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Carbon monoxide poisoning

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The following patients may be encountered during an emergency department (ED) shift: a 7-year-old with a first-time seizure, an 80-year-old with syncope, a family with a flulike illness, a pregnant patient with vomiting and dizziness, a 45-year-old with chest pain, a comatose patient from a house fire, and a factory worker with a headache. Although these complaints may sound diverse, carbon monoxide (CO) exposure may account for all of these clinical scenarios. CO exposure often goes unrecognized and can lead to significant morbidity and mortality. Rapid recognition and appropriate therapy can improve outcomes significantly.

Epidemiology and sources

CO is a colorless, odorless, nonirritating gas produced primarily as a result of incomplete combustion of any carbonaceous fossil fuel. CO poisoning accounts for an estimated 40,000 annual ED visits the United States. [1] CO is the leading cause of poisoning mortality in the United States [2,3] and may be responsible for more than half of all fatal poisonings worldwide [4]. The Centers for Disease Control and Prevention reported that from 1968 to 1998, 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 [5]. An estimated 5000 to 6000 people die in the United States each year as a result of CO exposure [3]. The rate of accidental deaths seems to have declined from 1513 per year in 1979 to approximately 500 to 600 per year in the 1990s [3,6], likely owing to improved motor vehicle

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emissions policies and the use of catalytic converters [5,7]. Although most accidental deaths are due to house fires and automobile exhaust, consumer products contribute to approximately 180 to 200 annual deaths. The US Consumer Product Safety Commission summarized the 180 unintentional consumer product–related, non–fire-related CO deaths in 1998 as being associated with indoor heating systems (71%), stoves and other appliances (10%), charcoal grills (9%), camp stoves (6%), and water heaters (4%) [6]. Patients older than age 65, men, and ethanol-intoxicated patients seem to be at higher risk of dying as a result of fatal, unintentional, non–fire-related CO poisoning [6,8,9]. Unintentional deaths peak in the winter months, as heating systems are being used and windows are closed [3]. Box 1 lists CO sources.

Environmental CO exposure typically is less than 0.001%, or 10 parts per million (ppm) [10], but may be higher in urban areas [11]. The amount of CO absorbed by the body depends on minute ventilation, duration of exposure, and concentrations of CO and oxygen in the environment [12–15]. After cooking with a gas stove, indoor air concentrations of CO may reach 100 ppm [11]. A cigarette smoker is exposed to an estimated 400 to 500 ppm of CO while actively smoking [4]. Automobile exhaust may contain 10% (100,000 ppm) CO [16]. Before catalytic converters, closed environment exposure to car exhaust could produce death within 30 minutes [7]. Exposure to 70 ppm may lead to carboxyhemoglobin (CO-Hgb) levels of 10% at

Box 1. Sources of carbon monoxide

Endogenous
Normal heme catabolism by heme oxygenase
Increased in hemolytic anemia, sepsis

Exogenous
Incomplete combustion of carbonaceous fossil fuel
House fires
Automobile exhaust
Propane-powered vehicles (forklifts, ice skating rink resurfacers)
Gas-powered furnaces, ovens, fireplaces
Heaters
Indoor grills
Camp stoves
Boat exhaust
Cigarette smoke

Methylene chloride
Solvent found primarily in paint remover
Endogenously converted to carbon monoxide after inhalational exposure

equilibrium (approximately 4 hours) [2,17], and exposure to 350 ppm may lead to CO-Hgb levels of 40% at equilibrium [4,17]. The current Occupational Safety and Health Administration permissible exposure limit for CO exposure in workers is 50 ppm averaged over an 8-hour workday [18].

In addition to the aforementioned sources, CO poisoning has been reported in children riding in the back of pickup trucks [19], recreational boaters [20,21], factory workers operating propane-powered forklifts [22–24], and persons in an ice skating rink using propane-powered resurfacing machines [25,26]. Also, winter snow may obstruct vehicular exhaust systems resulting in CO poisoning [27]. Fatalities are reported with recreational boaters swimming underneath the swim platform near the boat exhaust [28] and campers using gas-powered stoves in outdoor tents [29]. In the winter, misuse of a gas stove or burning charcoal briquettes for heating purposes is predictive of high CO-Hgb levels [30–32]. Another source is methylene chloride, a solvent found in paint remover and aerosol propellants, which is converted in the body to CO after inhalational exposure [33–35].

Endogenous production of CO occurs during heme catabolism by heme oxygenase but should not produce CO-Hgb levels greater than 1%; however, in hemolytic anemia, CO-Hgb may increase to 3% to 4% [16,36,37]. Severe sepsis has been shown to elevate endogenous CO production [38].

A patient who presents from a house fire or after a suicide attempt with automobile exhaust may not represent a diagnostic dilemma. A family presenting to the ED with symptoms of nausea and vomiting or a patient with a headache resolving after ED arrival can be misdiagnosed easily, however, and discharged back to the dangerous environment and subsequently suffer more serious exposures. An estimated one third of CO poisoning may go undetected, emphasizing the importance of entertaining the diagnosis in patients with suggestive symptoms [11,39,40].

Pathophysiology

Hemoglobin binding

The pathophysiology of CO poisoning initially was thought to be due exclusively to the cellular hypoxia imposed by replacing oxyhemoglobin by CO-Hgb and producing a relative anemia [41]. CO binds to hemoglobin with an affinity more than 200 times that of oxygen [12,42,43] and causes a leftward shift in the oxygen-hemoglobin dissociation curve, decreasing oxygen delivery to the tissues and resulting in tissue hypoxia [43].

Direct cellular toxicity

CO poisoning is much more complex than initially presumed and has mechanisms of toxicity beyond the formation of CO-Hgb. In a classic study, Goldbaum et al [44] showed that dogs breathing 13% CO died within 1 hour

after achieving CO-Hgb levels of 54% to 90%. Exchange transfusion with blood containing 80% CO-Hgb to otherwise healthy dogs resulted in no toxic effects, however, 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 [45–49].

