Review Articles

Current Concepts

CARBON MONOXIDE POISONING

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CARBON monoxide intoxication continues to be one of the most common causes of morbidity due to poisoning in the United States.[1,2] It may be intentional or accidental, and exposure may be lethal. Approximately 600 accidental deaths due to carbon monoxide poisoning are reported annually in the United States,[3] and the number of intentional carbon monoxide–related deaths is 5 to 10 times higher.[1] The rate of accidental death caused by carbon monoxide from motor vehicles is higher in the northern United States and peaks during the winter months.[4] The intentional deaths occur year-round without significant peaks.[1] The severe winter of 1995–1996 was associated with increased numbers of reported injuries from carbon monoxide exposure.[5,6] In the winter of 1997–1998, the unusually high number of deaths from carbon monoxide was related to the use of poorly ventilated gasoline-powered generators during a severe ice storm in the northeastern United States.

SOURCES OF CARBON MONOXIDE

Carbon monoxide is a product of the incomplete combustion of hydrocarbons. The concentration of carbon monoxide in the atmosphere is usually less than 0.001 percent. The levels are higher in urban areas than in rural areas. Endogenous carbon monoxide production from the catabolism of hemoglobin is a component of normal biochemical processes. A low base-line level of carboxyhemoglobin is detectable in every person. Tobacco smoke is an important source of carbon monoxide. Blood carboxyhemoglobin commonly reaches a level of 10 percent in smokers and may even exceed 15 percent, as compared with 1 to 3 percent in nonsmokers.[7-9]

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The sources of exogenous carbon monoxide that cause poisoning include motor vehicle exhaust fumes, poorly functioning heating systems, and inhaled smoke.[10] Propane-operated forklifts have been implicated as a cause of headache in warehouse workers.[11] "Cleaner" fuels such as propane and methane undergo more complete combustion but have also been reported to be sources of carbon monoxide poisoning.

The carbon monoxide in motor vehicle exhaust fumes accounts for the majority of deaths from carbon monoxide poisoning in the United States.[12] Of the 11,547 accidental carbon monoxide deaths reported between 1979 and 1988, motor vehicle exhaust accounted for 57 percent.[1] In a series of 56 motor vehicle–associated deaths reported from 1980 to 1995, 43 percent were due to faulty exhaust systems, 39 percent to operation in an improperly ventilated structure, and 18 percent to the use of a fuel-burning heating device in the passenger compartment.[4] Lethal concentrations of carboxyhemoglobin can be achieved within 10 minutes in the confines of a closed garage.[13] Carbon monoxide from motor vehicles can also cause death in semienclosed spaces or in working or living quarters adjacent to garages.[12]

An often overlooked source of carbon monoxide poisoning is methylene chloride, a common component of paint remover and other solvents. Methylene chloride is readily absorbed through the skin and lungs as a vapor and circulates to the liver, where its metabolism results in the generation of carbon monoxide.[14]

PATHOPHYSIOLOGY

Carbon monoxide is a colorless, odorless, and nonirritant toxic gas that is easily absorbed through the lungs. The amount of gas absorbed is dependent on the minute ventilation, the duration of exposure, and the relative concentrations of carbon monoxide and oxygen in the environment.[15] Carbon monoxide is principally eliminated by the lungs as an unchanged gas. Less than 1 percent is oxidized to carbon dioxide.[16] Ten to 15 percent of carbon monoxide is bound to proteins, including myoglobin and cytochrome-*c* oxidase.[17] Less than 1 percent of the absorbed gas exists in solution.

Carbon monoxide toxicity appears to result from a combination of tissue hypoxia and direct carbon monoxide–mediated damage at the cellular level. Carbon monoxide competes with oxygen for binding to hemoglobin. The affinity of hemoglobin for carbon monoxide is 200 to 250 times as great as its affinity for oxygen.[18] The consequences of this competitive binding are a shift of the oxygen–hemoglo-

bin dissociation curve to the left and its alteration to a more hyperbolic shape (Fig. 1). These alterations result in impaired release of oxygen at the tissue level and cellular hypoxia.[19] The binding of carbon monoxide to hemoglobin alone does not account for all of the pathophysiologic consequences observed. In studies in animals, transfusion of blood with highly saturated carboxyhemoglobin but minimal free carbon monoxide does not reproducibly result in clinical symptoms.[20] This observation suggests that the small fraction of free carbon monoxide dissolved in plasma has an important role.

