischemic cardiac changes, neurological deficits, significant metabolic acidosis, or COHb greater than 25% (12). Despite clear effectiveness of HBO_2, there still does exist a substantial portion of survivors with permanent neurocognitive and affective sequelae (estimated 10,000–20,000 new cases per year depending on HBO_2 utilization), illustrating the need for research on new therapies (12, 63, 76, 82).

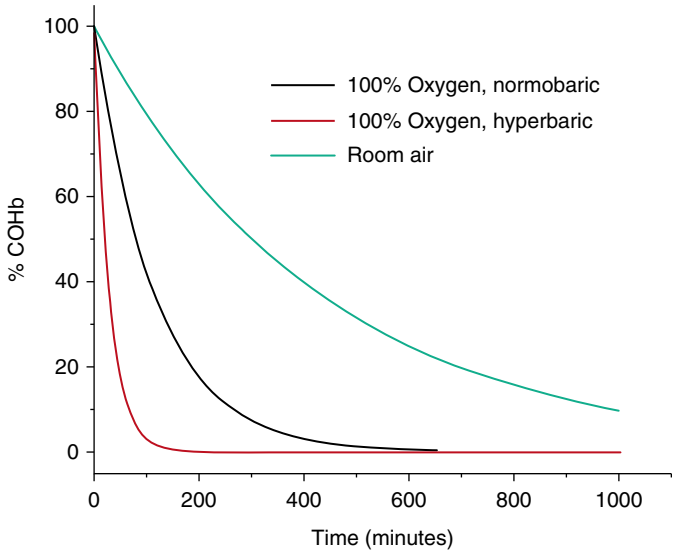

Figure 3. Decay of the carboxyhemoglobin (COHb) species under therapeutic treatments. Half-life values of COHb in room air (320 min), 100% normobaric oxygen (74 min), and 100% hyperbaric oxygen (HBO_2; 20 min) determined from Refs. 12, 74, 75, 77–79.

Fire-related and Intentional Poisonings

Between 50 and 75% of fire-related injuries likely have some component of CO

Table 1. Hyperbaric Oxygen Trials versus Control Shows Mixed Evidence of Benefit

Reference No.	Intervention	Reference	Evaluation	Events		Benefit
				Treated	Control	
83	No LOC: HBO_2 (2.0 ATA) × 60 min	NBO_2 6 h	Neurologic symptoms at 1 mo	51/159	50/158	N
	LOC: 2× HBO_2 (2.0 ATA) × 90 min	1× HBO_2 (2.0 ATA) × 90 m				
84	HBO_2 (2.8 ATA) × 30 min then (2.0 ATA) × 90 min	NBO_2 until asymptomatic	Delayed neurologic sequelae 4 wk follow-up	0/30	7/30	Y
85	HBO_2 (2.5 ATA) × 90 min	12 h NBO_2	1 mo persistent neurologic symptoms	69/299	73/276	N
86	HBO_2 (2.8 ATA) × 100 min × 3–6 d	NBO_2 × 100 min sham for 3–6 d	Neuropsychologic testing 1 mo	34/52	20/34	N
82	HBO_2 1× (3 ATA × 1 h; 2 ATA × 1 h) then 2× (2 ATA) × 90 min	NBO_2 sham treatment	Cognitive sequelae at 6 wk, 6 mo, and 1 yr	19/76	35/76	Y
87	HBO_2 (2.0 ATA) × 60 m, NBO_2 × 4 h	NBO_2 6 h	Neurologic assessment 1 mo	29/74	33/79	N
88	LOC: HBO_2 (2.0 ATA) × 1 h + 4 h NBO_2	NBO_2 6 h	1 mo questionnaire + physical exam	33/93	29/86	N
	Coma: 2× HBO_2 (2.0 ATA) 1x h + 4 h NBO_2	1× HBO_2 + 4h NBO_2		42/105	25/101	N
89	HBO_2 (2.5 ATA) x2 h + 10 h NBO_2	NBO_2 × 12 h	3 wk EEG impairments or not	0/8	6/10	Y

Definition of abbreviations: ATA = atmospheres; HBO_2 = hyperbaric oxygen; LOC = loss of consciousness; N = no; NBO_2 = normobaric oxygen; Y = yes. A metaanalysis (90) concluded that there is no clear benefit to HBO_2 in terms of delayed neurologic sequelae; however, with the significant heterogeneity in outcome measures and the treatments themselves, it is difficult to draw conclusions from metaanalyses on HBO_2.

poisoning (9). In house fires, CO poisoning is commonly associated with cyanide poisoning, and these patients should be empirically treated for cyanide poisoning (12, 93). In the United States, almost 15,000 cases of CO poisoning are intentional each year. Coingestion of other substances causing alteration of consciousness must also be considered when assessing those with intentional poisoning, in whom up to 40% have a coingestion (5). Intentional poisonings with the intent for self-harm necessitate psychiatric referral (12).