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 theory helps to explain why CO-Hgb levels do not correlate with the severity of clinical effects [50–54]. 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

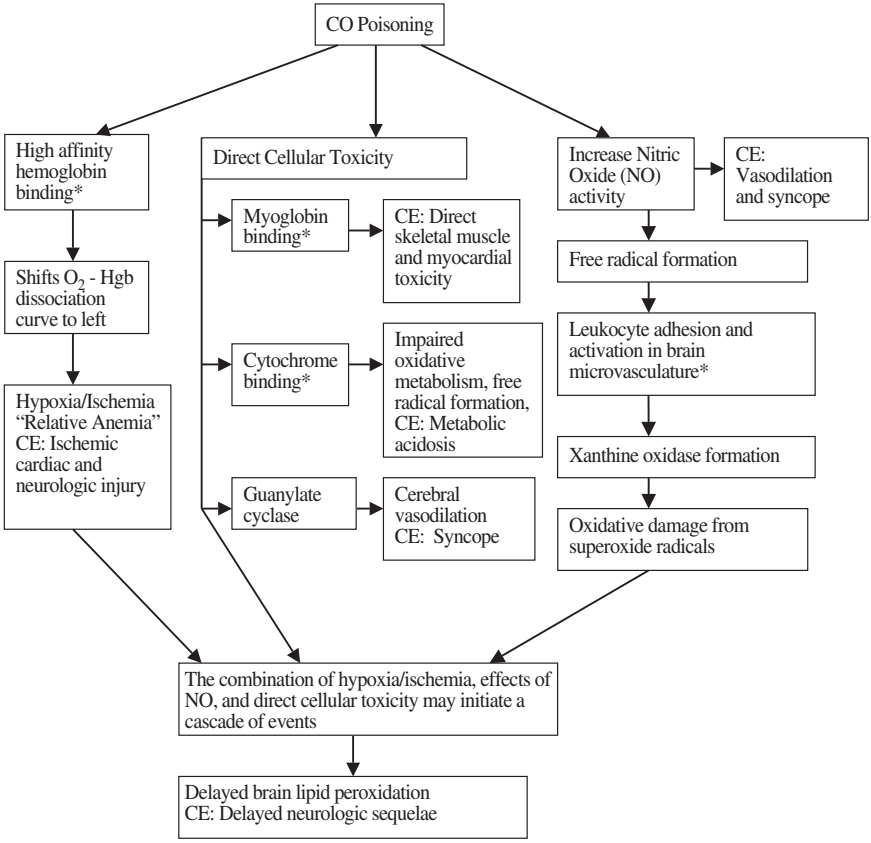

Fig. 1. Pathophysiology of carbon monoxide poisoning. *Potential hyperbaric oxygen therapy target. CE, clinical effect.

cytochrome aa_3 in vitro [55,56], and the disruption of oxidative metabolism via cytochrome oxidase may lead to the generation of oxygen free radicals [40,57]. Cellular respiration also may be impaired via inactivation of mitochondrial enzymes and impaired electron transport from oxygen radicals (ie, peroxynitrite) produced after CO exposure [40,58,59]. Cellular energy metabolism is inhibited even after normalization of CO-Hgb levels [54,60], which may explain prolonged clinical effects after CO-Hgb levels decrease [13]. Binding to myoglobin may reduce oxygen availability in the heart and lead to arrhythmias and cardiac dysfunction [13,61,62] and may contribute to direct skeletal muscle toxicity and rhabdomyolysis [63–66]. CO also stimulates guanylyl cyclase, which increases cyclic guanosine monophosphate resulting in cerebral vasodilation, which has been associated with loss of consciousness in an animal model of CO poisoning [67,68].

Nitric oxide

The role of nitric oxide (NO) and other oxygen free radicals has been researched extensively in the setting of CO poisoning. Many animal studies have shown cerebral vasodilation after exposure to CO, which is associated temporally with loss of consciousness and increased NO levels [69–72]. This finding has led to speculation that clinically syncope may be related to NO-mediated cerebral vessel relaxation and low blood flow. NO also is a peripheral vasodilator [73] and may result in systemic hypotension, although this has not been studied in the setting of CO poisoning. The presence of systemic hypotension in CO poisoning is correlated with the severity of cerebral lesions, however, particularly in watershed areas of perfusion (ie, basal ganglia, white matter, hippocampus) [13,53,74–77].

NO also seems 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) [78]. NO may affect the adherence of neutrophils to the endothelium, potentially by affecting the function of neutrophil adhesion molecules such as β_2-integrin [58,78]. Neutrophil adherence to the microvasculature seems to lead to xanthine oxidase activation, oxidative radical formation, oxidative damage, and ultimately brain lipid peroxidation, which is thought to be responsible for DNS [40,58,72,78–82].

Brain lipid peroxidation after CO exposure seems to be a postischemic reperfusion phenomenon, mediated by alterations in cerebral blood flow and oxidative free radical damage [40,57,72,79,82–84]. A period of hypotension and unconsciousness may be required for lipid peroxidation to occur [82]. Although the exact sequence of events is not known, the experimental administration of NO synthase inhibitors has been found to inhibit cerebral vasodilation [48] and oxidative damage [72].

Other potential mechanisms of CO toxicity include excitotoxicity (ie, glutamate-mediated neuronal injury) [85–87], increased atherogenesis

[88,89], involvement with cytochrome P-450 [13,90], and apoptosis [85]. 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 [10,30,91–93]. Table 1 lists common symptoms [2,10,94]. Initial symptoms after CO exposure include headache, nausea, and dizziness [95,96]. As exposure increases, patients develop more pronounced and severe symptoms, with oxygen-dependent organs showing the earliest signs of injury. The brain and the heart are the most oxygen-dependent organs and are most sensitive to the toxic effects of CO.

