ELSEVIER
SAUNDERS

Clin Lab Med 26 (2006) 99–125

CLINICS IN
LABORATORY
MEDICINE

Toxicity Associated with Carbon Monoxide

Louise W. Kao, MD[a,b,*], Kristine A. Nañagas, MD[a,b]

[a]*Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN, USA*
[b]*Medical Toxicology of Indiana, Indiana Poison Center, Indianapolis, IN, USA*

Carbon monoxide (CO) has been called a "great mimicker." The clinical presentations associated with CO toxicity may be diverse and nonspecific, including syncope, new-onset seizure, flu-like illness, headache, and chest pain. Unrecognized CO exposure may lead to significant morbidity and mortality. Even when the diagnosis is certain, appropriate therapy is widely debated.

Epidemiology and sources

CO is a colorless, odorless, nonirritating gas produced primarily by incomplete combustion of any carbonaceous fossil fuel. CO is the leading cause of poisoning mortality in the United States [1,2] and may be responsible for more than half of all fatal poisonings worldwide [3]. An estimated 5000 to 6000 people die in the United States each year as a result of CO exposure [2]. From 1968 to 1998, the Centers for Disease Control reported that non–fire-related CO poisoning caused or contributed to 116,703 deaths, 70.6% of which were due to motor vehicle exhaust and 29% of which were unintentional [4]. Although most accidental deaths are due to house fires and automobile exhaust, consumer products such as indoor heaters and stoves contribute to approximately 180 to 200 annual deaths [5]. Unintentional deaths peak in the winter months, when heating systems are being used and windows are closed [2].

Portions of this article were previously published in Holstege CP, Rusyniak DE: Medical Toxicology. 89:6, Med Clin North Am, 2005; with permission.

* Corresponding author. Department of Emergency Medicine, Indiana State University School of Medicine, 1701 North Senate Boulevard, Indianapolis, IN 46206.
E-mail address: lkao@clarian.org (L.W. Kao).

0272-2712/06/$ - see front matter
doi:10.1016/j.cll.2006.01.005 *labmed.theclinics.com*

Environmental CO exposure is typically less than 0.001%, or 10 ppm [6], but it may be higher in urban areas [7]. The amount of CO absorbed by the body is dependent on minute ventilation, duration of exposure, and concentrations of CO and oxygen in the environment [8–11]. After cooking with a gas stove, indoor air concentrations of CO may reach 100 ppm [7]. A cigarette smoker is exposed to an estimated 400 to 500 ppm of CO while actively smoking [3]. Automobile exhaust may contain as much as 10% (100,000 ppm) CO [12]. Exposure to 70 ppm may lead to carboxyhemoglobin (CO-Hgb) levels of 10% at equilibrium (approximately 4 hours) [1,13], and exposure to 350 ppm may lead to CO-Hgb levels of 40% at equilibrium [3,13]. The current Occupational Safety and Health Administration permissible limit for CO exposure in workers is 50 ppm averaged over an 8-hour work day [14].

In addition to the above sources, CO poisoning has been reported in children riding in the back of pickup trucks [15], recreational boaters [16,17], factory workers operating propane-powered forklifts [18–20], and persons in an ice skating rink using propane-powered resurfacing machines [21,22]. Fatalities are reported in the cases of recreational boaters swimming underneath the swim platform near the boat exhaust [23] and campers using gas-powered stoves in outdoor tents [24]. In the winter, misuse of a gas stove or burning charcoal briquettes for heating purposes is predictive of high CO-Hgb levels [25–27]. Another source is methylene chloride, a solvent found in paint remover and aerosol propellants, which is converted by the liver to CO after exposure [28–30].

Endogenous production of CO occurs during heme catabolism by heme oxygenase but should not produce CO-Hgb levels in excess of 1%. However, in hemolytic anemia, CO-Hgb may increase to 3% to 4% [12,31,32]. Severe sepsis has also been shown to elevate endogenous CO production [33].

A patient who presents from a house fire or after a suicide attempt with automobile exhaust may not represent a diagnostic dilemma. However, a family presenting with symptoms of nausea and vomiting or a patient with a headache that is improving can easily be misdiagnosed and discharged back to the dangerous environment where they may subsequently suffer more serious exposures.

Pathophysiology

Hemoglobin binding

The pathophysiology of CO poisoning was initially thought to be due exclusively to the cellular hypoxia imposed by replacing oxyhemoglobin with CO-Hgb and producing a relative anemia [34]. CO binds to hemoglobin with an affinity more than 200 times that of oxygen [8,35,36]. It causes a leftward shift in the oxygen–hemoglobin dissociation curve, decreasing oxygen delivery to the tissues and resulting in tissue hypoxia [36].

Direct cellular toxicity

CO poisoning is much more complex than was initially presumed, and it clearly has mechanisms of toxicity beyond the formation of CO-Hgb. In a classic study, Goldbaum and colleagues [37] demonstrated that dogs breathing 13% CO died within 1 hour after achieving CO-Hgb levels from 54% to 90%. However, exchange transfusion with blood containing 80% CO-Hgb to otherwise healthy dogs resulted in no toxic effects, despite resultant CO-Hgb levels of 57% to 64%, suggesting that CO toxicity is not dependent on CO-Hgb formation. Other studies have corroborated the findings of morbidity and mortality due to CO poisoning independent of hypoxia or CO-Hgb formation [38–42].

The current understanding of the pathophysiology of CO poisoning relates its clinical effects to a combination of hypoxia/ischemia due to CO-Hgb formation and direct CO toxicity at the cellular level. This combination helps to explain why CO-Hgb levels do not correlate with the severity of clinical effects [43–47]. An outline of some of the proposed mechanisms is presented in Fig. 1.

Protein binding (cytochromes, myoglobin, guanylyl cyclase)

CO binds to many heme-containing proteins other than hemoglobin, including cytochromes, myoglobin, and guanylyl cyclase. CO binds to cytochrome a3 in vitro [48,49], and the disruption of oxidative metabolism may lead to the generation of oxygen free radicals [50,51]. Cellular respiration may also be impaired by inactivation of mitochondrial enzymes and impaired electron transport from oxygen radicals (ie, peroxynitrite) produced after CO exposure [50,52,53]. Cellular energy metabolism is inhibited even after normalization of CO-Hgb levels [47,54], which may explain the prolonged clinical effects after CO-Hgb levels decrease [9]. Binding to myoglobin may reduce oxygen availability in the heart and lead to arrhythmias and cardiac dysfunction [9,55,56]; it may also contribute to direct skeletal muscle toxicity and rhabdomyolysis [57–60]. CO also stimulates guanylyl cyclase, which increases cyclic guanylyl monophosphate, resulting in cerebral vasodilatation, which has been associated with loss of consciousness in an animal model of CO poisoning [61,62].

Nitric oxide

The role of nitric oxide (NO) and other oxygen free radicals has been extensively researched in the setting of CO poisoning. Many animal studies have shown cerebral vasodilatation after exposure to CO, which is temporally associated with loss of consciousness and increased NO levels [63–66]. This evidence has led to speculation that, clinically, syncope may be related to NO-mediated cerebral vessel relaxation and low blood flow. NO is also a peripheral vasodilator [67] and may result in systemic hypotension, although this effect has not been studied in the setting of CO poisoning. However, the presence of

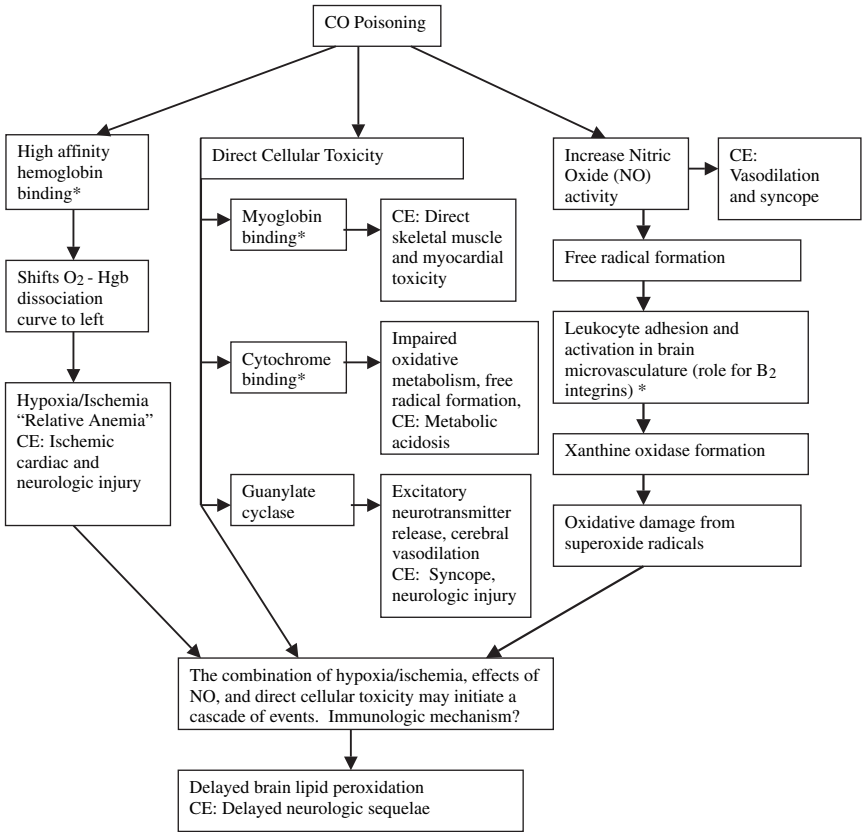

Fig. 1. Proposed pathophysiology of CO poisoning. *Potential hyperbaric oxygen therapy target. CE, clinical effect.

systemic hypotension in CO poisoning is correlated with the severity of cerebral lesions, particularly in watershed areas of perfusion (ie, basal ganglia, white matter, hippocampus) [9,46,68–71].

NO also appears to play a pivotal role in a cascade of events culminating in oxidative damage to the brain, which may be responsible for the clinical syndrome of delayed neurologic sequelae (DNS) [72]. NO may affect the adherence of neutrophils to the endothelium, potentially by affecting the function of neutrophil adhesion molecules such as B_2-integrin [52,72]. Neutrophil adherence to the microvasculature appears to lead to xanthine oxidase activation, oxidative radical formation, oxidative damage, and ultimately to brain lipid peroxidation, which is thought to be the underlying process responsible for the clinical syndrome of DNS [50,52,66,72–76].