Recent investigations suggest other mechanisms of carbon monoxide–mediated toxicity. One hypothesis is that carbon monoxide–induced tissue hypoxia may be followed by reoxygenation injury to the central nervous system. Hyperoxygenation facilitates the production of partially reduced oxygen species, which in turn can oxidize essential proteins and nucleic acids, resulting in typical reperfusion injury.[21] In addition, carbon monoxide exposure has been shown to cause lipid peroxygenation (degradation of unsaturated fatty acids), leading to reversible demyelinization of central nervous system lipids.[22] Carbon monoxide exposure also creates substantial oxidative stress on cells, with production of oxygen radicals resulting from the conversion of xanthine dehydrogenase to xanthine oxidase.[23]

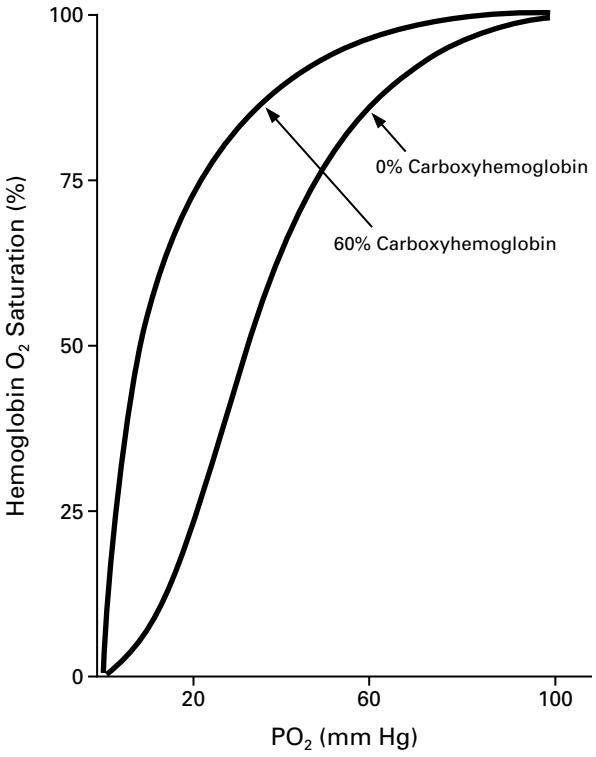

Figure 1. Oxygen–Hemoglobin Dissociation Curve.

The presence of carboxyhemoglobin shifts the curve to the left and changes it to a more hyperbolic shape. This results in a decrease in oxygen-carrying capacity and impaired release of oxygen at the tissue level.

Carbon monoxide exposure has an especially deleterious effect on pregnant women, because of the greater sensitivity of the fetus to the harmful effects of the gas. Data from studies in animals suggest a significant lag time in carbon monoxide uptake between mother and fetus. Fetal steady states can occur up to 40 hours after maternal steady states are achieved. The final carboxyhemoglobin levels in the fetus may significantly exceed the levels in the mother.[24] The exaggerated leftward shift of fetal carboxyhemoglobin makes tissue hypoxia more severe by causing less oxygen to be released to fetal tissues.[7] Although the teratogenicity of carbon monoxide is controversial, the risk of fetal injury seems to be increased by carbon monoxide.[25-27]

CLINICAL SIGNS AND SYMPTOMS

The clinical symptoms of carbon monoxide poisoning are nonspecific and can suggest a broad range of diagnostic possibilities. The signs and symptoms of nonlethal carbon monoxide exposure may mimic those of a nonspecific viral illness. Since viral illnesses and carbon monoxide exposure both peak during the winter, a substantial number of initial misdiagnoses may occur.[28] Carbon monoxide poisoning often occurs in concert with other medical emergencies, such as smoke inhalation, and may affect many people at the same time.[29]