Early neurologic manifestations include dizziness and headache. Increasing exposure may produce altered mental status, confusion, syncope,

Table 1
Clinical signs and symptoms associated with carbon monoxide poisoning

Severity	Signs and symptoms
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 references 2 and 10.

seizure, acute strokelike syndromes, and coma. Isolated seizures have been reported in pediatric patients [97,98]. Abnormalities on neuroimaging studies, particularly bilateral globus pallidus lesions, often are seen in significant CO poisoning [99–102]. The presence of systemic hypotension in CO poisoning is correlated with the severity of central nervous system structural damage [13,53,74–77].

Early cardiovascular effects of CO poisoning are manifested as a response to hypoxia [103]. 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 [40,52]. Hypotension may result from myocardial injury secondary to hypoxia-ischemia, direct myocardial depressant activity from myoglobin binding, peripheral vasodilation, or a combination of the aforementioned [84] and may persist even after neurologic and metabolic symptoms have resolved [104].

CO poisoning exacerbates underlying cardiovascular disease, making this group of patients particularly susceptible to cardiovascular disturbances [39,105]. Low-level experimental CO exposures producing CO-Hgb levels of 2% to 6% in patients with documented coronary artery disease have produced dysrhythmias and decreased latency to the development of cardiac ischemia during stress testing [106–108]. CO exposure lowers the threshold for malignant ventricular dysrhythmias [61]. In patients with undiagnosed underlying coronary artery disease, CO exposure may act as a stress test similar to anemia. Even in healthy volunteers, CO exposure has been found to result in nonspecific electrocardiogram changes [96], and myocardial infarction has been reported in CO poisoning in the absence of underlying coronary disease [109].

CO poisoning also may result in rhabdomyolysis and acute renal failure, potentially as a direct toxic effect of CO on skeletal muscle [63–65]. Cutaneous blisters [110] and noncardiogenic pulmonary edema [111–113] have been reported in patients with severe CO poisoning. The ''cherry red'' skin color often discussed in textbooks is not seen commonly in practice [10,40,111].

CO binds more tightly to fetal than adult hemoglobin, making infants particularly vulnerable to its effects [114]. Occult CO poisoning may present as an acute life-threatening event in an infant [115]. Even older pediatric patients are more susceptible to the effects of CO because of higher metabolic rate and oxygen uptake [116,117]. Symptoms in pediatric patients are often nonspecific, such as nausea and vomiting, and can be misdiagnosed as a viral illness easily [93,115]. An increased incidence of syncope and lethargy is reported in the pediatric patients compared with adults [116].

CO exposure in pregnant patients 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 [118,119]. In humans, adverse fetal outcomes,

such as stillbirth, anatomic malformations, and neurologic disability, are associated with more severe maternal exposure [120–123]. Even in mildly symptomatic mothers, the effects on the fetus can be severe, however, including anatomic malformations and fetal demise [121,124]. When autopsy is performed, fetal brain damage is generally apparent, particularly in the basal ganglia and globus pallidus [120,125]. 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 [120,121,126,127].

Delayed

The effects of CO are not confined to the period immediately after exposure. Persistent or delayed neurologic effects also have 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 DNS, may manifest as almost any conceivable neurologic and 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 [39,128–132].

The true incidence of DNS is difficult to determine, with estimates ranging from less than 1% to 47% of patients after CO poisoning [51,112,129–131,133–135]. The large variability in incidence is explained at least partially by a lack of consistency in defining DNS using clinical, subclinical (ie, neuropsychometric testing results), self-reported, or combination criteria. The two largest case series are from Korea, where CO poisoning is common owing to the use of coal stoves for cooking and heating [129,130]. 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 the development of DNS was 2 to 40 days (mean 22.4 days). Of patients followed up, 75% recovered within 1 year. The incidence of DNS increased in accordance with the duration of unconsciousness experienced by the patient and with age older than 30 [130]. Another large series reporting 2967 patients with CO poisoning had findings almost identical to the above-mentioned cohort. Greater than 90% of patients who developed DNS in this series were unconscious during the acute intoxication, and the incidence of DNS was disproportionately higher in older patients (50–79 years old) and nonexistent in patients younger than 30 years old [129].

In general, patients who present with a more symptomatic initial clinical picture are the most likely to develop persistent sequelae or DNS. DNS occurs most frequently in patients who present comatose, older patients, and perhaps patients with a prolonged exposure [23,51,129,130,133,135–138]. Neuropsychometric testing abnormalities have been associated with decreased level of consciousness at presentation, particularly if the duration of unconsciousness exceeds 5 minutes [133,137].

Variable definitions of DNS are used by different investigators and 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 with unknown clinical and prognostic significance. Abnormalities found on neuropsychometric testing in CO-exposed patients may be explained partially by confounders. Patients who are acutely ill, suicidal, or depressed or have coingestion of other intoxicants may perform poorly on these tests [139–142]. In addition, these patients generally do not have a baseline for comparison [13,143]. Despite these limitations, neuropsychometric testing provides an objective measure of cognitive function, which can be used to screen and follow CO-poisoned patients.

Chronic

Chronic, low-level CO exposure, such as may be seen in a workplace, also has been linked to various symptoms, such as headache, dizziness, anorexia, apathy, insomnia, and personality disturbance [23,24,144–146]. Chronic CO exposure may accelerate atherosclerosis, although other risk factors, such as smoking, confound the picture [105]. In addition, chronic CO exposure has been associated with polycythemia and cardiomegaly, likely secondary to chronic hypoxia [103].