Brain lipid peroxidation after CO exposure appears to be a postischemic reperfusion phenomenon, mediated by alterations in cerebral blood flow as well as oxidative free radical damage [50,51,66,73,76–78]. A period of

hypotension and unconsciousness may be required for lipid peroxidation to occur [76]. Although the exact sequence of events is not known, the experimental administration of nitric oxide synthase inhibitors has been found to inhibit both cerebral vasodilatation [41] and oxidative damage [66]. Newer research has postulated an immune-mediated mechanism of DNS. Rats made immunologically tolerant to myelin basic protein (MBP) before CO poisoning did not suffer learning decrements, nor did they exhibit the typical degree of brain histologic changes seen in rats that were not immunologically tolerant. The authors hypothesize that CO poisoning induces biochemical and antigenic changes in MBP, which may react with products of lipid peroxidation to produce an immunologic cascade [79].

Other potential mechanisms of CO toxicity include excitotoxicity (ie, glutamate-mediated neuronal injury) [80–82], increased atherogenesis [83,84], involvement with cytochrome p450 [9,85], and apoptosis [80]. Further research is likely to continue to elucidate the complex pathophysiology of CO poisoning.

Clinical effects: acute

The clinical effects of CO poisoning are diverse and easily confused with other illnesses, such as nonspecific viral illness, benign headache, and various cardiovascular and neurologic syndromes [6,25,86–88]. Box 1 lists common signs and symptoms reported in the literature [1,6,89].

Initial symptoms after CO exposure include headache, nausea, and dizziness [90,91]. As exposure increases, patients develop more pronounced and severe symptoms, with oxygen-dependent organs (the brain and the heart) showing the earliest signs of injury.

Early neurologic manifestations include dizziness and headache. Increasing exposure may produce altered mental status, confusion, syncope, seizure, acute stroke-like syndromes, and coma. Isolated seizures have been reported in pediatric patients [92,93]. Abnormalities on neuroimaging studies, particularly bilateral globus pallidus lesions, are often seen in significant CO poisoning [94–97]. The presence of systemic hypotension in CO poisoning is correlated with the severity of central nervous system structural damage [9,46,68–71].

Early cardiovascular effects of CO poisoning are manifested by tachycardia in response to hypoxia [98]. More significant exposures result in hypotension, dysrhythmia, ischemia, infarction, and, in extreme cases, cardiac arrest. Early deaths after CO exposure may be due to cardiac dysrhythmias [45,50]. Hypotension may result from myocardial injury due to hypoxia/ischemia, direct myocardial depressant activity from myoglobin binding, peripheral vasodilatation, or a combination of these factors [78]. It may persist even after neurologic and metabolic symptoms have resolved [99].

CO poisoning exacerbates underlying cardiovascular disease, making this group of patients particularly susceptible to cardiovascular disturbances

Box 1. Clinical signs and symptoms associated with carbon monoxide poisoning

Mild
- Headache
- Nausea
- Vomiting
- Dizziness
- Blurred vision

Moderate
- Confusion
- Syncope
- Chest pain
- Dyspnea
- Weakness
- Tachycardia
- Tachypnea
- Rhabdomyolysis

Severe
- Palpitations
- Dysrhythmias
- Hypotension
- Myocardial ischemia
- Cardiac arrest
- Respiratory arrest
- Noncardiogenic pulmonary edema
- Seizures
- Coma

Data from Cobb N, Etzel RA. Unintentional carbon monoxide-related deaths in the United States, 1979 through 1988. JAMA 1991;266(5):659–63; and Forbes WH, Sargent F, Roughton FJW. The rate of carbon monoxide uptake by normal men. Am J Physiol 1945;143(4):594–608.

[100,101]. Low-level experimental CO exposures producing CO-Hgb levels from 2% to 6% in patients who had documented coronary artery disease have produced dysrhythmias and decreased latency to the development of cardiac ischemia during stress testing [102–104]. CO exposure lowers the threshold for malignant ventricular dysrhythmias [55]. In patients with undiagnosed underlying coronary artery disease, CO exposure may act as a stress test, much like anemia. Even in healthy volunteers, CO exposure has been found to result in nonspecific ECG changes [91]. Myocardial infarction has been reported in CO poisoning in the absence of underlying coronary disease [105].

CO poisoning may also result in rhabdomyolysis and acute renal failure, potentially as a direct toxic effect of CO on skeletal muscle [57–59]. Cutaneous blisters [106] and noncardiogenic pulmonary edema [107–109] have been reported in patients with severe CO poisoning. The ''cherry red'' skin color often discussed in textbooks is not commonly seen in practice [6,50,107].

CO binds more tightly to fetal than adult hemoglobin, making infants particularly vulnerable to its effects [110]. Occult CO poisoning may present as an acute life-threatening event in the infant [111]. Even older pediatric patients are more susceptible to the effects of CO because of their higher metabolic rate and oxygen uptake [112,113]. Symptoms in pediatric patients are often nonspecific, such as nausea and vomiting, and may easily be misdiagnosed as a viral illness [88,111]. An increased incidence of syncope and lethargy is reported in the pediatric population compared with adults [112].

CO exposure in the pregnant patient presents a unique scenario. CO crosses the placenta readily, and animal studies have shown that, with maternal CO exposure, fetal CO-Hgb levels reach a higher peak and eliminate more slowly than maternal CO-Hgb [114,115]. In humans, adverse fetal outcomes, such as stillbirth, anatomic malformations, and neurologic disability, are clearly associated with more severe maternal exposure [116–119]. However, even in mildly symptomatic mothers, the effects on the fetus may be severe, including anatomic malformations and fetal demise [117,120]. When autopsy is performed, fetal brain damage is generally apparent, particularly in the basal ganglia and globus pallidus [116,121]. Earlier gestational age of the fetus during CO exposure has been associated with anatomic malformations, whereas functional disturbances and poor neurologic development are reported after CO exposure at any gestational age [116,117,122,123].

Clinical effects: delayed

The effects of CO are not confined to the period immediately after exposure. Persistent or delayed neurologic effects have also been reported. Most intriguing is a syndrome of apparent recovery from acute CO poisoning followed by behavioral and neurologic deterioration after a latency period of 2 to 40 days. This syndrome, often referred to as DNS, may manifest as almost any conceivable neurologic or psychiatric symptom, including memory loss, confusion, ataxia, seizures, urinary and fecal incontinence, emotional lability, disorientation, hallucinations, parkinsonism, mutism, cortical blindness, psychosis, and gait and other motor disturbances [100,124–128].

The true prevalence of DNS is difficult to determine, with estimates ranging from less than 1% to 47% of patients after CO poisoning [44,108,125–127,129–131]. The large variability in prevalence is at least partially explained by a lack of consistency in defining DNS using clinical, subclinical (eg, neuropsychometric testing results), self-reported, or combination criteria.

The two largest case series are from Korea, where CO poisoning is common because of the use of coal stoves for cooking and heating [125,126]. Of 2360 victims of acute CO poisoning, DNS were diagnosed in 65 patients. Symptoms included mental deterioration, memory impairment, gait disturbance, urinary and fecal incontinence, and mutism. The rate of DNS in this series was 2.75% of all CO-poisoned patients and 11.8% of the subset of hospitalized patients. The lucid interval between recovery from the initial exposure and development of DNS was 2 to 40 days (mean 22.4 days). Of those patients who were followed, 75% recovered within 1 year. The incidence of DNS increased with the duration of unconsciousness experienced by the patient and with age greater than 30 [126]. Another large series reporting on 2967 patients who had CO poisoning had findings almost identical to the cohort already described. More than 90% of patients who developed DNS in this series were unconscious during the acute intoxication, and the incidence of DNS was disproportionally higher in older patients (50–79 years) and nonexistent in patients less than 30 years of age [125].

In general, patients who present with a more symptomatic initial clinical picture are the most likely to develop persistent or delayed neurologic sequelae. DNS occurs most frequently in patients who present comatose, in older patients, and perhaps in those with a prolonged exposure [19,44,125,126,129,131–134]. Neuropsychometric testing abnormalities have been associated with decreased level of consciousness at presentation, particularly when the duration of unconsciousness exceeds 5 minutes [129,133].

Various definitions of DNS are used by investigators; the term may refer to clinical symptoms, neuropsychometric test abnormalities, or a combination of the two. Although using gross neurologic abnormalities to define DNS may underestimate subtle cognitive dysfunction, neuropsychometric testing may reveal subclinical and perhaps temporary cognitive dysfunction of unknown clinical and prognostic significance. Abnormalities found on neuropsychometric testing in CO-exposed patients may be partially explained by confounders. Patients who are acutely ill, suicidal, depressed, or have coingestion of other intoxicants may perform poorly on these tests [135–138]. In addition, these patients generally do not have a baseline for comparison [9,139]. Despite these limitations, neuropsychometric testing provides an objective measure of cognitive function that can be used to screen and follow CO-poisoned patients.

Clinical effects: chronic

Although some authors have hypothesized that chronic CO poisoning may be more pervasive and cause more morbidity and mortality than is currently recognized, the evidence to substantiate these claims is less than compelling, partially because of the inherent difficulties in quantifying both degree of exposure and degree of neurologic impairment [140–143]. Case reports and case series have been published that describe a syndrome of

headache, nausea, lightheadedness, cerebellar dysfunction, and cognitive and mood disorders in association with chronic, low-level CO exposure. However, all these reports have uncontrolled confounding factors and lack data regarding the exposure [20,144–150]. These symptoms typically abate once the patient is removed from the environment [19,20,145,148,151]. Other problems that have been speculatively associated with chronic CO exposure include low birth weight [13,152–154], reduced exercise performance [98,155], and exacerbation of cardiac disease, although other risk factors, such as smoking, confound the picture [101,151,156]. In addition, chronic CO exposure has been associated with polycythemia and cardiomegaly, probably due to chronic hypoxia [98].

Diagnosis

A high index of suspicion is essential in making the diagnosis of occult CO poisoning. In prospective observational studies, patients presenting to the ED with winter flu–like syndrome were found to have CO-Hgb levels ranging from 3% to 24%; the possibility of CO exposure must be entertained in patients who have this ED presentation [25,86,87]. Important historical factors to elicit include the use of gas stoves for heating and cohabitants with similar symptoms [25,27,157]. In addition, patients whose symptoms are associated with particular environments (eg, workplace), activities (eg, boating), or appliances (eg, use of stove, fireplace) may be suffering from CO exposure.