Long-Term Consequences and Follow-Up

Survivors of acute CO poisoning exhibit a near doubling of long-term mortality when compared with a standard population (94). This is more pronounced in those who had an intentional exposure than those with an accidental exposure (94). Major causes of death include alcoholism, motor vehicle accidents, other accidents, and intentional self-harm, suggesting underlying neurological or psychiatric complications (5). The quality of life for survivors is severely affected; one study looking at patients 51 days after poisoning found lower cognitive performance, more depression, and more posttraumatic stress disorder (95). Follow-up is recommended within 1–2 months of poisoning to assess the development of neurocognitive deficits, depression, or anxiety, and, if present, this requires referral for neurocognitive evaluation (12). Additional care and attention should be given to standard medical issues as well, with the increased risk of myocardial infarction (51). More research should be performed on the long-term follow-up of patients with CO poisoning, as there are clear long-term consequences to survivors.

Future Directions

Prevention

With still substantial morbidity from CO poisoning, despite effective HBO_2 therapy, interventions have been directed at CO poisoning prevention through public health campaigns (96). "The Invisible Killer" campaign by the U.S. Consumer Product Safety Commission aims to educate the public on symptoms of CO poisoning, sources of CO poisoning, and preventive measures to reduce CO exposure (97). Both the U.S. Centers for Disease Control and Prevention and the U.S. Consumer Product Safety Commission currently recommend placement of a CO alarm in every home (97, 98). Unfortunately, there is no study demonstrating the efficacy of CO alarms for reducing either morbidity or mortality. The catalytic converter has reduced CO emissions by automobiles by 75% since its 1975 introduction, and decreased unintentional motor vehicle–related CO death rates by greater than 80% (6). All of these measures can reduce the incidence of serious exposure, yet there have been no recent new options for therapy.

Nonpharmacologic Options

Several nonpharmacological treatments for CO poisoning have been tested, using the removal of CO from the blood stream through CO dissociation from Hb (Figure 4). Although none has demonstrated improved neuorocognitive outcomes, many show promising early results and should be further studied. At the turn of the 20th century, CO poisoning was treated with high concentration of O_2 in combination with CO_2, based on ideas that CO poisoning created a total body deficit of CO_2 (99). Early animal studies showed that the addition of CO_2 to O_2