Diagnosis

A high index of suspicion is essential to make the diagnosis of occult CO poisoning. In prospective observational studies, patients presenting to the ED with winter flu–like syndrome may have CO-Hgb levels ranging from 3% to 24%, and the possibility of CO exposure must be entertained in patients presenting to the ED with these symptoms [30,91,92]. Historical factors that are important to elicit include the use of gas stoves for heat and cohabitants with similar symptoms [30,32,147]. In addition, patients whose symptoms are associated with particular environments (ie, workplace), activities (ie, boating), or use of appliances (ie, 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 of 10%, perhaps slightly higher immediately after smoking [10,148]. Low CO-Hgb levels (<15–20%) correlate well with mild symptoms, such as nausea and headache [30,95,96], and levels greater than 60% to 70% are usually rapidly fatal [13]. Intermediate levels do not seem to correlate well with symptoms or with prognosis, however, so treatment decisions cannot be based solely on CO-Hgb levels [36,40,100,149–151]. 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 [51]. The wide overlap between blood levels and clinical symptoms underscores the difficulty in 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 [36,94]. A patient who attains a high CO-Hgb level after a brief, high-level exposure may not manifest any clinical toxicity [151], whereas a patient who attains the identical CO-Hgb level after a prolonged lower level exposure may be significantly symptomatic. Also, because CO-Hgb levels decline with time and with oxygen therapy, an initial CO-Hgb level may not reflect accurately 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 settings, exhaled CO levels measured by using a Breathalyzer-type device can help to confirm the diagnosis, whether in the prehospital or ED setting [23,152].

CO-Hgb levels should be measured via a co-oximeter, which measures total hemoglobin concentration, oxyhemoglobin, and deoxyhemoglobin and concentrations of abnormal hemoglobins, such as CO-Hgb and methemoglobin, by differentiating wavelength absorbance values [16]. 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 [153]. In an animal model, the accuracy was maintained at CO-Hgb levels exceeding 60% [154].

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 measured pulse oximetry by finger probe and the true pulse oximetry obtained spectrophotometrically via co-oximeter, has been found to approximate the CO-Hgb level. As the CO-Hgb level rises, the degree of pulse oximetry overestimation increases [155–157].

Other diagnostic testing

Other diagnostic testing in the CO-poisoned patient depends on the clinical scenario and may include arterial blood gas monitoring, electrolytes, cardiac markers, blood urea nitrogen and creatinine, creatine phosphokinase, chest radiograph, electrocardiogram, 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, or adverse sequelae after CO poisoning [112,113,150,158]. Lactate has been used as a marker for severe poisoning [150]. Chest radiograph may show evidence of noncardiogenic pulmonary edema in the severely poisoned patient. Electrocardiogram may show nonspecific changes, dysrhythmias, or changes associated with myocardial ischemia. Cardiac markers and creatine phosphokinase may be elevated. In the setting of smoke inhalation, concomitant cyanide toxicity may be seen with CO poisoning [111,159]. Fetal monitoring and other tests of fetal well-being may help to detect fetal compromise in a CO-poisoned pregnant patient [160].

Neuropsychometric testing

A battery of neuropsychometric tests has been developed specifically to screen for cognitive dysfunction as a result of CO poisoning [161]. 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 improve scores after HBOT, particularly on the trail making test (Fig. 2) [161]. Volunteers exposed to CO were found to perform poorly on the CONSB compared with controls without CO exposure [162].

Neuropsychometric testing discussed in the literature may refer to the CONSB or tests such as the mini-mental status examination, Weschler adult intelligence scale–revised, Weschler memory scale–revised, and others. The utility of neuropsychometric testing in CO poisoning in the ED has yet to be determined, and significant controversy exists regarding their value. Although CO-poisoned patients have been shown to perform poorly on neuropsychometric tests, abnormalities may not be explained exclusively by CO exposure. Patients attempting suicide with means other than CO

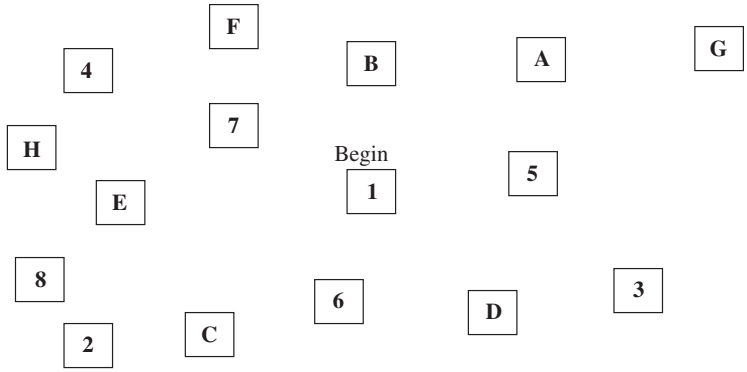

Fig. 2. Sample trail making test. *Instructions:* Draw a line from the number 1 to the letter A, from the number 2 to the letter B, and so on without lifting the pencil. The examiner may prompt the patient. The score is the total time in seconds for task completion.

perform as poorly on neuropsychometric testing as patients attempting suicide with CO [163]. Improvement in neuropsychometric testing after HBOT therapy in CO-poisoned patients often is cited as evidence for the effectiveness of HBOT. Other factors could result in neuropsychometric test improvement, however, such as motivation, practice effect due to repetition of the test, improvement of mental status overall, and metabolism of coingestants or cointoxicants [50,139–142]. 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 [50,131,140,164,165].

CT of the brain in patients with severe CO exposure may show signs of cerebral infarction secondary to hypoxia, ischemia, and hypotension induced by severe CO exposure; however, a well-reported finding is bilateral globus pallidus low-density lesions (Fig. 3) [99–102]. The development of this lesion has been correlated with local low blood flow to the globus pallidus [77], metabolic acidosis, and hypotension [74,75] during CO poisoning in animal models. Globus pallidus lesions may be delayed several days after initial presentation [166] and may resolve with time [137,167]. Concomitant white matter lesions also may be seen [99,102]. 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 in patients with CO exposure may show diffuse, symmetric white matter lesions, predominantly in the periventricular areas, although the centrum semiovale, deep subcortical white matter, thalamus, basal ganglia, and hippocampus also may be affected [137,168–170].