Carboxyhemoglobin levels

Serum CO-Hgb levels should be obtained from patients suspected of CO exposure. A nonsmoker would be expected to have a baseline level of less than 1% to 3% from endogenous production and background environmental exposure, whereas smokers may have levels as high as 10%, perhaps slightly higher immediately after smoking [6,158]. Low CO-Hgb levels (<15%–20%) are well correlated with mild symptoms, such as nausea and headache [25,90,91], and levels greater than 60% to 70% are usually rapidly fatal [9]. However, intermediate levels do not appear to correlate well with symptoms or with prognosis; therefore, treatment decisions cannot be based solely on CO-Hgb levels [31,50,95,159–161]. In one series, CO-Hgb levels ranged from 5% to 47% in minimally symptomatic or asymptomatic patients, 10% to 64% in patients who were found unconscious but awoke on hospital arrival, and 1% to 53% in patients who remained comatose [44]. The wide overlaps among blood levels and clinical symptoms underscore the difficulty of using levels alone to determine severity of exposure. The severity of clinical symptoms is related not only to the concentration of CO but also to the duration of exposure [31,89]. Therefore, a patient who attains a high CO-Hgb level after a brief, high-level exposure may not manifest any clinical

toxicity [161], whereas a patient who attains the same CO-Hgb level after a prolonged lower-level exposure may be significantly symptomatic. It is also important to remember that, because CO-Hgb levels decline with time and with oxygen therapy, an initial CO-Hgb level may not accurately reflect the magnitude of a patient's exposure if it is drawn at a time that is remote from the exposure or after oxygen therapy has been instituted. Prehospital providers can be helpful by reporting CO air levels at the scene of exposure or by providing blood drawn shortly after exposure. In some circumstances, exhaled CO levels measured by using a Breathalyzer-type device may help to confirm the diagnosis, whether in the prehospital or hospital setting [19,162].

CO-Hgb levels should be measured with a co-oximeter, which measures total hemoglobin concentration, oxyhemoglobin, deoxyhemoglobin, and concentrations of abnormal hemoglobins, such as CO-Hgb and methemoglobin, by differentiating wavelength absorbance values [12]. Routine blood gas analyzers without co-oximeters calculate rather than measure oxyhemoglobin saturation and do not recognize the contribution of abnormal hemoglobins. Arterial sampling is not necessary, because prospective comparison of arterial and venous CO-Hgb levels in poisoned patients has shown a high degree of correlation [163]. In an animal model, the accuracy was maintained at CO-Hgb levels exceeding 60% [164].

Pulse oximetry

Pulse oximetry may be falsely elevated in the setting of significant CO poisoning, because CO-Hgb is difficult to distinguish from oxyhemoglobin by wavelength. The pulse oximetry gap, defined as the difference between the pulse oximetry measured by finger probe and the true pulse oximetry obtained spectrophotometrically with a co-oximeter, has been found to approximate the CO-Hgb level. Therefore, as the CO-Hgb level rises, the degree of pulse oximetry overestimation increases [165–167].

Other diagnostic testing

Other diagnostic testing in the CO-poisoned patient is dependent on the clinical scenario and may include complete blood count, arterial blood gas monitoring, electrolytes, cardiac markers, blood urea nitrogen, creatinine, creatine phosphokinase, chest radiography, ECG, neuropsychometric testing, and neuroimaging studies. The presence of metabolic acidosis, presumably from a combination of hypoxia, inhibition of cellular respiration, and increased metabolic demand, has been found to correlate with exposure duration, severity of clinical symptoms, and adverse sequelae after CO poisoning [108,109,160,168]. Lactate has been used as a marker for severe poisoning [160]. Chest radiography may show evidence of noncardiogenic pulmonary edema in the severely poisoned patient. ECG may demonstrate nonspecific changes, dysrhythmias, or changes associated with myocardial ischemia. Cardiac markers and creatine phosphokinase may be

elevated [169]. In the setting of smoke inhalation, concomitant cyanide toxicity may occur with CO poisoning [107,170]. In the setting of chronic CO poisoning, polycythemia may be seen as a response to chronic hypoxia. Fetal monitoring may be helpful to detect fetal compromise in the CO-poisoned pregnant patient [171]. Most recently, the role of biochemical markers of brain damage (neuron-specific enolase, S-100 beta) after CO poisoning has been investigated [172–174]. In one series of 38 CO-poisoned patients, S-100 beta levels correlated well with severity of illness [173].

Neuropsychometric testing

A battery of neuropsychometric tests has been developed specifically to screen for cognitive dysfunction as a result of CO poisoning [175]. The Carbon Monoxide Neuropsychological Screening Battery (CONSB) consists of six subtests assessing general orientation, digit span, trail making, digit symbol, aphasia, and block design. CO-poisoned patients without concomitant drug and alcohol ingestion were found to score worse than controls before hyperbaric oxygen therapy (HBOT) and to have improved scores after HBOT, particularly on the trail making test (Fig. 2) [175]. Volunteers exposed to CO were found to perform more poorly on the CONSB than controls without CO exposure [176].

The term neuropsychometric testing in the literature may refer to the CONSB or tests such as the Mini–Mental Status Exam, Weschler Adult Intelligence Scale—Revised, Weschler Memory Scale—Revised, and others. The utility of neuropsychometric testing in CO poisoning in the ED setting has yet to be determined, and significant controversy exists regarding its value. Although CO-poisoned patients have been shown to perform more poorly on neuropsychometric tests, abnormalities may not be explained exclusively by

Instructions: Draw a line from the number 1 to the letter A, from the number 2 to the letter B, and so on without lifting the pencil. The examiner may prompt the patient. The score is the total time in seconds for task completion.

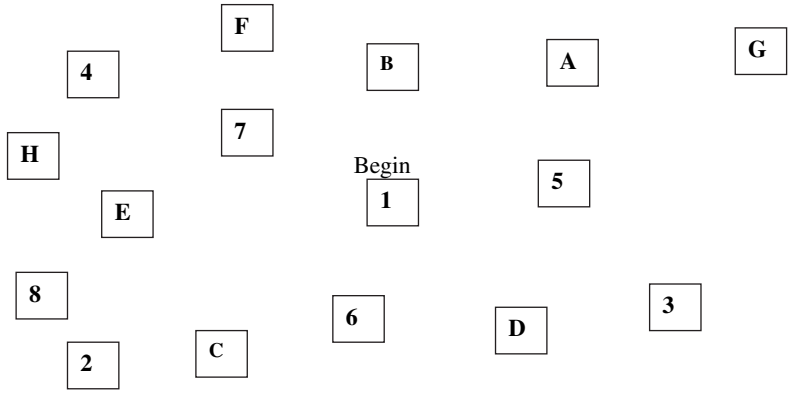

Fig. 2. Sample neuropsychometric trail-making test.

CO exposure. Patients attempting suicide by means other than CO perform as poorly on neuropsychometric tests as patients who attempt suicide with CO [177]. Improvement in neuropsychometric testing after HBOT in CO-poisoned patients is often cited as evidence for the effectiveness of HBOT. However, other factors could result in neuropsychometric test improvement, such as motivation, practice effect due to repetition of the test, improvement of overall mental status, and metabolism of coingestants or cointoxicants [43,135–138]. In addition, it is unknown whether neuropsychometric test abnormalities alone are associated with deleterious outcomes for patients with CO exposure. Despite these limitations, neuropsychometric testing provides an objective means of evaluating cognitive function. Some use these tests to assist in treatment decision making and to follow patients during recovery, although this practice is not uniform [43,127,136,178,179].

CT of the brain in patients who have severe CO exposure may show signs of cerebral infarction due to hypoxia, ischemia, and hypotension induced by severe CO exposure. However, an interesting and well-reported finding is bilateral globus pallidus low-density lesions (Fig. 3) [94–97]. The development of this lesion has been correlated with local low blood flow to the globus pallidus [71], metabolic acidosis, and hypotension [68,69].) during CO poisoning in animal models. Globus pallidus lesions may be delayed for as long as several days after initial presentation [180] and may resolve with time [133,181]. Concomitant white matter lesions may also be seen [94,97]. Although globus pallidus lesions are not pathognomonic for CO poisoning and may be seen in other intoxications, such as methanol or hydrogen sulfide poisoning, their presence should alert the clinician to the possibility of CO exposure. MRI in patients who have CO exposure may show diffuse,

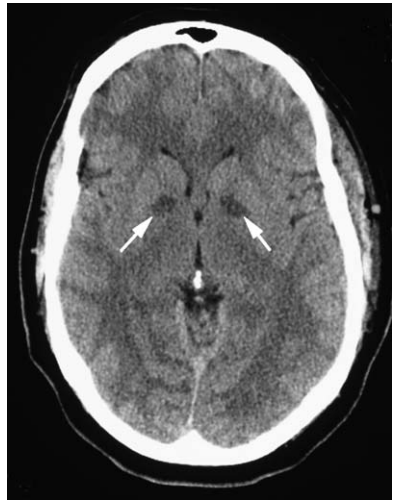

Fig. 3. Bilateral globus pallidus lesions seen on CT of the brain after CO poisoning.

symmetric white matter lesions, predominantly in the periventricular areas, although the centrum semiovale, deep subcortical white matter, thalamus, basal ganglia, and hippocampus may also be affected [133,150,182,183].

Patients who have abnormal neuroimaging findings after CO exposure are more likely to have poorer outcomes, such as death or persistent functional neurologic impairment, than are those with normal neuroimaging studies [94,95,97,128,133,150]. However, exceptions exist, and the results of neuroimaging studies do not always accurately predict outcome [128,150].

Single photon emission computed tomography (SPECT) scanning, electroencephalography, and quantitative MRI have been studied as adjunctive diagnostic tests in CO-exposed patients but are not widely available [183–185]. SPECT scanning in particular may correlate better than other neuroimaging findings with the development of delayed neurologic sequelae [186].

Treatment

Treatment of the CO-poisoned patient begins with supplemental oxygen and aggressive supportive care, including airway management, blood pressure support, and stabilization of cardiovascular status. When occult CO poisoning is discovered, other patients may remain at the scene and should be warned and evacuated until the source is identified and the environment is safe.