Table 1 shows the variety of acute symptoms reported by patients after exposure to carbon monoxide in a number of clinical series.[11,30,31] Patients often present with tachycardia and tachypnea, which are compensatory mechanisms for cellular hypoxia. Headache, nausea, and vomiting are common symptoms. Presyncope, syncope, and seizures may result from cellular hypoxia and cerebral vasodilatation, which can also lead to cerebral edema. Angina, pulmonary edema, and arrhythmias may result from increased cardiac output caused by cellular hypoxia, carbon monoxide–myoglobin binding, and diminished oxygen release.[32-34] In patients with underlying pulmonary or cardiac disease, the symptoms of their disease may be worsened by impaired oxygen release.[35] The classic findings of cherry-red lips, cyanosis, and retinal hemorrhages occur rarely.[36] Erythematous lesions with bullae over bony prominences have been described but are not specific for carbon monoxide poisoning. Necrosis of the sweat glands is a characteristic histologic feature.[37]

The severity of symptoms ranges from mild (constitutional symptoms) to severe (coma, respiratory depression, and hypotension). It is important to recognize that carboxyhemoglobin levels do not corre-

TABLE 1. ACUTE SYMPTOMS REPORTED BY 196 PATIENTS AFTER EXPOSURE TO CARBON MONOXIDE.*

SYMPTOM	PERCENTAGE OF PATIENTS
Headache	91
Dizziness	77
Weakness	53
Nausea	47
Difficulty in concentrating or confusion	43
Shortness of breath	40
Visual changes	25
Chest pain	9
Loss of consciousness	6
Abdominal pain	5
Muscle cramping	5

*Data are from Ely et al.,[11] Myers et al.,[30] and Burney et al.[31]

late well with the severity of symptoms in a substantial number of cases. The duration of exposure appears to be an important factor mediating toxicity. Being in a carbon monoxide–containing environment for one hour or more may increase morbidity.[38] If no dissolved carbon monoxide is present in the plasma, the symptoms can be minimal even with extremely high levels of carboxyhemoglobin, as experiments in animals show.[20] Therefore, the decision whether to administer hyperbaric oxygen therapy cannot be made only on the basis of carboxyhemoglobin levels.[30,39]

DELAYED NEUROPSYCHIATRIC SYNDROME

Many patients with carbon monoxide poisoning do not have acute signs of cerebral impairment. Delayed onset of neuropsychiatric symptoms after apparent recovery from the acute intoxication has been described 3 to 240 days after exposure. The syndrome is estimated to occur in 10 to 30 percent of victims, but the reported incidence varies widely.[40-42] Symptoms such as cognitive and personality changes, parkinsonism, incontinence, dementia, and psychosis have been described.[42,43] No clinical or laboratory results predict which patients are at risk for this complication, but advanced age appears to be a risk factor. Recovery from delayed neuropsychiatric syndrome occurs in 50 to 75 percent of affected persons within one year.[42] Different abnormalities have been shown by computed tomography, molecular resonance imaging, and single-photon-emission computed tomography. The regions most commonly involved include the globus pallidus and the deep white matter.[42,44]

Delayed neuropsychiatric sequelae after exposure to carbon monoxide have been the subject of several reports.[42,45] The mechanisms are uncertain, but hypoxia alone is not sufficient to explain the observed clinical manifestations. Postischemic reperfusion injury as well as the effects of carbon monoxide on vascular endothelium and oxygen-radical–mediated brain lipid peroxygenation may also have a role.[46] In addition, nitric oxide liberated from platelets at the time of carbon monoxide exposure has been linked to central nervous system damage.[47]

DIAGNOSIS

Because carbon monoxide poisoning has no pathognomonic signs or symptoms, a high level of suspicion, particularly among primary care clinicians and emergency medicine specialists, is essential for making the diagnosis. The measurement of carbon monoxide levels alone may be insufficient to rule out the diagnosis, but in the majority of cases, increased levels of carboxyhemoglobin will be diagnostic. Serum levels of carboxyhemoglobin may already have fallen substantially at the time of presentation to the emergency department. Therefore, elevated carbon monoxide values in the exhaled air of the patients or in the ambient air at the scene of exposure can help confirm the diagnosis. This latter test can be performed by fire departments and should be encouraged. Blood obtained on the scene by emergency medical technicians may also be helpful for confirming the diagnosis.