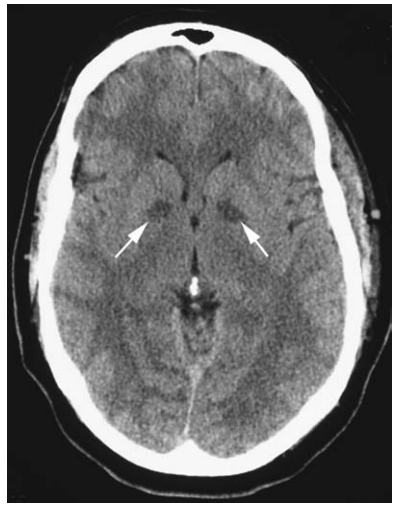

Fig. 3. Bilateral low-density lesions in the globus pallidus seen after carbon monoxide poisoning (*arrows*).

Patients with abnormal neuroimaging findings are more likely to have poorer outcomes, such as death or persistent functional neurologic impairment, after CO exposure than patients with normal neuroimaging studies [99,100,102,132,137,169]. Exceptions exist, however, and the results of neuroimaging studies do not always predict outcome accurately [132,169].

Single-photon emission CT (SPECT), electroencephalography, and quantitative MRI have been studied as adjunctive diagnostic tests in CO-exposed patients but generally are not widely available in the ED [170–172]. SPECT in particular may correlate better than other neuroimaging findings with the development of delayed neurologic sequelae [173].

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 resulting from CO poisoning and to accelerate elimination of CO from the body. Whether this oxygen should be given under increased pressure with HBOT, or under ambient pressures (normobaric oxygen [NBO]) is a subject of much debate. HBOT is not universally available and is not entirely risk-free. HBOT may have a role in preventing adverse

neurologic sequelae in CO poisoning, however, and is indicated for selected patients. HBOT consists of the delivery of 100% oxygen within a pressurized chamber resulting in a manyfold increase in the dissolved oxygen in the body (partial pressure of oxygen 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% [174,175]. 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 [176]. 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 [12,177–179]. Wide individual variation exists, however, and prolonged exposures may result in prolonged half-life [177,180].

HBOT for CO poisoning was first discussed by Haldane in the 1890s and first used in the 1960s [181]. Because CO toxicity was initially thought to result entirely from the relative anemia imposed by the formation of CO-Hgb, HBOT was thought beneficial merely by accelerating the dissociation of CO from hemoglobin. As understanding of the pathophysiology of CO poisoning and of HBOT has evolved, however, it seems that HBOT has other effects. HBOT has been shown in CO-poisoned animals not only to reduce CO binding to hemoglobin [177,182], but also to reduce CO binding to other heme-containing proteins, such as cytochrome aa_3, that affect cellular metabolism [183,184]. HBOT also may alter neutrophil adhesion to endothelium [185,186], decrease free radical–mediated oxidative damage [183,185], reduce neurologic deficits [81], and reduce overall mortality [71,187] compared with NBO. Other animal studies have found that HBOT does not prevent neuronal injury in the setting of CO poisoning [81,188], and oxygen has the potential to increase oxidative damage resulting from increased generation of free radicals [57,175,185].

Several case series comment on the apparent efficacy of HBOT compared with NBO in reducing adverse neurologic outcomes. In one series, 131 CO-poisoned patients were treated with HBOT, and 82 patients were treated with NBO. Treatment decisions were made at the discretion of the treating physician. The incidence of DNS in this series was zero in the HBOT group and 12.1% in the NBO group. DNS was defined by neuropsychometric testing [131]. Another series of 31 patients treated with HBOT and 79 treated with NBO showed a "poor outcome" in 6 of 31 (19.4%) HBOT patients and 35 of 79 (44.3%) NBO patients. A poor outcome was defined as impairment ranging from memory loss to death [189]. In contrast, patients presenting comatose after CO exposure have experienced a complete recovery even without the use of HBOT [190]. As one would intuit, more severe CO exposures result in greater morbidity and mortality despite HBOT. One series of patients treated with HBOT after CO-induced cardiac arrest yielded no survivors [191]. Patients presenting with acidosis or

hypoxia or patients receiving HBOT more than 6 hours after exposure tend to show increased morbidity and mortality [112]. Even in this population, however, late HBOT may result in improved neurologic function [141, 192–196].

Six prospective, randomized, controlled trials compared HBOT with NBO for CO poisoning (Table 2) [134,172,197–200]. Four of these studies showed a benefit of HBOT, and two of the studies did not. The data and conclusions drawn from these studies are conflicting and highlight the controversy surrounding the utility of HBOT. As a result 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 [141,201,202]. A Cochrane Review including three of these trials [134,197,199] concluded that the overall odds ratio for benefit of HBOT was 0.82 (95% confidence interval 0.41–1.66) using an outcome measure of symptoms at 1 month [203]. The study by Weaver et al [201], considered by many to be the most methodologically rigorous [141,196,204], was published after the Cochrane Review.

Raphael et al [134] performed a prospective, randomized, single-blind study comparing HBOT with NBO for acute CO poisoning. Patients without loss of consciousness were randomized to either NBO or HBOT. Patients with loss of consciousness were randomized to either one or two HBOT sessions. The authors concluded no beneficial effect of HBOT over NBO in patients without loss of consciousness and no beneficial effects of one versus two HBOT sessions in patients with loss of consciousness. This study has been criticized for using broad inclusion criteria, using only 2.0 ATA in their HBOT protocol; not using standardized neuropsychometric tests; not stratifying patients according to time to treatment; and using insensitive outcome measures [205–207].

Ducasse et al [172] performed a prospective, randomized, nonblinded study to evaluate HBOT versus NBO in alert patients with mild CO poisoning. They found that more patients were symptomatic in the NBO group at 2 and 12 hours and that HBOT resulted in more rapid resolution of CO-Hgb levels. These investigators concluded that HBOT reduces clinical recovery time. This study enrolled only a few patients with mild CO toxicity, was nonblinded, and used outcome measures of questionable significance [141].