High-flow oxygen therapy should be administered immediately to treat hypoxia due to CO poisoning and also to accelerate elimination of CO from the body. Whether this oxygen should be given under increased pressure with HBOT or under ambient pressures (ie, normobaric oxygen [NBO]) is a subject of much debate. HBOT is neither universally available nor entirely risk free. However, HBOT may have a role in preventing adverse neurologic sequelae in the setting of CO poisoning and is indicated for selected patients. HBOT consists of the delivery of 100% oxygen within a pressurized chamber, resulting in a manifold increase in the dissolved oxygen in the body (PaO_2 up to 2000 mm Hg). One hundred percent oxygen at ambient pressure provides 2.09 vol%—one third of the body's requirement—whereas 2.5 atmospheres absolute (ATA) provides 5.62 vol% [187,188]. Interestingly, HBOT at 3.0 ATA was found in a porcine study to provide enough dissolved oxygen to supply the body's needs in the near-absence of hemoglobin [189]. Increasing the partial pressure of oxygen decreases the half life of CO-Hgb. The reported half life of CO-Hgb is 240 to 320 minutes at room air (21% oxygen), 40 to 80 minutes at 100% oxygen, and approximately 20 minutes at 100% HBOT at 2.5 to 3.0 ATA [8,190–192]. Wide individual variation exists, however, and prolonged exposures may result in prolonged half life [190,193].

HBOT for CO poisoning was first discussed by Haldane in the 1890s and first used in the 1960s [194]. Because CO toxicity was initially thought to result entirely from the relative anemia imposed by the formation of

CO-Hgb, HBOT was thought to be beneficial merely by accelerating the dissociation of CO from hemoglobin. However, as our understanding of the pathophysiology of CO poisoning and of HBOT has evolved, it appears that HBOT has other effects. HBOT has been shown in CO-poisoned animals not only to reduce CO binding to hemoglobin [190,195] but also to reduce CO binding to other heme-containing proteins, such as cytochrome a3, that affect cellular metabolism [196,197]. HBOT may also alter neutrophil adhesion to endothelium [198,199], decrease free radical–mediated oxidative damage [196,198], reduce neurologic deficits [75], and reduce overall mortality [65,200] when compared with NBO. Other animal studies have found that HBOT does not prevent neuronal injury in the setting of CO poisoning [75,201], and oxygen has the potential to increase oxidative damage owing to increased generation of free radicals [51,188,198].

Six prospective randomized controlled trials compare HBOT with NBO for CO poisoning [130,185,203–206]. Four of these studies show a benefit for HBOT; two do not. The data and conclusions drawn from these studies are conflicting and highlight the controversy surrounding the utility of HBOT. Because of significant variations in study design, HBOT and NBO protocols used, outcomes measured, and patient population included, it is difficult to draw firm conclusions based on the weight of the evidence. Development of a consensus on the definition of DNS and validation of diagnostic parameters for DNS would strengthen future investigations [137,207,208]. A recent Cochrane review [209] including three of these trials [130,203,205] concluded that the overall odds ratio (OR) for benefit of HBOT was 0.82 (95% confidence interval [CI], 0.41–1.66) using an outcome measure of symptoms at 1 month. The study by Weaver and colleagues [206], considered by many to be the most methodologically rigorous [137,202,210], was published after the Cochrane review.

Although more research is needed in this area, the unwillingness of some authors to advocate further randomized controlled trials underscores the considerable controversy regarding HBOT for CO poisoning. Some believe that withholding HBOT from CO-poisoned patients in future trials would be unethical, because of their firm belief in the efficacy of this treatment [45,211,214]. Others believe that further trials would be unethical because the paucity of data on the effectiveness of HBOT therapy does not justify the risk and expense of transferring patients to HBOT treatment facilities [212]. Still others have expressed concern that HBOT supporters appear to be located in facilities that offer HBOT [211,213].

No widespread agreement exists regarding selection of patients for HBOT in the setting of CO poisoning [188,211], and no reliable method of identifying patients at high risk for neurologic sequelae is available [137,202,215]. Based on the available knowledge regarding the pathophysiology of CO poisoning and the current clinical data, broad criteria for recommending HBOT for CO poisoning have included any history of LOC, neurologic symptoms, cardiovascular dysfunction, metabolic acidosis,

abnormalities on neuropsychometric testing, pregnancy with an elevated (>15%–20%) CO-Hgb level, persistent symptoms despite NBO, and a significantly high CO-Hgb level. Many practitioners use a CO-Hgb level greater than 25% as criterion for HBOT [8,137,188,210,215–217]. A survey of hyperbaric centers revealed that more than three fourths of the responders use HBOT for coma, focal neurologic deficits, ischemic changes on EKG, abnormal psychometric testing, and transient LOC [179]. Because CO exacerbates underlying heart disease, cardiac dysfunction in the setting of CO poisoning should be treated with standard therapy (eg, antidysrhythmics, aspirin, nitrates), high-flow oxygen, and consideration of HBOT [1].

Although they acknowledge the lack of data to substantiate various criteria and treatment protocols, the members of the Undersea and Hyperbaric Medical Society [137] recommend HBOT therapy for CO-poisoned patients with LOC (transient or prolonged), neurologic signs, cardiovascular dysfunction, or severe metabolic acidosis. They recognize that many practitioners use abnormal neuropsychometric testing and absolute CO-Hgb levels (typically >25%) to guide treatment decisions. Although they could not absolutely define a high-risk population for neurologic sequelae, they believe that patients at the extremes of age and those with neurologic abnormalities, LOC, or a CO-Hgb level greater than 25% "require special consideration." Although the efficacy of one HBOT treatment protocol over another has not been determined [139,202,210,218–220], one session of HBOT at 2.5 to 3.0 ATA is recommended initially, with further sessions considered if symptoms persist [137,208,215]. Physicians treating CO-poisoned patients who do not meet criteria for HBOT should consider administration of 100% oxygen for 6 to 12 hours delivered by tight-fitting face mask [9,137,202,212,219,221]. Infants and children receive the same HBOT protocols as adults [222]. The safety of HBOT in pregnancy has been questioned, but many authors recommend HBOT for the pregnant patient in the setting of CO poisoning, because of the potential benefit to both mother and fetus and the difficulty of assessing intrauterine hypoxia [118,120,123,171,223,224]. A maternal CO-Hgb level greater than 15% to 20%, evidence of fetal distress, or other standard criteria for HBOT in CO poisoning are often cited as indications for HBOT in the CO-poisoned pregnant patient [1,171,215]. Pregnant women may require longer treatment with oxygen than the nonpregnant patient [114,115,119,223,225]. Box 2 lists suggested indications for HBOT in CO poisoning.

HBOT is not entirely risk free. Most commonly, patients complain of painful barotrauma affecting the ears and sinuses, and patients with claustrophobia are often unable to tolerate the close confines of a monoplace hyperbaric chamber (ie, sized for a single individual). Other, less common risks include oxygen toxicity seizures, pulmonary edema and hemorrhage, decompression sickness, including pneumothorax and nitrogen emboli, and fire hazard [44,226–228]. The only absolute contraindication to HBOT is an untreated pneumothorax [215]. Relative contraindications include

Box 2. Suggested indications for hyperbaric oxygen therapy in carbon monoxide poisoning

Strongly consider for

(1) Neurologic findings
  (a) Altered mental status
  (b) Coma
  (c) Focal neurologic deficits
  (d) Seizures
(2) Pregnancy with CO-Hgb levels >15%
(3) History of loss of consciousness

Possibly consider for

Cardiovascular compromise (ischemia, infarction, dysrhythmia)
Metabolic acidosis
Extremes of age
Abnormal neuropsychometric testing results
Persistent symptoms despite normobaric oxygen

Data from Tomaszewski C. Carbon monoxide. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al, editors. Goldfrank's toxicologic emergencies. 7th edition. New York: McGraw-Hill; 2002. p. 1478–97; and Hampson NB, Mathieu D, Piantadosi CA, et al. Carbon monoxide poisoning: interpretation of randomized clinical trials and unresolved treatment issues. Undersea Hyperb Med 2001; 28(3):157–64.

claustrophobia, otosclerosis or other scarring of middle ear, bowel obstruction, significant chronic obstructive pulmonary disease, particularly with bullae formation, and requirement of care beyond what may be provided in a monoplace chamber (eg, tracheal suctioning in burns). In addition, if the patient requires emergency intervention (eg, defibrillation) while undergoing HBOT, several minutes are required to decompress the patient safely before interventions may proceed [188]. One retrospective series of 297 patients, 41 of whom had serious cardiovascular complications, showed that all but one manifested their cardiovascular distress before HBOT. Few complications occurred during HBOT. The authors concluded that most patients at risk for emergent cardiovascular decompensation can be identified before they enter the HBOT chamber [229]. Because of the significant controversy still surrounding the appropriate treatment for CO-poisoned patients, a standard of care regarding HBOT for these patients is difficult to define. A risk-benefit analysis should be considered for each individual patient, depending on other concomitant medical needs, and discussed with the patient or family.

Other treatments tried for CO poisoning in the past have included hyperventilation, hypothermia, osmotherapy, fluid restriction, and glucocorticoids, none of which were found effective [109,230]. Ongoing research is being

performed to delineate the possible roles of free radical scavengers, monoamine oxidase inhibitors [54], and N-methyl D-aspartate (NMDA) blockers [82].

Prevention

The widespread use of catalytic converters on automobiles and improved emissions policies have resulted in a significant decline in accidental CO poisoning deaths [4,231]. Prevention of high indoor concentrations of CO is optimal and can be accomplished by frequent inspection and maintenance of furnaces, stoves, and fireplaces, avoidance of indoor unvented combustion sources such as grills and space heaters, careful use of gas stoves, and installation of CO detectors [3]. In the United States, CO alarms are designed to activate within 189 minutes of 70 ppm exposure, 50 minutes of 150 ppm exposure, or 15 minutes of 400 ppm exposure [3]. Although the effectiveness of CO detectors may be limited in the significant proportion of victims of fatal CO poisoning who succumb while asleep or under the influence of alcohol, appropriate and widespread use is likely to decrease the incidence of occult indoor CO poisoning [232].

Summary

CO is an ubiquitous poison with many sources of exposure. CO poisoning produces diverse signs and symptoms that are often subtle and may be easily misdiagnosed. Failure to diagnose CO poisoning may result in significant morbidity and mortality and permit continued exposure to a dangerous environment.