Venous blood samples are adequate for measurements of carboxyhemoglobin,[48] although arterial samples allow for the additional determination of coexisting acidosis. Carboxyhemoglobin has to be measured directly with a spectrophotometer. Pulse oximetry cannot distinguish carboxyhemoglobin from oxyhemoglobin at the wavelengths that are commonly employed by most oximeters (pulse-oximetry gap).[49,50]

When the diagnosis of carbon monoxide poisoning has been established, a detailed neurologic examination and neuropsychological testing should be performed to document neurologic and neuropsychiatric abnormalities, which may be subtle. The Carbon Monoxide Neuropsychological Screening Battery is a frequently used tool that takes 30 minutes to administer and provides a base line for assessing subsequent changes in mental status.[51] Computed tomographic imaging of the head is not helpful in establishing the diagnosis of carbon monoxide intoxication, but it may be used to rule out other conditions that might result in changes in mental status or loss of consciousness in patients presenting to an acute care facility.

TREATMENT

The carbon monoxide–intoxicated patient must first be removed from the source of carbon monoxide production without endangering the health of the

rescuing personnel. Firefighters must use breathing apparatus not only to supply oxygen but also to protect against carbon monoxide poisoning. High-flow oxygen, preferably 100 percent as normobaric oxygen, should be administered to the patient immediately. Oxygen shortens the half-life of carboxyhemoglobin by competing at the binding sites of hemoglobin and improves tissue oxygenation.[52] Oxygen should be administered until the carboxyhemoglobin level has become normal. In patients with carbon monoxide poisoning who have been rescued from a fire, special consideration should be given to the respiratory status and the airway, since urgent or prophylactic intubation may be necessary.

Most patients can be evaluated and treated in an ambulatory setting. Hospitalization should be considered for patients with severe poisoning, serious underlying medical problems, or accompanying injuries. Patients often have concomitant problems, including smoke inhalation and burns, that require specialized treatment and may necessitate transfer to specialized facilities.

Since carbon monoxide may affect others who have been exposed to the same source, appropriate local agencies, usually the fire department, should be alerted to investigate the source of the intoxication and arrange for all other possible victims to be screened.

NORMOBARIC VERSUS HYPERBARIC OXYGEN

Carbon monoxide elimination is related to minute ventilation, the duration of exposure, and the fraction of inspired oxygen (FiO_2). The half-life of carboxyhemoglobin is 4 to 6 hours when the patient is breathing room air, 40 to 80 minutes when the patient is breathing 100 percent oxygen, and only 15 to 30 minutes when the patient is breathing hyperbaric oxygen.[53] In 1895 Haldane showed that hyperbaric oxygen prevented carbon monoxide poisoning in mice,[54] and since 1962 hyperbaric oxygen has been used to treat carbon monoxide poisoning.[55]

The indications for hyperbaric-oxygen therapy have recently been reviewed in the *Journal*.[56] Hyperbaric-oxygen therapy hastens the resolution of symptoms. It is unclear whether hyperbaric-oxygen therapy influences the rate of late sequelae or mortality in non–life-threatening carbon monoxide poisoning, since different studies have led to conflicting conclusions.[57,58] Coma is an undisputed indication for hyperbaric-oxygen therapy. Outcome studies of hyperbaric-oxygen therapy have not yet identified other circumstances in which this therapy is clearly indicated.[59] The indications for this therapy in patients with mild-to-moderate cerebral dysfunction are particularly disputed. Nonetheless, suggestions are available to help physicians decide whether to administer hyperbaric-oxygen therapy (Table 2).[60]