Thom et al [197] performed a prospective, randomized, nonblinded trial to assess the incidence of DNS in patients receiving HBOT or NBO after mild-to-moderate CO poisoning. They concluded a possible beneficial effect of HBOT in preventing DNS, but recommended further study. This study has been criticized for lack of double blinding, unclear randomization and consent procedures, excluding sick patients, using a small control group for

Table 2
Prospective trials of hyperbaric oxygen treatment for carbon monoxide poisoning

Ref	Methods	HBO protocol	NBO protocol	Outcomes measured	HBO benefit?	Results
134	Randomized Single blind Those without LOC: NBO vs. HBO Those with LOC: 1 session HBO vs. 2	Group A (−LOC): 2 h at 2 ATA and 4 h 100% NBO Group B1 (+LOC): 2 h at 2 ATA and 4 h 100% NBO Group B2 (+LOC): 2 h at 2 ATA × 2 (2–12 h apart) and 4 h 100% NBO	Group A (−LOC): 6 h 100% NBO	Self-assessment questionnaire and PE at 1 month	No	$N = 649$ In those without LOC, no benefit shown for HBO ($p = 0.75$) In those with LOC, no benefit to 2 sessions compared to 1 ($P = 0.75$) 8–12.5% per group lost to follow up Patients included in intent-to-treat analysis even if refused treatment or lost to follow-up
172	Randomized Nonblinded	2 h at 2.5 ATA and 4 h 100% NBO and 6 h 50% NBO	6 h 100% NBO and 6 h 50% NBO	PE and CO-Hgb levels at arrival, 2 and 12 h EEG at 1 and 21 d	Yes	$N = 26$ At 2 and 12 h more NBO patients were symptomatic ($P < 0.05$) HBO better CO-Hgb level and PE at 2 h, but differences by discharge More abnormal EEGs in NBO group at 21 d
197	Randomized Nonblinded	30 min at 2.8 ATA, then 90 min at 2 ATA	100% NBO until symptom resolutionn	NPT and PE after HBO, NPT at 3–4 wk, telephone follow-up at 3 mo	Yes	$N = 65$ More in NBO group had DNS (95% CI 3.2–3) Sometimes testing deferred to 12 h after treatment 84% follow-up rate

198	Randomized Nonblinded Multicenter	90 min at 2.5 ATA	12 h 100% NBO	"Close follow-up" at 1, 3, 6, and 12 mo	Yes at 3 mo No at 6 mo	$N = 575$ Published in abstract form only At 3 mo more NBO patients have "persistent neurologic manifestations" (P = 0.1) No difference at 6 mo
199	Randomized Double blind	60 min at 2.8 ATA qd × 3 d If abnormal PE or NPT, HBO qd × 6 d, with 100% O_2 between treatments	100 min 100% NBO at 1.0 ATA qd × 3 d If abnormal PE or NPT, NBO qd × 6 d, with 100% O_2 in between treatments	NPT and PE after HBO and at 1 mo	No	$N = 191$ More DNS in HBO group ($P = 0.03$) No benefit of HBO shown 46% lost to follow-up at 1 mo Included patients with coingestants
200	Randomized Double blind	3 sessions of HBO at intervals of 6–12 h Session 1: 1 h at 3 ATA and 1 h at 2 ATA Sessions 2 and 3: 2 h at 2 ATA	3 sessions NBO at intervals of 6–12 h Session 1: 150 min 100% NBO at 1 ATA Sessions 2 and 3: 2 h 100% NBO at 1 ATA	NPT after 1st and 3rd treatment, 2 wk, 6 wk, 6 mo, and 1 y PE before 1st treatment, after 3rd treatment Questionnaire at 2 wk and 6 wk	Yes	$N = 152$ Cognitive sequelae less frequent in the HBO group at 6 wk (OR 0.39, 95% CI 0.2–0.78, $P = .007$) Cerebellar dysfunction more common in the NBO group 180 patients declined enrollment for other than exclusion criteria

Abbreviations: ATA, atmospheres absolute; CO-Hgb, carboxyhemoglobin; DNS, delayed neurologic sequelae; EEG, electroencephalography; HBO, hyperbaric oxygen; LOC, loss of consciousness; NBO, normobaric oxygen; NPT, neuropsychometric testing; PE, physical examination.

neuropsychometric testing comparisons, inconsistent location and conditions for neuropsychometric testing, and the presence of greater comorbidity in the NBO group at randomization [208,209].

Mathieu et al [198] performed a randomized, nonblinded, multicenter clinical trial in noncomatose patients presenting within 12 hours of CO exposure with CO-Hgb levels greater than 10%. Patients received either HBOT or NBO. Persistent symptoms were identified in more NBO patients at 3 months, but at 6 months and at 1 year, the groups were similar. This study has been published in abstract form only.

From the previous data, many practitioners used HBOT for CO poisoning until a study was completed that cast more doubt on the efficacy of HBOT. Scheinkestel et al [199] performed a randomized, controlled, double-blinded trial to assess neurologic sequelae in patients with mild, moderate, or severe CO poisoning treated with HBOT or NBO. All patients with CO poisoning other than pregnant patients, burn victims, or children were randomized to 60 minutes of HBOT at 2.8 ATA daily for 3 days ($n = 104$) or 100 minutes of 100% NBO administered in the HBOT chamber daily for 3 days (''sham HBOT'') ($n = 87$). All patients were treated with high-flow oxygen in between experimental treatments. Patients in either group were treated for an additional 3 days if clinical symptoms persisted or if neuropsychometric testing was abnormal. Outcome measures were neuropsychometric testing results and physical examination at completion of three treatments and at 1 month. Scheinkestel et al [199] found that after three treatments, the HBOT patients had significantly worse clinical symptoms and worse neuropsychometric test results, and at 1-month follow-up, more patients in the HBOT group continued to have neurologic sequelae. Although this was the first study to use a double-blinded design and specifically to include severely CO-poisoned patients, it has been criticized for including patients whose exposure was due to suicidal intent, who had consumed cointoxicants, and who had a history of depression. It also was criticized for using nonstandard HBOT and NBO protocols, nonstandard neuropsychometric testing, and cluster randomization and for the low follow-up rate (46%) [210–215].