Treatment of CO poisoning begins with inhalation of supplemental oxygen and aggressive supportive care. HBOT accelerates dissociation of CO from hemoglobin and may also prevent DNS. Absolute indications for HBOT for CO poisoning remain controversial, although most authors would agree that HBOT is indicated in patients who are comatose or neurologically abnormal, have a history of LOC with their exposure, or have cardiac dysfunction. Pregnancy with an elevated CO-Hgb level ($>15\%$–20%) is also widely considered an indication for treatment. HBOT may be considered in patients who have persistent symptoms despite NBO, metabolic acidosis, abnormalities on neuropsychometric testing, or significantly elevated levels. The ideal regimen of oxygen therapy has yet to be determined, and significant controversy exists regarding HBOT treatment protocols. Often the local medical toxicologist, poison control center, or hyperbaric unit may assist the treating physician with decisions regarding therapy.

References

[1] Tomaszewski C. Carbon monoxide. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al, editors. Goldfrank's toxicologic emergencies. 7th edition. New York: McGraw-Hill; 2002. p. 1478–97.

[2] Cobb N, Etzel RA. Unintentional carbon monoxide-related deaths in the United States, 1979 through 1988. JAMA 1991;266(5):659–63.
[3] Raub JA, Mathieu-Nolf M, Hampson NB, et al. Carbon monoxide poisoning—a public health perspective. Toxicology 2000;145(1):1–14.
[4] Mott JA, Wolfe MI, Alverson CJ, et al. National vehicle emissions policies and practices and declining US carbon monoxide–related mortality. JAMA 2002;288(8): 988–95.
[5] Mah JC. Non-fire carbon monoxide deaths and injuries associated with the use of consumer products: annual estimates—1998. US Consumer Product Safety Commission (Bethesda, MD). Available at: http://www.cpsc.gov/library/data.html. Accessed February 4, 2005.
[6] Ernst A, Zibrak JD. Carbon monoxide poisoning. N Engl J Med 1998;339(22):1603–8.
[7] Abelsohn A, Sanborn MD, Jessiman BJ, et al. Identifying and managing adverse environmental health effects. 6. Carbon monoxide poisoning. CMAJ 2002;166(13): 1685–90.
[8] Ilano AL, Raffin TA. Management of carbon monoxide poisoning. Chest 1990;97(1): 165–9.
[9] Olson KR. Carbon monoxide poisoning: mechanisms, presentation, and controversies in management. J Emerg Med 1984;1(3):233–43.
[10] Forbes WH, Sargent F, Roughton FJW. The rate of carbon monoxide uptake by normal men. Am J Physiol 1945;143(4):594–608.
[11] Roughton FJW. The kinetics of the reaction $CO + O_2Hb <-> O_2 + COHb$ in human blood at body temperature. Am J Physiol 1945;143(4):609–20.
[12] Widdop B. Analysis of carbon monoxide. Ann Clin Biochem 2002;39(4):378–91.
[13] Raub JA, Benignus VA. Carbon monoxide and the nervous system. Neurosci Biobehav Rev 2002;26(8):925–40.
[14] Administration OSHA. Occupational safety and health guidelines for carbon monoxide. Available at: http://www.osha.gov/SLTC/healthguidelines/carbonmonoxide/recognition.html. Accessed February 4, 2005.
[15] Hampson NB, Norkool DM. Carbon monoxide poisoning in children riding in the back of pickup trucks. JAMA 1992;267(4):538–40.
[16] Anonymous. Carbon-monoxide poisoning resulting from exposure to ski-boat exhaust—Georgia, June 2002. MMWR Morbid Mortal Wkly Rep 2002;51(37):829–30.
[17] Silvers SM, Hampson NB. Carbon monoxide poisoning among recreational boaters. JAMA 1995;274(20):1614–6.
[18] Anonymous. From the Centers for Disease Control and Prevention. Carbon monoxide poisoning associated with use of LPG-powered (propane) forklifts in industrial settings—Iowa, 1998. JAMA 2000;283(3):331–2.
[19] Ely EW, Moorehead B, Haponik EF. Warehouse workers' headache: emergency evaluation and management of 30 patients with carbon monoxide poisoning. Am J Med 1995;98(2): 145–55.
[20] Fawcett TA, Moon RE, Fracica PJ, et al. Warehouse workers' headache. Carbon monoxide poisoning from propane-fueled forklifts. J Occup Med 1992;34(1):12–5.
[21] Pelham TW, Holt LE, Moss MA. Exposure to carbon monoxide and nitrogen dioxide in enclosed ice arenas. Occup Environ Med 2002;59(4):224–33.
[22] Anonymous. Carbon monoxide poisoning at an indoor ice arena and bingo hall—Seattle, 1996. From the Centers for Disease Control and Prevention. JAMA 1996;275(19): 1468–9.
[23] Anonymous. From the Centers for Disease Control and Prevention. Houseboat-associated carbon monoxide poisonings on Lake Powell—Arizona and Utah, 2000. JAMA 2001; 285(5):530–2.
[24] Anonymous. From the Centers for Disease Control and Prevention. Carbon monoxide poisoning deaths associated with camping—Georgia, March 1999. JAMA 1999;282(14): 1326.

[25] Heckerling PS, Leikin JB, Maturen A, et al. Predictors of occult carbon monoxide poisoning in patients with headache and dizziness. Ann Intern Med 1987;107(2): 174–6.
[26] Hampson NB, Kramer CC, Dunford RG, et al. Carbon monoxide poisoning from indoor burning of charcoal briquets. JAMA 1994;271(1):52–3.
[27] Wrenn K, Connors GP. Carbon monoxide poisoning during ice storms: a tale of two cities. J Emerg Med 1997;15(4):465–7.
[28] Rioux JP, Myers RA. Hyperbaric oxygen for methylene chloride poisoning: report on two cases. Ann Emerg Med 1989;18(6):691–5.
[29] Nager EC, O'Connor RE. Carbon monoxide poisoning from spray paint inhalation. Acad Emerg Med 1998;5(1):84–6.
[30] Langehennig PL, Seeler RA, Berman E. Paint removers and carboxyhemoglobin. N Engl J Med 1976;295(20):1137.
[31] Piantadosi CA. Diagnosis and treatment of carbon monoxide poisoning. Respir Care Clin N Am 1999;5(2):183–202.
[32] Naik JS, O'Donaughy TL, Walker BR. Endogenous carbon monoxide is an endothelial-derived vasodilator factor in the mesenteric circulation. Am J Physiol Heart Circ Physiol 2003;284(3):H838–45.
[33] Zegdi R, Perrin D, Burdin M, et al. Increased endogenous carbon monoxide production in severe sepsis. Intensive Care Med 2002;28(6):793–6.
[34] Haldane J. Medicolegal contributions of historical interest. The action of carbonic oxide on man. Forensic Sci 1972;1(4):451–83.
[35] Sendroy J, Liu SH, Van Slyke DO. The gasometric estimation of the relative affinity constant for carbon monoxide and oxygen in whole blood at 38C. Am J Physiol 1929;90: 511–2.
[36] Roughton FJW, Darling RC. The effect of carbon monoxide on the oxyhemoglobin dissociation curve. Am J Physiol 1944;141:17–31.
[37] Goldbaum LR, Ramirez RG, Absalon KB. What is the mechanism of carbon monoxide toxicity? Aviat Space Environ Med 1975;46(10):1289–91.
[38] Goldbaum LR, Orellano T, Dergal E. Mechanism of the toxic action of carbon monoxide. Ann Clin Lab Sci 1976;6(4):372–6.
[39] Orellano T, Dergal E, Alijani M, et al. Studies on the mechanism of carbon monoxide toxicity. J Surg Res 1976;20(5):485–7.
[40] Ramirez RG, Albert SN, Agostin JC, et al. Lack of toxicity of transfused carboxyhemoglobin. Surg Forum 1974;25:165–8.
[41] Meilin S, Rogatsky GG, Thom SR, et al. Effects of carbon monoxide on the brain may be mediated by nitric oxide. J Appl Physiol 1996;81(3):1078–83.
[42] Mendelman A, Zarchin N, Meilin S, et al. Blood flow and ionic responses in the awake brain due to carbon monoxide. Neurol Res 2002;24(8):765–72.
[43] Rottman SJ. Carbon monoxide screening in the ED. Am J Emerg Med 1991;9(2): 204–5.
[44] Norkool DM, Kirkpatrick JN. Treatment of acute carbon monoxide poisoning with hyperbaric oxygen: a review of 115 cases. Ann Emerg Med 1985;14(12):1168–71.
[45] Myers RA. Carbon monoxide poisoning. J Emerg Med 1984;1(3):245–8.
[46] Okeda R, Funata N, Takano T, et al. The pathogenesis of carbon monoxide encephalopathy in the acute phase—physiological and morphological correlation. Acta Neuropathol (Berl) 1981;54(1):1–10.
[47] Brown SD, Piantadosi CA. Recovery of energy metabolism in rat brain after carbon monoxide hypoxia. J Clin Invest 1992;89(2):666–72.
[48] Hill BC. The pathway of CO binding to cytochrome c oxidase. Can the gateway be closed? FEBS Lett 1994;354(3):284–8.
[49] Chance B, Erecinska M, Wagner M. Mitochondrial responses to carbon monoxide toxicity. Ann N Y Acad Sci 1970;174(1):193–204.