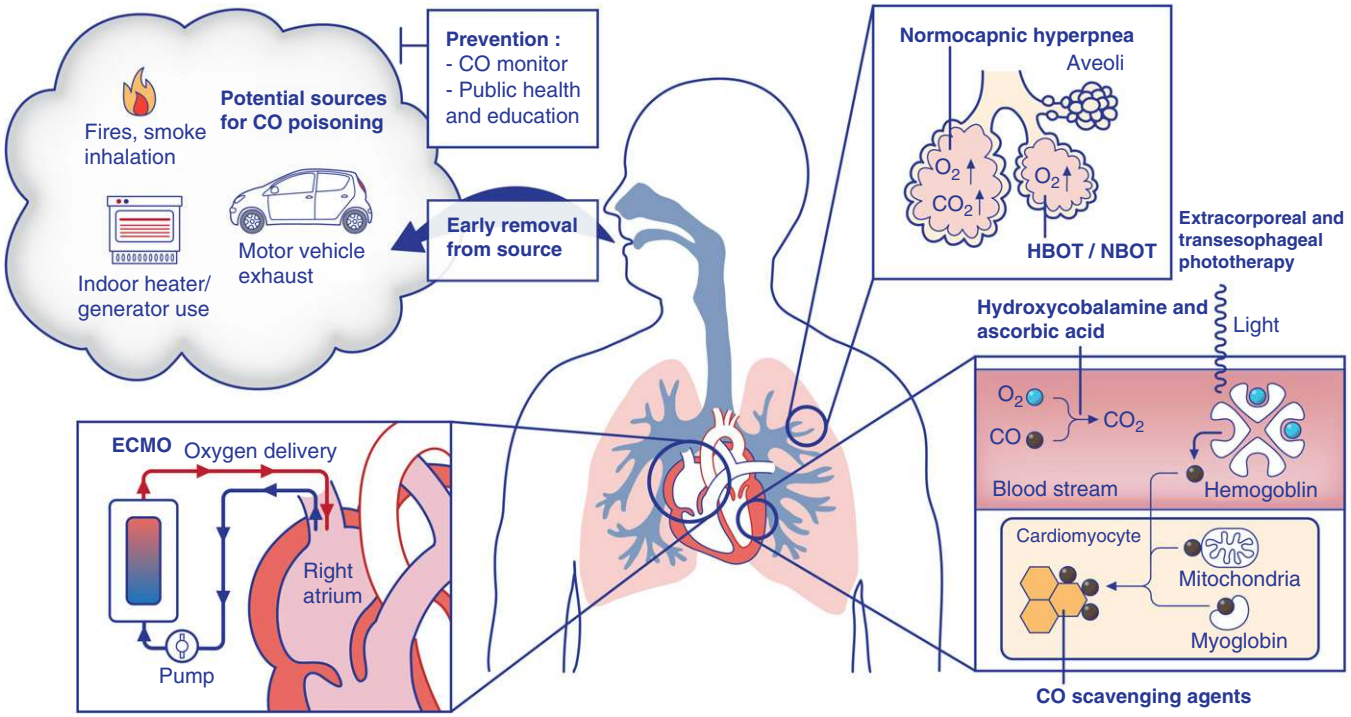

Figure 4. Current and future therapeutic targets of CO poisoning. Prevention and early removal from the CO-poisoned environments are tenants to current management. Hyperbaric oxygen therapy (HBOT) and normobaric oxygen therapy (NBOT) increase the partial pressure of oxygen in the alveoli, increasing the rate of CO dissociation from hemoglobin (Hb; *see* Figure 3). Normocapnic hyperpnea increases ventilation through delivery of CO_2 in addition to increasing the partial pressure of O_2. Hydroxycobalamine and ascorbic acid increase the rate of CO conversion to carbon dioxide (CO_2). Extracorporeal membrane oxygenation (ECMO) supports blood pressure and gas exchange, delivering oxygen even in the setting of acute respiratory distress syndrome from inhalational injury. Phototherapy increases the dissociation of CO from Hb in the blood stream. Finally, CO-scavenging agents, such as porphyrine complexes or modified globin proteins, bind to CO from cellular heme proteins, and act as a "sink," removing CO from the body when excreted.

increased the dissociation of CO from Hb; however, this was due to the effect of increased ventilation from CO_2 and not from a total body deficit (99) (Figure 4). Fisher and colleagues (100, 101) have recently developed a method for normocapnic hyperpnea that allows for an increase in minute ventilation, and thus increased clearance of COHb, without harmful hypercapnia. This technique accelerates COHb elimination in dogs and humans, and is quite simply delivered (100, 101).

Other methods, although more invasive than NBO_2 or HBO_2, have been explored. In the setting of a house fire, a patient who had significant inhalational injury with acute respiratory distress syndrome, 40% COHb, refractory hypoxia, and shock, extracorporeal membrane oxygenation was able to provide immediate improvement in oxygenation, reduction of COHb, and reversal of cardiovascular collapse (102). The likely mechanism behind such improvement was the restoration of systemic oxygenation through immediately improved gas exchange with extracorporeal support (Figure 4) (89, 102). Another extracorporeal therapy, photodynamic blood illumination, was proposed as a way to dissociate CO from Hb in *ex vivo* blood exposed to an illuminator (Figure 4) (103). A recent study also used photodissociation in mouse models, achieved through both an open-chest model and transesophageal phototherapy, both of which reduced the COHb half-life in mouse blood (104, 105).

Pharmacologic Options

Ideally, a therapy could be provided immediately on site by emergency medical services, aided by portable CO oximetry to measure COHb, or in the emergency department. This could eliminate many pitfalls of current therapeutic interventions, improving portability, limiting treatment delays, and allowing for improved therapy in severely ill patients not able to tolerate HBO_2.

Roderique and colleagues (106) proposed using hydroxocobalamin and ascorbic acid to mediate conversion of CO to CO_2 (Figure 4). Although, in one study, this showed decreased Hb-CO half-life and decreased CO-induced brain hypoxia in rodents, the animals did not have improved cognitive performance (106).