Weaver et al [200] performed a randomized, controlled, double-blind clinical trial comparing HBOT with NBO in patients presenting less than 24 hours after CO exposure with symptoms or elevated CO-Hgb levels. Patients received a total of three treatments of either HBOT or NBO. The HBOT arm consisted of 60 minutes of HBOT at 3.0 ATA followed by 60 minutes at 2.0 ATA for the first session, followed by 120 minutes of HBOT at 2.0 ATA 6 to 12 hours apart for two more sessions ($n = 76$). The NBO arm consisted of 120 to 150 minutes of 100% NBO 6 to 12 hours apart, administered in the HBOT chamber (''sham'' HBOT) ($n = 76$). Outcomes were assessed using neuropsychometric testing performed after the first and third treatments, 2 weeks, 6 weeks, 6 months, and 1 year and physical examination before the first and after the third treatments. Questionnaires

were administered at 2 weeks and 6 weeks. Cognitive sequelae were diagnosed based on having at least one abnormal neuropsychometric subtest at 6 weeks. Cognitive sequelae were less frequent in the HBO group at 6 weeks (odds ratio 0.39, 95% confidence interval 0.2–0.78, $P = .007$). This study is considered the most rigorous and well-controlled study performed to date but has been criticized for the small number of intubated patients, lack of functional performance as an outcome measure, increased incidence of cerebellar dysfunction in the NBO group at randomization, choice of neuropsychometric testing, inclusion of patients with exposure to gases other than CO, and using a nonstandard HBOT protocol [204, 216–218]. In a subgroup analysis of the aforementioned patient population, HBOT was found to improve outcome specifically in patients with loss of consciousness, metabolic acidosis, CO-Hgb level greater than 25%, and age older than 50 [219].

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 [52,209,220]. Others believe that further trials would be unethical because the paucity of data regarding the effectiveness of HBOT therapy does not justify the risk and expense of transferring patients to HBOT treatment facilities [212]. Others have expressed concern that HBOT supporters seem to be in facilities that offer HBOT [209,215].

No widespread agreement exists regarding selection of patients for HBOT in the setting of CO poisoning [175,209], and a reliable method to identify patients at high risk for neurologic sequelae is not available [141,196,221]. Based on the available knowledge regarding the pathophysiology of CO poisoning and the current clinical data available, broad criteria for recommending HBOT for CO poisoning have included any history of loss of consciousness, neurologic symptoms, cardiovascular dysfunction, metabolic acidosis, abnormalities on neuropsychometric testing, pregnancy with an elevated (>15–20%) CO-Hgb level, persistent symptoms despite NBO, and significantly high CO-Hgb level. Many practitioners use a CO-Hgb level greater than 25% as a criterion for HBOT [12,141,175,204,221–223]. A survey of HBOT centers revealed that more than three fourths of the responders use HBOT for coma, focal neurologic deficits, ischemic changes on electrocardiogram, abnormal psychometric testing, and transient loss of consciousness [165]. Because CO exacerbates underlying heart disease, cardiac dysfunction in CO poisoning should be treated with standard therapy (eg, antidysrhythmics, aspirin, nitrates) and high-flow oxygen, and HBOT should be considered [2].

Recognizing that data to substantiate using various criteria and treatment protocols are lacking, the members of the Undersea and Hyperbaric Medical Society recommend HBOT therapy for CO-poisoned

patients with loss of consciousness (either transient or prolonged), neurologic signs, cardiovascular dysfunction, or severe metabolic acidosis. They acknowledge that many practitioners use abnormal neuropsychometric testing and absolute CO-Hgb levels (typically >25%) to guide treatment decisions. Although they could not define absolutely a high-risk population for developing neurologic sequelae, patients in the extremes of age, patients with neurologic abnormalities, patients with loss of consciousness, and patients with a CO-Hgb level greater than 25% ''require special consideration'' [141]. Although the efficacy of one HBOT treatment protocol over another has not been determined [143,196,204,224–226], one session of HBOT at 2.5 to 3.0 ATA is recommended initially, with further sessions considered if symptoms persist [141,202,221]. Patients not meeting criteria for HBOT should receive 6 to 12 hours of 100% oxygen delivered by tight-fitting facemask [13,141,196,212,225,227]. Infants and children receive the same HBOT protocols as adults [228]. The safety of HBOT in pregnancy has been questioned, but many authors recommend HBOT for pregnant patients with CO poisoning because of the potential benefit to the mother and fetus and the difficulty of assessing intrauterine hypoxia [122,124,127, 160,229,230]. A maternal CO-Hgb level greater than 15% to 20%, evidence of fetal distress, and other standard criteria for HBOT in CO poisoning often are cited as indications for HBOT in CO-poisoned pregnant patients [2,160,221]. Pregnant women may require longer treatment with oxygen than nonpregnant patients [118,119,123,229,231]. 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 (sized for a single individual) hyperbaric chamber (Fig. 4). Other, less common risks include oxygen toxicity, seizures, pulmonary edema and hemorrhage, decompression sickness including pneumothorax and nitrogen emboli, and fire hazard [51,232–234]. The only absolute contraindication to HBOT is an untreated pneumothorax [221]. Relative contraindications include 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 can be provided in a monoplace chamber (ie, tracheal suctioning in burns). In addition, if the patient requires emergency intervention (ie, defibrillation) while undergoing HBOT, several minutes are required to decompress the patient safely before interventions can proceed [175]. 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 [235]. Because of the significant controversy still surrounding the most appropriate treatment of

Box 2. Indications for hyperbaric oxygen therapy in carbon monoxide poisoning

Currently Accepted Indications
1) Neurologic findings
   a. Altered mental status
   b. Coma
   c. Focal neurologic deficits
   d. Seizures
2) Pregnancy with CO-Hgb levels > 15–20%
3) History of loss of consciousness

Considered for:
Cardiovascular compromise (ischemia, infarction, dysrhythmia)
Metabolic acidosis
Extremes of age
Elevated CO-Hgb level (>25–40%)
Abnormal neuropsychometric testing results
Persistent symptoms despite normobaric oxygen

Data from references 2 & 141.