TABLE 2. SUGGESTED INDICATIONS FOR HYPERBARIC-OXYGEN THERAPY IN PATIENTS WITH CARBON MONOXIDE POISONING.*

Coma
Any period of unconsciousness
Any abnormal score on the Carbon Monoxide Neuropsychological Screening Battery
Carboxyhemoglobin level ≥40%
Pregnancy and carboxyhemoglobin level >15%
Signs of cardiac ischemia or arrhythmia
History of ischemic heart disease and carboxyhemoglobin level >20%
Recurrent symptoms for up to 3 wk
Symptoms that do not resolve with normobaric oxygen after 4–6 hr

*Data are from Myers and Thom.[60]

Once the diagnosis of carbon monoxide poisoning has been established, the physician must decide whether hyperbaric-oxygen therapy is indicated, and if so, make appropriate arrangements for a safe transfer to the nearest facility. More than 340 single-occupant chambers are available in the United States.[61] Information on the location and use of decompression chambers is available by telephone from the Divers Alert Network at Duke University at 919-684-8111. Callers should request the Divers Alert Network on-call staff.

PREVENTION

Awareness of the dangers of carbon monoxide and public education are the keys to decreasing morbidity and mortality from carbon monoxide poisoning. Primary prevention is aimed at decreasing production of and exposure to carbon monoxide. The Environmental Protection Agency and the Occupational Safety and Health Administration provide regulations and suggestions,[62-64] and general information is easily available from sources such as the American Gas Association. In particular, the current regulations of the Occupational Safety and Health Administration prohibit the exposure of workers to carbon monoxide levels exceeding 35 ppm, averaged over an 8-hour workday, with an upper limit of 200 ppm over a 15-minute period.[62] Fuel-burning heating systems require regular professional maintenance and appropriate ventilation. Motor vehicles should not remain in enclosed spaces with the engine running, and the exhaust pipe must be free of obstructions (particularly snow and leaves). Outdoor gas grills should not be operated indoors. Media campaigns should warn the public about the dangers of carbon monoxide at times of increased risk, such as anticipated cold spells and snowstorms. Members of minority groups and non–English-speakers are at greatest

risk, and public education must be tailored to reach these parts of the population.[65,66]

Secondary prevention efforts should be aimed at warning people about potentially harmful carbon monoxide concentrations in the environment. Although carbon monoxide detectors are inexpensive and widely available, they should not be considered a substitute for proper maintenance of appliances. There are currently no standard recommendations regarding their use in the home or the workplace.

We are indebted to Dr. Henry Koziel for his critical review of the manuscript.

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CORRECTION

Carbon Monoxide Poisoning

To the Editor: Ernst and Zibrak (Nov. 26 issue)[1] state that coma is an undisputed indication for hyperbaric-oxygen therapy, but this claim has not been proved[2] and might be misleading. Neurocognitive sequelae can develop in comatose patients with carbon monoxide poisoning who are treated with hyperbaric oxygen,[3] and patients with severe carbon monoxide poisoning can have a normal functional and cognitive recovery without hyperbaric oxygen.[4]

Interim analysis of an ongoing randomized clinical trial[5] and one completed randomized clinical trial[6] of the role of hyperbaric oxygen therapy in acute carbon monoxide poisoning have failed to demonstrate differences in outcomes between patients treated with normobaric oxygen and those treated with hyperbaric oxygen. Both of these trials enrolled comatose patients with carbon monoxide poisoning. We acknowledge that some authorities recommend that such patients receive hyperbaric oxygen, but there is no compelling data from clinical trials indicating that they require hyperbaric oxygen. There are risks associated with hyperbaric oxygen, including those related to oxygen transport, barotrauma affecting the middle and inner ear, and in cases of carbon monoxide poisoning, a 1 to 3 percent probability of a seizure induced by hyperbaric oxygen.[6,7]

In an ongoing longitudinal follow-up study conducted at our institution, approximately 30 percent of the patients with acute carbon monoxide poisoning have neurocognitive problems one year after poisoning. Of these patients, approximately one third have the delayed neuropsychiatric syndrome and two thirds have persistent neurocognitive problems, primarily difficulties with memory and executive function.[5,8] Unfortunately, the clinical and laboratory findings at presentation are not predictive of long-term outcome. The effect of hyperbaric oxygen on long-term outcome is still unknown. We agree that carbon monoxide poisoning is common and may be associated with substantial neurocognitive morbidity[8] and that patients should be treated with 100 percent oxygen and possibly with hyperbaric oxygen.