Kitagishi and colleagues (107) have developed a cyclodextrin-encapsulated porphyrin complex that can bind CO with 100 times the affinity of Hb (Figure 4). When infused into rats in normal atmospheric conditions, it bound endogenously produced CO and was excreted into the urine (107). There are known toxic effects of cyclodextrin, such as nephrotoxicity, that could limit the use of such a strategy (108). Testing of this porphyrin complex in a CO poisoning model has not yet been reported.

A new class of modified globin proteins is currently in development, and has shown potential for the treatment of CO poisoning (109) (Figure 4). These agents have shown both *in vitro* and *in vivo* to have great affinity for CO (high k_{on} and low k_{off}),

Table 2. Alternative Strategies for Treating Carbon Monoxide Poisoning Targeting Downstream Effects

Agent (Ref. No.)	Species	Effect
Inflammation		
Allopurinol (110)	Rats	Reduced neuronal death, reduced expression of proinflammatory markers, and improved performance in Morris water maze
Corticosteroids plus amifostine (111)	Rats	Reduced lipid peroxides
Methylprednisolone plus memantine (112)	Humans	Case report: reversed delayed neurocognitive deficits that appeared at Week 3 by Week 12
Ketamine (113)	Rats	Reduced cerebral edema, blood lactate levels, and improved survival
Oxidative stress		
Hydrogen sulfide (114)	Rats	Improved cognitive function, reduced apoptosis and inflammatory response, decreased oxidative damage in brains
Fructose-1,6-diphosphate (115)	Mice	Reduced impairment of memory function, improved mortality
Magnesium sulfate (116)	Rats	Protective versus oxidative damage in cerebrum
Cardiac dysfunction		
Levosimendan (117)	Humans	Case report: improved ejection fraction in stunned myocardium
Atenolol (118)	Rats	Pretreatment associated with increased contraction band necrosis
Nimodipine (115)	Mice	Decreased impairment of memory function and improved mortality rate
Verapamil (113)	Rats	No improvement in survival, blood pressure, blood lactate, or cerebral edema

acting as scavengers for CO, increasing the elimination rate of CO from red blood cell Hb and tissues. By binding CO directly from heme-containing proteins, such as COX, there could also be greater effects on the non–Hb-CO manifestations of CO poisoning, such as mitochondrial poisoning, ischemia–reperfusion, and inflammation, that could ultimately improve neurocognitive or cardiovascular outcomes. Although still being tested in preclinical animal models, this emerging new concept of an antidotal therapy has potential.

Alternative Strategies

Methods to manage the downstream effects of CO poisoning versus directly removing CO have also been investigated, albeit never in dedicated trials in humans Table 2 (110–118). Therapies targeting inflammation and oxidative stress induced by CO poisoning may be effective.

Nodal blocking agents seem to have a mixed picture despite CO poisoning being proarrhythmic (113, 115, 118). Ionotropes can be used to support severe cardiac dysfunction with shock or hypotension. One study showed that levosimendan can reverse stunned myocardium (117). Although no one has studied empiric antiplatelet or anticoagulation in CO poisoning, this could be an area of further study, especially in high-risk patients (50, 119).

Therapies targeting the downstream effects of CO poisoning show some promise. More research into reversing or preventing the antiinflammatory damage, oxidative stress, or cardiac dysfunction induced by CO poisoning should be performed in the future.

Conclusions

CO poisoning is the most common human poisoning, with no available antidotal therapy. HBO_2 is an effective therapy, with the number needed to treat to prevent one case of likely permanent neurocognitive deficit of 5 (derived from the study by Weaver and colleagues [82]), and number needed to treat of 4 in patients older than 36 years (63, 82). Still, many survivors suffer long-term morbidity, and some have increased long-term mortality. The pathophysiology of CO poisoning involves the reduction of global oxygen delivery and the inhibition of mitochondrial respiration. Downstream effects relate to reperfusion injury and the induction of oxidative and inflammatory signaling pathways. Beyond public awareness and public safety efforts, which have been effective in prevention, there is an unmet clinical need for better therapies for the most common of human poisonings. Future developments may include nonpharmacologic therapies that enhance CO dissociation from Hb in red blood cells and pharmacologic antidotes that could potentially be given immediately on site, such as CO-scavenging molecules. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Elfy Chiang for her help with creating the images used in this manuscript.

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