[50] Hardy KR, Thom SR. Pathophysiology and treatment of carbon monoxide poisoning. J Toxicol Clin Toxicol 1994;32(6):613–29.
[51] Zhang J, Piantadosi CA. Mitochondrial oxidative stress after carbon monoxide hypoxia in the rat brain. J Clin Invest 1992;90(4):1193–9.
[52] Thom SR, Ohnishi ST, Ischiropoulos H. Nitric oxide released by platelets inhibits neutrophil B2 integrin function following acute carbon monoxide poisoning. Toxicol Appl Pharmacol 1994;128(1):105–10.
[53] Radi R, Rodriguez M, Castro L, et al. Inhibition of mitochondrial electron transport by peroxynitrite. Arch Biochem Biophys 1994;308(1):89–95.
[54] Piantadosi CA, Tatro L, Zhang J. Hydroxyl radical production in the brain after CO hypoxia in rats. Free Rad Biol Med 1995;18(3):603–9.
[55] DeBias DA, Banerjee CM, Birkhead NC, et al. Effects of carbon monoxide inhalation on ventricular fibrillation. Arch Environ Health 1976;31(1):42–6.
[56] Sangalli BC, Bidanset JH. A review of carboxymyoglobin formation: a major mechanism of carbon monoxide toxicity. Vet Hum Toxicol 1990;32(5):449–53.
[57] Florkowski CM, Rossi ML, Carey MP, et al. Rhabdomyolysis and acute renal failure following carbon monoxide poisoning: two case reports with muscle histopathology and enzyme activities. J Toxicol Clin Toxicol 1992;30(3):443–54.
[58] Wolff E. Carbon monoxide poisoning with severe myonecrosis and acute renal failure. Am J Emerg Med 1994;12(3):347–9.
[59] Herman GD, Shapiro AB, Leikin J. Myonecrosis in carbon monoxide poisoning. Vet Hum Toxicol 1988;30(1):28–30.
[60] Richardson RS, Noyszewski EA, Saltin B, et al. Effect of mild carboxy-hemoglobin on exercising skeletal muscle: intravascular and intracellular evidence. Am J Physiol 2002; 283(5):R1131–9.
[61] Barinaga M. Carbon monoxide: killer to brain messenger in one step. Science 1993; 259(5093):309.
[62] Verma A, Hirsch DJ, Glatt CE, et al. Carbon monoxide: a putative neural messenger. Science 1993;259(5093):381–4.
[63] Meyer-Witting M, Helps S, Gorman DF. Acute carbon monoxide exposure and cerebral blood flow in rabbits. Anaesth Intensive Care 1991;19(3):373–7.
[64] Sinha AK, Klein J, Schultze P, et al. Cerebral regional capillary perfusion and blood flow after carbon monoxide exposure. J Appl Physiol 1991;71(4):1196–200.
[65] Jiang J, Tyssebotn I. Cerebrospinal fluid pressure changes after acute carbon monoxide poisoning and therapeutic effects of normobaric and hyperbaric oxygen in conscious rats. Undersea Hyperb Med 1997;24(4):245–54.
[66] Ischiropoulos H, Beers MF, Ohnishi ST, et al. Nitric oxide production and perivascular tyrosine nitration in brain after carbon monoxide poisoning in the rat. J Clin Invest 1996; 97(10):2260–7.
[67] Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345(8): 588–95.
[68] Ginsberg MD, Myers RE, McDonagh BF. Experimental carbon monoxide encephalopathy in the primate. II. Clinical aspects, neuropathology, and physiologic correlation. Arch Neurol 1974;30(3):209–16.
[69] Koehler RC, Jones MD Jr, Traystman RJ. Cerebral circulatory response to carbon monoxide and hypoxic hypoxia in the lamb. Am J Physiol 1982;243(1):H27–32.
[70] Okeda R, Funata N, Song SJ, et al. Comparative study on pathogenesis of selective cerebral lesions in carbon monoxide poisoning and nitrogen hypoxia in cats. Acta Neuropathol (Berl) 1982;56(4):265–72.
[71] Song SY, Okeda R, Funata N, et al. An experimental study of the pathogenesis of the selective lesion of the globus pallidus in acute carbon monoxide poisoning in cats. Acta Neuropathol (Berl) 1983;61:232–8.

[72] Thom SR, Kang M, Fisher D, et al. Release of glutathione from erythrocytes and other markers of oxidative stress in carbon monoxide poisoning. J Appl Physiol 1997;82(5): 1424–32.
[73] Thom SR. Leukocytes in carbon monoxide–mediated brain oxidative injury. Toxicol Appl Pharmacol 1993;123(2):234–47.
[74] Thom SR, Fisher D, Manevich Y. Roles for platelet-activating factor and *NO-derived oxidants causing neutrophil adherence after CO poisoning. Am J Physiol Heart Circ Physiol 2001;281(2):H923–30.
[75] Tomaszewski C, Rosenberg N, Wanthen J, et al. Prevention of neurological sequelae from carbon monoxide by hyperbaric oxygen in rats. Neurology 1992;42(Suppl 3):196.
[76] Thom SR. Carbon monoxide–mediated brain lipid peroxidation in the rat. J Appl Physiol 1990;68(3):997–1003.
[77] Thom SR. Dehydrogenase conversion to oxidase and lipid peroxidation in brain after carbon monoxide poisoning. J Appl Physiol 1992;73(4):1584–9.
[78] Penney DG. Acute carbon monoxide poisoning: animal models: a review. Toxicology 1990; 62(2):123–60.
[79] Thom SR, Bhopale VM, Fisher D, et al. Delayed neuropathology after carbon monoxide poisoning is immune-mediated. Proc Natl Acad Sci U S A 2004;101(37):13660–5.
[80] Piantadosi CA, Zhang J, Levin ED, et al. Apoptosis and delayed neuronal damage after carbon monoxide poisoning in the rat. Exp Neurol 1997;147(1):103–14.
[81] Penney DG, Chen K. NMDA receptor–blocker ketamine protects during acute carbon monoxide poisoning, while calcium channel–blocker verapamil does not. J Appl Toxicol 1996;16(4):297–304.
[82] Ishimaru H, Katoh A, Suzuki H, et al. Effects of N-methyl-D-aspartate receptor antagonists on carbon monoxide–induced brain damage in mice. J Pharmacol Exp Ther 1992;261(1):349–52.
[83] Lightfoot NF. Chronic carbon monoxide exposure. Proc R Soc Med 1972;65(9):798–9.
[84] Thom SR, Fisher D, Xu YA, et al. Role of nitric oxide–derived oxidants in vascular injury from carbon monoxide in the rat. Am J Physiol 1999;276(3 Pt 2):H984–92.
[85] Estabrook RW, Franklin MR, Hildebrandt AG. Factors influencing the inhibitory effect of carbon monoxide on cytochrome P-450–catalyzed mixed function oxidation reactions. Ann N Y Acad Sci 1970;174(1):218–32.
[86] Dolan MC, Haltom TL, Barrows GH, et al. Carboxyhemoglobin levels in patients with flu-like symptoms. Ann Emerg Med 1987;16(7):782–6.
[87] Heckerling PS. Occult carbon monoxide poisoning: a cause of winter headache. Am J Emerg Med 1987;5:201–4.
[88] Baker MD, Henretig FM, Ludwig S. Carboxyhemoglobin levels in children with nonspecific flu-like symptoms. J Pediatr 1988;113(3):501–4.
[89] Burney RE, Wu SC, Nemiroff MJ. Mass carbon monoxide poisonings: clinical effects and results of treatment in 184 victims. Ann Emerg Med 1982;11(8):394–9.
[90] Stewart RD, Peterson JE, Baretta ED, et al. Experimental human exposure to carbon monoxide. Arch Environ Health 1970;21(2):154–64.
[91] Stewart RD, Peterson JE, Fisher TN, et al. Experimental human exposure to high concentrations of carbon monoxide. Arch Environ Health 1973;26(1):1–7.
[92] Herman LY. Carbon monoxide poisoning presenting as an isolated seizure. J Emerg Med 1998;16(3):429–32.
[93] Mori T, Nagai K. Carbon-monoxide poisoning presenting as an afebrile seizure. Pediatr Neurol 2000;22(4):330–1.
[94] Silver DA, Cross M, Fox B, et al. Computed tomography of the brain in acute carbon monoxide poisoning. Clin Radiol 1996;51(7):480–3.
[95] Jones JS, Lagasse J, Zimmerman G. Computed tomographic findings after acute carbon monoxide poisoning. Am J Emerg Med 1994;12(4):448–51.

[96] Miura T, Mitomo M, Kawai R, et al. CT of the brain in acute carbon monoxide intoxication: characteristic features and prognosis. AJNR Am J Neuroradiol 1985;6(5):739–42.
[97] Sawada Y, Takahashi M, Ohashi N, et al. Computerised tomography as an indication of long-term outcome after acute carbon monoxide poisoning. Lancet 1980;1(8172):783–4.
[98] Penney DG. Hemodynamic response to carbon monoxide. Environ Health Perspect 1988; 77:121–30.
[99] Yanir Y, Shupak A, Abramovich A, et al. Cardiogenic shock complicating acute carbon monoxide poisoning despite neurologic and metabolic recovery. Ann Emerg Med 2002; 40(4):420–4.
[100] Thom SR, Keim LW. Carbon monoxide poisoning: a review. Epidemiology, pathophysiology, clinical findings, and treatment options including hyperbaric oxygen therapy. J Toxicol Clin Toxicol 1989;27(3):141–56.
[101] Atkins EH, Baker EL. Exacerbation of coronary artery disease by occupational carbon monoxide exposure: a report to two fatalities and a review of the literature. Am J Ind Med 1985;7(1):73–9.
[102] Aronow WS, Isbell MW. Carbon monoxide effect on exercise-induced angina pectoris. Ann Intern Med 1973;79(3):392–5.
[103] Sheps DS, Herbst MC, Hinderliter AL, et al. Production of arrhythmias by elevated carboxyhemoglobin in patients with coronary artery disease. Ann Intern Med 1990;113(5): 343–51.
[104] Allred EN, Bleecker ER, Chaitman BR, et al. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. N Engl J Med 1989;321(21):1426–32.
[105] Marius-Nunez AL. Myocardial infarction with normal coronary arteries after acute exposure to carbon monoxide. Chest 1990;97(2):491–4.
[106] Myers RA, Snyder SK, Majerus TC. Cutaneous blisters and carbon monoxide poisoning. Ann Emerg Med 1985;14(6):603–6.
[107] Thom SR. Smoke inhalation. Emerg Med Clin North Am 1989;7(2):371–87.
[108] Goulon M, Barois A, Rapin M, et al. Carbon monoxide poisoning and acute anoxia due to breathing coal tar gas and hydrocarbons. Journal of Hyperbaric Medicine 1986;1(1):23–41.
[109] Krantz T, Thisted B, Strom J, et al. Acute carbon monoxide poisoning. Acta Anaesthesiol Scand 1988;32(4):278–82.
[110] Vreman HJ, Mahoney JJ, Stevenson DK. Carbon monoxide and carboxyhemoglobin. Adv Pediatr 1995;42:303–34.
[111] Foster M, Goodwin SR, Williams C, et al. Recurrent acute life-threatening events and lactic acidosis caused by chronic carbon monoxide poisoning in an infant. Pediatrics 1999;104(3): e34.
[112] Crocker PJ, Walker JS. Pediatric carbon monoxide toxicity. J Emerg Med 1985;3(6):443–8.
[113] Liebelt EL. Hyperbaric oxygen therapy in childhood carbon monoxide poisoning. Curr Opin Pediatr 1999;11(3):259–64.
[114] Longo LD, Hill EP. Carbon monoxide uptake and elimination in fetal and maternal sheep. Am J Physiol 1977;232(3):H324–30.
[115] Longo LD. Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. Ann N Y Acad Sci 1970;174(1):312–41.
[116] Norman CA, Halton DM. Is carbon monoxide a workplace teratogen? Ann Occup Hyg 1990;34(4):335–47.
[117] Caravati EM, Adams CJ, Joyce SM, et al. Fetal toxicity associated with maternal carbon monoxide poisoning. Ann Emerg Med 1988;17(7):714–7.
[118] Koren G, Sharav T, Pastuszak A, et al. A multicenter, prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy. Reprod Toxicol 1991;5(5): 397–403.
[119] Farrow JR, Davis GJ, Roy TM, et al. Fetal death due to nonlethal maternal carbon monoxide poisoning. J Forensic Sci 1990;35(6):1448–52.