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To the Editor: The development of the carbon monoxide detector is potentially the most important advance in the prevention of carbon monoxide poisoning over the past 10 years. A recent study estimated that these detectors could have helped save 78 lives between 1980 and 1995 in the state of New Mexico alone.[1] Even more lives might have been saved in temperate climates. The use of chemical-reagent detectors (with a threshold response of about 100 parts per million) should be discouraged in favor of electronic detectors.[1] At least 68 cases of occult carbon monoxide poisoning were uncovered by detectors in the first three months after an ordinance mandating their installation was implemented in Chicago.[2]

Contrary to what Ernst and Zibrak state, national and local standards do exist for electronic carbon monoxide detectors. Underwriters Laboratories has published standards used by manufacturers of carbon monoxide detectors since 1991.[3] These detectors approved by Underwriters Laboratories are designed to sound an alarm when ambient carbon monoxide levels are reached that would cause a carboxyhemoglobin level of 10 percent or greater in a person engaged in work requiring heavy exertion. In 1994, Chicago became one of the first large metropolitan areas to require residential carbon monoxide detectors.[4] St. Louis, Albany, New York, and Fort Lee, New Jersey, are among the other municipalities that have such ordinances. Also, the National Fire Protection Association has published recommended practices for the installation of household carbon monoxide–warning

equipment.[5] It is clear that electronic carbon monoxide detectors are effective tools for ameliorating the public health problem of carbon monoxide poisoning and that they can help unmask ``the silent killer.´´

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To the Editor: One clinical scenario was conspicuously absent from the review article by Ernst and Zibrak: Physicians may be called to assist in the care of patients who have been exposed to carbon monoxide through the breakdown of anesthetic in desiccated carbon dioxide absorbents during the delivery of inhaled anesthesia in closed or semiclosed breathing circuits.[1] Although most anesthetics are stable in the presence of normally hydrated carbon dioxide absorbents, improper care of machines used to deliver anesthesia may cause desiccation of the absorbents, which can result in the formation of carbon monoxide through chemical reactions involving difluoromethyl ethers,[2] which include such popular anesthetics as enflurane, isoflurane, and desflurane. Because a period of 24 to 48 hours is required for desiccation of these absorbents, most cases of intraoperative carbon monoxide poisoning occur during the first delivery of general anesthesia through an anesthesia machine on Monday mornings.

Improved care of anesthesia machines has been shown to reduce the incidence of carbon monoxide exposure from approximately 1 in 200 to 1 in 2000 first cases,[3] but some remote or seldom-used facilities may be at particularly high risk. Exposure can be severe; carboxyhemoglobin concentrations over 30 percent have been documented in humans,[4] and animals have been exposed to lethal concentrations of over 80 percent carboxyhemoglobin in clinical scenarios.[5] It is possible that most exposure goes undetected because monitoring for carbon monoxide or carboxyhemoglobin is not routine in these circumstances, because the symptoms of carbon monoxide poisoning are masked by the effects of general anesthesia, and because, after the patient emerges from anesthesia, signs and symptoms remain nonspecific.

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To the Editor: As Ernst and Zibrak point out, carbon monoxide poisoning accounts for about 600 accidental deaths and 3000 suicides each year. Cerebral symptoms are often prominent and may progress to brain death. Because cardiorespiratory symptoms and frank injury to the heart have been observed and because of an early unsuccessful attempt at heart transplantation,[1] there has been a reluctance to consider victims of carbon monoxide poisoning who have been declared brain-dead as potential organ donors.

Several reports of such victims serving as successful donors of kidneys,[2] livers,[3] hearts,[4] and even a lung[5] indicate that careful evaluation of organ function in these victims can identify organs that are suitable for transplantation. All these reports came from outside the United States.