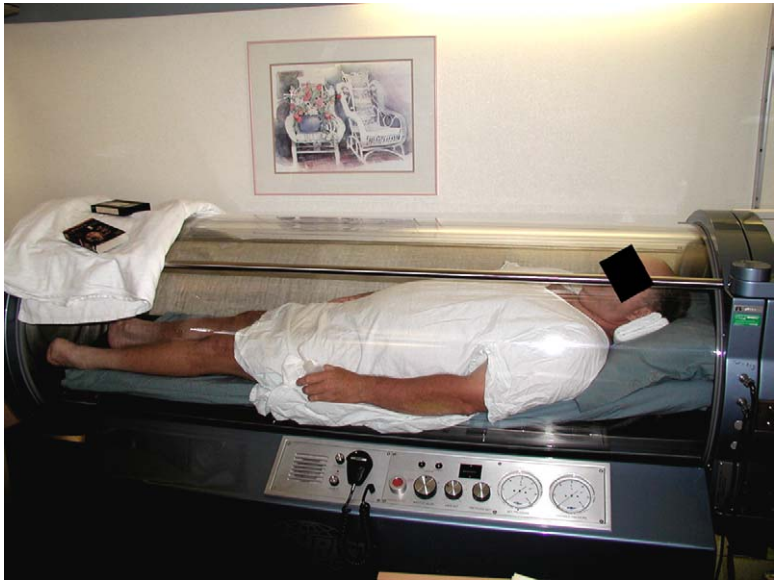

Fig. 4. Monoplace hyperbaric oxygen chamber.

a CO-poisoned patient, a standard of care regarding HBOT for CO-poisoned 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 have been found to be effective [113,236]. Research is ongoing to delineate the possible role of free radical scavengers, monoamine oxidase inhibitors [60], and *N*-methyl-D-aspartate blockers [87].

Disposition

ED physicians are faced with difficult decisions when trying to determine the disposition of a CO-poisoned patient. Although many patients with mild poisoning can be treated in an ambulatory setting with high-flow oxygen, patients with moderate or severe poisoning or concurrent medical problems may need to be admitted [10,12,237,238]. Mild poisoning is defined by some authors as a CO-Hgb level less than 25% and mild gastrointestinal symptoms (nausea, vomiting) or mild neurologic symptoms (headache, dizziness, blurry vision) [2,12]. Before discharging a patient from the ED, however, the source of CO poisoning may require investigation, and other symptomatic cohabitants may be referred for evaluation.

Admission should be considered for patients with symptoms of moderate or severe CO poisoning, such as altered mental status or persistent neurologic or cardiovascular dysfunction. These patients may have comorbidities, such as concurrent cardiac ischemia, burns, or hemodynamic instability, each of which requires specialized care [221,239]. Not all facilities have the capability to provide this specialized care in addition to HBOT. The decision of whether or not to transfer becomes complicated by further questions regarding where to transfer and which of the patient's medical needs takes precedence over the others. There also are questions regarding which patient populations would benefit most from transfer and if the risk of transferring an unstable patient outweighs the benefit of HBOT [13,204,209,210]. The decision is complicated further if the receiving facility has a monoplace chamber, which may not be suitable for an unstable patient who needs frequent interventions [209,221,239]. The Divers Alert Network (DAN) can provide information on the location and use of hyperbaric oxygen facilities (1-800-446-2671 or www.diversalertnetwork.org). The emergency physician also may contact the local poison center, medical toxicologist, or local hyperbaric unit for assistance.

Prevention

The widespread use of catalytic converters on automobiles and improved emissions policies have resulted in a significant decline in accidental CO

poisoning deaths [5,7]. 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 [4]. 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 [4]. Although the effectiveness of CO detectors may be limited in the significant proportion of victims of fatal CO poisoning who die while asleep or while under the influence of alcohol, appropriate and widespread use is likely to decrease the incidence of occult indoor CO poisoning [9].

Summary

CO is an insidious poison with many sources of exposure. CO poisoning produces diverse signs and symptoms, which often are subtle and can be misdiagnosed easily. Failure to diagnose CO poisoning may result in significant morbidity and mortality and allow continued exposure to a dangerous environment. In the ED, a high index of suspicion must be maintained for occult CO exposure. Headache, particularly when associated with certain environments, and flulike illness in the wintertime with symptomatic cohabitants should raise the index of suspicion in the ED significantly for occult CO poisoning.

Emergency treatment of CO poisoning begins with inhalation of supplemental oxygen and aggressive supportive care. HBOT accelerates dissociation of CO from hemoglobin and may prevent DNS. Absolute indications for HBOT for CO poisoning remain controversial, although most would agree that HBOT is indicated in patients who are comatose, are neurologically abnormal, have a history of loss of consciousness with their exposure, or have cardiac dysfunction. Pregnancy with an elevated CO-Hgb level (>15–20%) also is 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 protocols. The emergency physician may be confronted with the difficult decision regarding disposition and even transfer to a hyperbaric facility. Often the local medical toxicologist, poison control center, or hyperbaric unit can assist the emergency physician with the decision-making process.

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