[120] Cramer CR. Fetal death due to accidental maternal carbon monoxide poisoning. J Toxicol Clin Toxicol 1982;19(3):297–301.
[121] Ginsberg MD, Myers RE. Fetal brain injury after maternal carbon monoxide intoxication. Clinical and neuropathologic aspects. Neurology 1976;26(1):15–23.
[122] Woody RC, Brewster MA. Telencephalic dysgenesis associated with presumptive maternal carbon monoxide intoxication in the first trimester of pregnancy. J Toxicol Clin Toxicol 1990;28(4):467–75.
[123] Elkharrat D, Raphael JC, Korach JM, et al. Acute carbon monoxide intoxication and hyperbaric oxygen in pregnancy. Intensive Care Med 1991;17(5):289–92.
[124] Garland H, Pearce J. Neurological complications of carbon monoxide poisoning. Q J Med 1967;36(144):445–55.
[125] Min SK. A brain syndrome associated with delayed neuropsychiatric sequelae following acute carbon monoxide intoxication. Acta Psychiatr Scand 1986;73(1):80–6.
[126] Choi IS. Delayed neurologic sequelae in carbon monoxide intoxication. Arch Neurol 1983; 40(7):433–5.
[127] Myers RA, Snyder SK, Emhoff TA. Subacute sequelae of carbon monoxide poisoning. Ann Emerg Med 1985;14(12):1163–7.
[128] Lee MS, Marsden CD. Neurological sequelae following carbon monoxide poisoning: clinical course and outcome according to the clinical types and brain computed tomography scan findings. Mov Disord 1994;9(5):550–8.
[129] Smith JS, Brandon S. Morbidity from acute carbon monoxide poisoning at three-year follow-up. BMJ 1973;1(5849):318–21.
[130] Raphael JC, Elkharrat D, Jars-Guincestre MC, et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. Lancet 1989;2(8660):414–9.
[131] Shillito FH, Drinker CK, Shaughnessy TJ. The problem of nervous and mental sequelae in carbon monoxide poisoning. JAMA 1936;106(9):669–74.
[132] Kim JK, Coe CJ. Clinical study on carbon monoxide intoxication in children. Yonsei Med J 1987;28(4):266–73.
[133] Parkinson RB, Hopkins RO, Cleavinger HB, et al. White matter hyperintensities and neuropsychological outcome following carbon monoxide poisoning. Neurology 2002; 58(10):1525–32.
[134] Mathieu D, Nolf M, Durocher A, et al. Acute carbon monoxide poisoning. Risk of late sequelae and treatment by hyperbaric oxygen. J Toxicol Clin Toxicol 1985;23(4–6): 315–24.
[135] Schiltz KL. Failure to assess motivation, need to consider psychiatric variables, and absence of comprehensive examination: a skeptical review of neuropsychologic assessment in carbon monoxide research. Undersea Hyperb Med 2000;27(1):48–50.
[136] Seger D, Welch L. Carbon monoxide controversies: neuropsychologic testing, mechanism of toxicity, and hyperbaric oxygen. Ann Emerg Med 1994;24(2):242–8.
[137] Hampson NB, Mathieu D, Piantadosi CA, et al. Carbon monoxide poisoning: interpretation of randomized clinical trials and unresolved treatment issues. Undersea Hyperb Med 2001;28(3):157–64.
[138] Deschamps D, Geraud C, Julien H, et al. Memory one month after acute carbon monoxide intoxication: a prospective study. Occup Environ Med 2003;60(3):212–6.
[139] Gorman D, Drewry A, Huang YL, et al. The clinical toxicology of carbon monoxide. Toxicology 2003;187(1):25–38.
[140] Watkins CG, Strope GL. Chronic carbon monoxide poisoning as a major contributing factor in the sudden infant death syndrome. Am J Dis Child 1986;140(7):619.
[141] Halpern JS. Chronic occult carbon monoxide poisoning. J Emerg Nurs 1989;15(2 Pt 1): 107–11.
[142] Manuel J. A healthy home environment? Environ Health Perspect 1999;107(7):A352–7.
[143] Wright J. Chronic and occult carbon monoxide poisoning: we don't know what we're missing. Emerg Med J 2002;19(5):386–90.

[144] Devine SA, Kirkley SM, Palumbo CL, et al. MRI and neuropsychological correlates of carbon monoxide exposure: a case report. Environ Health Perspect 2002;110(10):1051–5.
[145] Gilbert GJ, Glaser GH. Neurologic manifestations of chronic carbon monoxide poisoning. N Engl J Med 1959;261(24):1217–20.
[146] Thorpe M. Chronic carbon monoxide poisoning. Can J Psychiatry 1994;39(1):59–61.
[147] Khan K, Sharief N. Chronic carbon monoxide poisoning in children. Acta Paediatr 1995; 84(7):742.
[148] Myers RA, DeFazio A, Kelly MP. Chronic carbon monoxide exposure: a clinical syndrome detected by neuropsychological tests. J Clin Psychol 1998;54(5):555–67.
[149] Knobeloch L, Jackson R. Recognition of chronic carbon monoxide poisoning. Wis Med J 1999;98(6):26–9.
[150] Pavese N, Napolitano A, De Iaco G, et al. Clinical outcome and magnetic resonance imaging of carbon monoxide intoxication. A long-term follow-up study. Ital J Neurol Sci 1999;20(3):171–8.
[151] Townsend CL, Maynard RL. Effects on health of prolonged exposure to low concentrations of carbon monoxide. Occup Environ Med 2002;59(10):708–11.
[152] Ritz B, Yu F, Chapa G, et al. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993 2000;11(5):502–11.
[153] Ritz B, Yu F, Fruin S, et al. Ambient air pollution and risk of birth defects in Southern California. Am J Epidemiol 2002;155(1):17–25.
[154] Fechter LD, Karpa MD, Proctor B, et al. Disruption of neostriatal development in rats following perinatal exposure to mild, but chronic carbon monoxide. Neurotoxicol Teratol 1987;9(4):277–81.
[155] Weir FW, Fabiano VL. Re-evaluation of the role of carbon monoxide in production or aggravation of cardiovascular disease processes. J Occup Med 1982;24(7):519–25.
[156] Morris RD, Naumova EN, Munasinghe RL. Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. Am J Public Health 1995;85(10):1361–5.
[157] Heckerling PS, Leikin JB, Terzian CG, et al. Occult carbon monoxide poisoning in patients with neurologic illness. J Toxicol Clin Toxicol 1990;28(1):29–44.
[158] Stewart RD, Baretta ED, Platte LR, et al. Carboxyhemoglobin levels in American blood donors. JAMA 1974;229(9):1187–95.
[159] Benignus VA, Kafer ER, Muller KE, et al. Absence of symptoms with carboxyhemoglobin levels of 16–23%. Neurotoxicol Teratol 1987;9(5):345–8.
[160] Sokal JA, Kralkowska E. The relationship between exposure duration, carboxyhemoglobin, blood glucose, pyruvate and lactate and the severity of intoxication in 39 cases of acute carbon monoxide poisoning in man. Arch Toxicol 1985;57(3):196–9.
[161] Davis SM, Levy RC. High carboxyhemoglobin level without acute or chronic findings. J Emerg Med 1984;1(6):539–42.
[162] Kurt TL, Anderson RJ, Reed WG. Rapid estimation of carboxyhemoglobin by breath sampling in an emergency setting. Vet Hum Toxicol 1990;32(3):227–9.
[163] Touger M, Gallagher EJ, Tyrell J. Relationship between venous and arterial carboxyhemoglobin levels in patients with suspected carbon monoxide poisoning. Ann Emerg Med 1995;25(4):481–3.
[164] Lopez DM, Weingarten-Arams JS, Singer LP, et al. Relationship between arterial, mixed venous, and internal jugular carboxyhemoglobin concentrations at low, medium, and high concentrations in a piglet model of carbon monoxide toxicity. Crit Care Med 2000;28(6): 1998–2001.
[165] Bozeman WP, Myers RA, Barish RA. Confirmation of the pulse oximetry gap in carbon monoxide poisoning. Ann Emerg Med 1997;30(5):608–11.
[166] Buckley RG, Aks SE, Eshom JL, et al. The pulse oximetry gap in carbon monoxide intoxication. Ann Emerg Med 1994;24(2):252–5.