The waiting list of the United Network for Organ Sharing on October 31, 1998, had 62,994 registrants (including 41,544 waiting for kidneys, 11,601 waiting for livers, 4184 waiting for hearts, 3088 waiting for

lungs, and 2235 waiting for pancreases or kidneys and pancreases). Many of these patients are in urgent need of transplants and are on life-support mechanisms. Therefore, the judicious evaluation of individual organ function of brain-dead victims of carbon monoxide poisoning could lead to a slight easing of the critical shortage of organ donors.

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To the Editor: In the excellent review article by Ernst and Zibrak, we must point out that Figure 1 (Oxygen–Hemoglobin Dissociation Curve) is mislabeled. This is readily apparent if one considers that with 60 percent carboxyhemoglobin one cannot have an oxygen saturation greater than 40 percent; otherwise, the total hemoglobin saturation would be greater than 100 percent. This is impossible, since oxygen and carbon monoxide bind competitively to iron atoms in hemoglobin.[1] Perhaps the authors intended to label the y axis ``(Hemoglobin $O_2$)÷([Hemoglobin $O_2$]+[Red Hemoglobin]) (%),´´ or equivalently, ``(Hemoglobin O_2)÷([Hemoglobin]–[Carboxyhemoglobin]) (%)´´ — i.e., the oxygen saturation of the noncarboxylated hemoglobin.

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The authors reply:

To the Editor: Our review of carbon monoxide poisoning concentrated on the more common sources of production that might be encountered by primary care and emergency medicine clinicians. Treatment is often based on recommendations, rather than evidence-based studies with conclusive results.

As pointed out by Dr. Woehlck, improperly maintained anesthesia circuits may be a cause of carbon monoxide poisoning. This, fortunately, is a rare circumstance not commonly encountered by practicing clinicians. Appropriate and diligent maintenance of anesthesia machines should alleviate this problem.

Carbon monoxide detectors are useful but have not been conclusively demonstrated to reduce morbidity and mortality. The cited study by Yoon et al.[1] is a descriptive analysis that does not actually compare an intervention group with a nonintervention group. We agree with Leikin et al. that carbon monoxide detectors have the potential to decrease the incidence of carbon monoxide poisoning in residential settings, but they are a form of secondary prevention and not a substitute for proper maintenance and appropriate use of heating equipment.

We agree with Weaver et al. that ``undisputed´´ may have been a poor choice of words for describing indications for hyperbaric-oxygen therapy in comatose patients. However, we continue to believe strongly that the weight of clinical empirical evidence supports this practice. Our review of the literature concerning neurologic dysfunction as a consequence of hyperbaric-oxygen therapy in patients with carbon monoxide poisoning fails to convince us of a uniform negative effect. In fact, hyperbaric oxygen appears to modify favorably the propensity of neurocognitive defects to develop and is considered the standard of care by most authorities.[2,3] Only further research can answer these questions more definitively.

We agree with Dr. Kauffman that victims of carbon monoxide poisoning need to be considered as potential organ donors. Carbon monoxide poisoning may lead to cellular damage in a variety of organ systems, but such an effect should not be considered an absolute contraindication to organ transplantation. Several reports in the literature confirm the feasibility of this approach.[4,5] This area also is in need of further research and protocols should be established to help alleviate the current shortage of organs.

Drs. Ryan and Cosentino correctly point out that the ordinate of Figure 1 of our article is mislabeled. This axis is intended to represent the relative oxygen saturation of the residual hemoglobin molecules not bound to carbon monoxide: 100–Z, where Z is the percent of total hemoglobin molecules bound to carbon monoxide. As suggested, the correct label is that used by Roughton: 100 (Hemoglobin

O_2)÷([Hemoglobin O_2]+[Red Hemoglobin]). For a given percentage of carboxyhemoglobin, this yields the ratio of oxygen-bound hemoglobin to the sum of oxygen-bound hemoglobin and reduced (unbound) hemoglobin. Thus for a carboxyhemoglobin concentration of 60 percent (as depicted in the figure), when all the remaining hemoglobin is bound to oxygen, and red hemoglobin is therefore 0 percent, the expression yields: 100 × (40 ÷ [40 + 0]), or 100 percent.

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