[167] Hampson NB. Pulse oximetry in severe carbon monoxide poisoning. Chest 1998;114(4): 1036–41.
[168] Larkin JM, Brahos GJ, Moylan JA. Treatment of carbon monoxide poisoning: prognostic factors. J Trauma 1976;16(2):111–4.
[169] Holstege CP, Baer AB, Eldridge DL, et al. Case series of elevated troponin I following carbon monoxide poisoning. J Toxicol Clin Toxicol 2004;42(5):742–3.
[170] Shusterman D, Alexeeff G, Hargis C, et al. Predictors of carbon monoxide and hydrogen cyanide exposure in smoke inhalation patients. J Toxicol Clin Toxicol 1996; 34(1):61–71.
[171] Van Hoesen KB, Camporesi EM, Moon RE, et al. Should hyperbaric oxygen be used to treat the pregnant patient for acute carbon monoxide poisoning? A case report and literature review. JAMA 1989;261(7):1039–43.
[172] Rasmussen LS, Poulsen MG, Christiansen M, et al. Biochemical markers for brain damage after carbon monoxide poisoning. Acta Anaesthesiol Scand 2004;48(4): 469–73.
[173] Brvar M, Mozina H, Osredkar J, et al. S100B protein in carbon monoxide poisoning: a pilot study. Resuscitation 2004;61(3):357–60.
[174] Brvar M, Mozina H, Osredkar J, et al. The potential value of the protein S-100B level as a criterion for hyperbaric oxygen treatment and prognostic marker in carbon monoxide poisoned patients. Resuscitation 2003;56(1):105–9.
[175] Messier LD, Myers RA. A neuropsychological screening battery for emergency assessment of carbon-monoxide-poisoned patients. J Clin Psychol 1991;47(5):675–84.
[176] Amitai Y, Zlotogorski Z, Golan-Katzav V, et al. Neuropsychological impairment from acute low-level exposure to carbon monoxide. Arch Neurol 1998;55(6):845–8.
[177] Hay PJ, Denson LA, van Hoof M, et al. The neuropsychiatry of carbon monoxide poisoning in attempted suicide: a prospective controlled study. J Psychosom Res 2002; 53(2):699–708.
[178] Myers RA, Britten JS. Are arterial blood gases of value in treatment decisions for carbon monoxide poisoning? Crit Care Med 1989;17(2):139–42.
[179] Hampson NB, Dunford RG, Kramer CC, et al. Selection criteria utilized for hyperbaric oxygen treatment of carbon monoxide poisoning. J Emerg Med 1995;13(2): 227–31.
[180] Hart IK, Kennedy PG, Adams JH, et al. Neurological manifestation of carbon monoxide poisoning. Postgrad Med J 1988;64(749):213–6.
[181] Vieregge P, Klostermann W, Blumm RG, et al. Carbon monoxide poisoning: clinical, neurophysiological, and brain imaging observations in acute disease and follow-up. J Neurol 1989;236(8):478–81.
[182] Zagami AS, Lethlean AK, Mellick R. Delayed neurological deterioration following carbon monoxide poisoning: MRI findings. J Neurol 1993;240(2):113–6.
[183] Gale SD, Hopkins RO, Weaver LK, et al. MRI, quantitative MRI, SPECT, and neuropsychological findings following carbon monoxide poisoning. Brain Inj 1999;13(4): 229–43.
[184] Denays R, Makhoul E, Dachy B, et al. Electroencephalographic mapping and 99mTc HMPAO single-photon emission computed tomography in carbon monoxide poisoning. Ann Emerg Med 1994;24(5):947–52.
[185] Ducasse JL, Celsis P, Marc-Vergnes JP. Non-comatose patients with acute carbon monoxide poisoning: hyperbaric or normobaric oxygenation? Undersea Hyperb Med 1995; 22(1):9–15.
[186] Choi IS, Kim SK, Lee SS, et al. Evaluation of outcome of delayed neurologic sequelae after carbon monoxide poisoning by technetium-99m hexamethylpropylene amine oxime brain single photon emission computed tomography. Eur Neurol 1995;35(3):137–42.
[187] Winter PM, Miller JN. Carbon monoxide poisoning. JAMA 1976;236(13):1502.

[188] Thom SR. Antidotes in depth: hyperbaric oxygen. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al, editors. Goldfrank's toxicologic emergencies. 7th edition. New York: McGraw-Hill; 2002. p. 1492–7.
[189] Boerema I, Meyne NG, Brummelkamp WH, et al. Life without blood. Arch Chir Neerl 1959;11:70.
[190] Pace N, Stajman E, Walker EL. Acceleration of carbon monoxide elimination in man by high pressure oxygen. Science 1950;111:652–4.
[191] Jay GD, McKindley DS. Alterations in pharmacokinetics of carboxyhemoglobin produced by oxygen under pressure. Undersea Hyperb Med 1997;24(3):165–73.
[192] Araki R, Nashimoto I, Takano T. The effect of hyperbaric oxygen on cerebral hemoglobin oxygenation and dissociation rate of carboxyhemoglobin in anesthetized rats: spectroscopic approach. Adv Exp Med Biol 1988;222:375–81.
[193] Peterson JE, Stewart RD. Absorption and elimination of carbon monoxide by inactive young men. Arch Environ Health 1970;21(2):165–71.
[194] Smith G. The treatment of carbon monoxide poisoning with oxygen at two atmospheres absolute. Ann Occup Hyg 1962;5:259–63.
[195] End E, Long CW. Oxygen under pressure in carbon monoxide poisoning. J Ind Hyg Toxicol 1942;24(10):302–6.
[196] Thom SR. Antagonism of carbon monoxide–mediated brain lipid peroxidation by hyperbaric oxygen. Toxicol Appl Pharmacol 1990;105(2):340–4.
[197] Brown SD, Piantadosi CA. Reversal of carbon monoxide–cytochrome c oxidase binding by hyperbaric oxygen in vivo. Adv Exp Med Biol 1989;248:747–54.
[198] Thom SR. Functional inhibition of leukocyte B2 integrins by hyperbaric oxygen in carbon monoxide–mediated brain injury in rats. Toxicol Appl Pharmacol 1993;123(2): 248–56.
[199] Thom SR, Mendiguren I, Nebolon M. Temporary inhibition of human neutrophil B2 integrin function by hyperbaric oxygen (HBO). Clin Res 1994;42:130A.
[200] Jiang J, Tyssebotn I. Normobaric and hyperbaric oxygen treatment of acute carbon monoxide poisoning in rats. Undersea Hyperb Med 1997;24(2):107–16.
[201] Gilmer B, Kilkenny J, Tomaszewski C, et al. Hyperbaric oxygen does not prevent neurologic sequelae after carbon monoxide poisoning. Acad Emerg Med 2002;9(1):1–8.
[202] Piantadosi CA. Carbon monoxide poisoning. N Engl J Med 2002;347(14):1054–5.
[203] Thom SR, Taber RL, Mendiguren II, et al. Delayed neuropsychologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. Ann Emerg Med 1995;25(4):474–80.
[204] Mathieu D, Wattel F, Mathieu-Nolf M, et al. Randomized prospective study comparing the effect of HBO versus 12 hours NBO in non comatose CO poisoned patients: results of the interim analysis. Undersea Hyperb Med 1996;23:7–8.
[205] Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. Med J Aust 1999; 170(5):203–10.
[206] Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002;347(14):1057–67.
[207] Weaver LK, Hopkins RO, Larson-Lohr V. Carbon monoxide poisoning: a review of human outcome studies comparing normobaric oxygen with hyperbaric oxygen. Ann Emerg Med 1995;25(2):271–2.
[208] Tibbles PM, Perrotta PL. Treatment of carbon monoxide poisoning: a critical review of human outcome studies comparing normobaric oxygen with hyperbaric oxygen. Ann Emerg Med 1994;24(2):269–76.
[209] Juurlink DN, Stanbrook MB, McGuigan MA. Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database Syst Rev 2000;2:CD002041.
[210] Thom SR. Hyperbaric-oxygen therapy for acute carbon monoxide poisoning. N Engl J Med 2002;347(14):1105–6.

[211] Olson KR, Seger D. Hyperbaric oxygen for carbon monoxide poisoning: does it really work? Ann Emerg Med 1995;25(4):535–7.
[212] Scheinkestel CD, Tuxen DV, Bailey M, et al. Hyperbaric oxygen in carbon monoxide poisoning. Authors of study clarify points that they made. BMJ 2000;321(7253):109–10 [author reply: 110–1].
[213] Unsworth IP. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. Was the best treatment protocol used? Med J Aust 1999;170(11):564–5.
[214] Kindwall EP. Hyperbaric treatment of carbon monoxide poisoning. Ann Emerg Med 1985; 14(12):1233–4.
[215] Tomaszewski CA, Thom SR. Use of hyperbaric oxygen in toxicology. Emerg Med Clin North Am 1994;12(2):437–59.
[216] Myers RA, Snyder SK, Linberg S, et al. Value of hyperbaric oxygen in suspected carbon monoxide poisoning. JAMA 1981;246(21):2478–80.
[217] Myers RAM, Thom SR. Carbon monoxide and cyanide poisoning. In: Kindwall EP, editor. Hyperbaric medicine practice. Flagstaff (AZ): Best Publishing; 1994. p. 357.
[218] Van Meter KW, Weiss L, Harch PG, et al. Should the pressure be off or on in the use of oxygen in the treatment of carbon monoxide–poisoned patients? Ann Emerg Med 1994; 24(2):283–8.
[219] Tibbles PM, Edelsberg JS. Hyperbaric oxygen therapy. N Engl J Med 1996;334(25): 1642–8.
[220] Geiderman JM, Ault MJ. Hyperbaric-oxygen therapy. N Engl J Med 1996;335(22):1684 [author reply: 1685–6].
[221] Finnerty JP. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2003; 348(6):557–60 [author reply: 557–60].
[222] Rudge FW. Carbon monoxide poisoning in infants: treatment with hyperbaric oxygen. South Med J 1993;86(3):334–7.
[223] Margulies JL. Acute carbon monoxide poisoning during pregnancy. Am J Emerg Med 1986;4(6):516–9.
[224] Brown DB, Mueller GL, Golich FC. Hyperbaric oxygen treatment for carbon monoxide poisoning in pregnancy: a case report. Aviat Space Environ Med 1992;63(11):1011–4.
[225] Hill EP, Hill JR, Power GG, et al. Carbon monoxide exchanges between the human fetus and mother: a mathematical model. Am J Physiol 1977;232(3):H311–23.
[226] Gabb G, Robin ED. Hyperbaric oxygen. A therapy in search of diseases. Chest 1987;92(6): 1074–82.
[227] Weaver LK, Hopkins RO, Elliott G. Carbon monoxide poisoning. N Engl J Med 1999; 340(16):1290 [author reply: 1292].
[228] Hampson NB, Simonson SG, Kramer CC, et al. Central nervous system oxygen toxicity during hyperbaric treatment of patients with carbon monoxide poisoning. Undersea Hyperb Med 1996;23(4):215–9.
[229] Sloan EP, Murphy DG, Hart R, et al. Complications and protocol considerations in carbon monoxide–poisoned patients who require hyperbaric oxygen therapy: report from a ten-year experience. Ann Emerg Med 1989;18(6):629–34.
[230] Pierce EC II, Zacharias A, Alday JM Jr, et al. Carbon monoxide poisoning: experimental hypothermic and hyperbaric studies. Surgery 1972;72(2):229–37.
[231] Vossberg B, Skolnick J. The role of catalytic converters in automobile carbon monoxide poisoning: a case report. Chest 1999;115(2):580–1.
[232] Yoon SS, Macdonald SC, Parrish RG. Deaths from unintentional carbon monoxide poisoning and potential for prevention with carbon monoxide detectors. JAMA 1998; 279(9):685–7.