CLINICAL PRACTICE

Carbon Monoxide Poisoning

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 39-year-old female executive has a several-month history of fatigue, headache, and memory lapse. Multiple specialists have performed evaluations, but no diagnosis has been established. During a period of feeling worse than usual, she called a friend, who arrived at the residence to find the woman semicomatose and called 911. The patient was given supplemental oxygen and transported to the emergency department, where she is alert and has nonfocal findings on examination. Her carboxyhemoglobin level is 18%. How should she be treated? What is the expected outcome?

THE CLINICAL PROBLEM

Carbon monoxide poisoning is common, resulting in more than 50,000 emergency department visits per year in the United States.[1] Sources of carbon monoxide include faulty furnaces, inadequate ventilation of heating sources, and exposure to engine exhaust.

The symptoms of carbon monoxide poisoning are nonspecific.[2] Mild exposures result in headache, myalgia, dizziness, or neuropsychological impairment.[3] Severe exposures to carbon monoxide result in confusion, loss of consciousness, or death (Fig. 1). Patients with subclinical exposures may recognize poisoning only after an acute event or on coincidental discovery of a carbon monoxide leak.

In physiologic amounts, endogenous carbon monoxide functions as a neurotransmitter.[4] At low levels, carbon monoxide may favorably modulate inflammation,[5] apoptosis,[6] and cell proliferation,[7] and it up-regulates mitochondrial biogenesis.[8] As the carbon monoxide exposure increases, poisoning results (Fig. 1).[5]

Carbon monoxide causes hypoxia by forming carboxyhemoglobin and shifting the oxyhemoglobin dissociation curve to the left (Fig. 2).[2] Carbon monoxide's affinity for hemoglobin is more than 200 times that of oxygen,[14] resulting in the formation of carboxyhemoglobin with even relatively low amounts of inhaled carbon monoxide. Carbon monoxide increases cytosolic heme levels, leading to oxidative stress,[12] and binds to platelet heme protein and cytochrome *c* oxidase,[14] interrupting cellular respiration[9] and causing production of reactive oxygen species,[13] which in turn leads to neuronal necrosis[13] and apoptosis.[11] Impaired cellular respiration provokes a stress response, including the activation of hypoxia-inducible factor 1α,[15] resulting in neurologic and cardiac protection[5] or injury, dependent on the dose of carbon monoxide, by means of gene regulation. Carbon monoxide exposure also causes inflammation through multiple pathways that are independent of the pathways to hypoxia, resulting in neurologic and cardiac injury.

Long-term, subacute exposures to carbon monoxide lasting more than 24 hours generally occur intermittently and may span weeks or even years. The incidence of long-term exposure is unknown. Symptoms of chronic poisoning may differ from those of acute poisoning and can include chronic fatigue, affective conditions and

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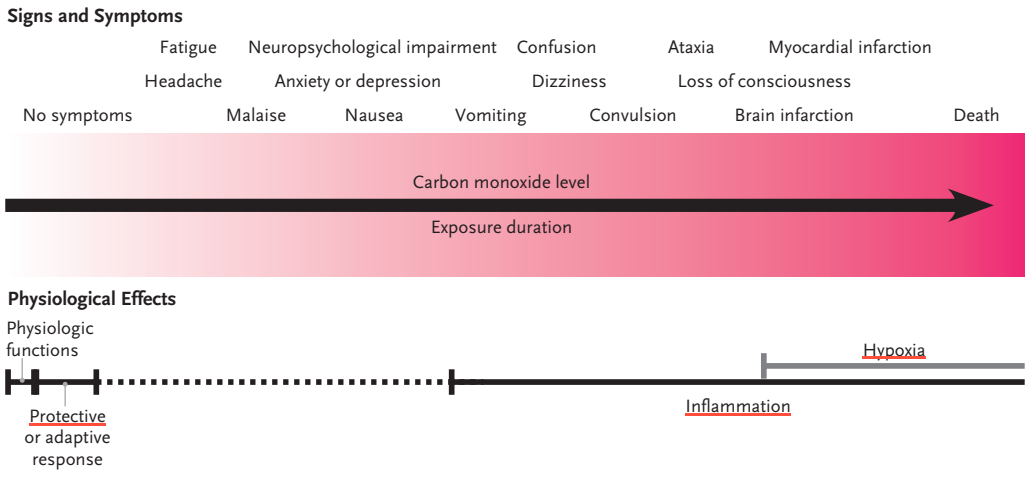


Figure 1. Spectrum of Symptoms and Effects of Exposure to Carbon Monoxide, According to the Level and Duration of Exposure.

In all humans, small amounts of carbon monoxide are present and are important for multiple physiologic functions, including neurotransmission. Exogenous exposure to amounts of carbon monoxide above physiologic levels can result in a protective or adaptive response, but exposure to even higher levels results in toxic effects. Toxic exposures can cause inflammation, followed by hypoxia, although there is uncertainty regarding the range of carbon monoxide exposures above which inflammation occurs (as indicated by the dashed line). The signs and symptoms of poisoning are highly variable, depending on the acuity and duration of the exposure.

emotional distress, memory deficits, difficulty working, sleep disturbances, vertigo, neuropathy, paresthesias, recurrent infections, polycythemia, abdominal pain, and diarrhea.[16]

Patients commonly have neuropsychological sequelae after carbon monoxide poisoning.[2,17,18] In one randomized trial, 46% of poisoned patients treated with normobaric oxygen had cognitive sequelae 6 weeks after poisoning,[17] and 45% had affective sequelae.[19] Other sequelae include gait and motor disturbances, peripheral neuropathy, hearing loss and vestibular abnormalities, and dementia and psychosis,[20] which can be permanent.

Magnetic resonance imaging (MRI) of the brain (performed for research purposes or, in some cases, for clinical indications, such as to rule out disorders unrelated to carbon monoxide exposure) may reveal abnormal findings after carbon monoxide poisoning (Fig. 3). In one prospective study of patients with carbon monoxide poisoning, brain MRI revealed increased numbers of T_2-weighted hyperintensities as compared with the numbers in a normative database.[21] Although the prevalence of imaging abnormalities is unknown, other studies of carbon monoxide–poisoned patients have reported basal-ganglia lesions[22] and atrophy of the hippocampi[23] and other structures[24] years after poisoning, as well as abnormal results of diffusion tensor imaging[25] 1 month after poisoning. However, none of these abnormalities are specific to carbon monoxide poisoning.

STRATEGIES AND EVIDENCE

SHORT-TERM MANAGEMENT

If emergency medical personnel are called, they should administer normobaric oxygen to the poisoned patient, by means of a nonrebreather reservoir face mask supplied with high-flow oxygen, or 100% oxygen, by means of an artificial airway, if appropriate. Poisoned patients should then be transported to an emergency department for evaluation.

Although the administration of normobaric oxygen hastens the elimination of carbon monoxide,[2,26] one trial did not show a reduction of cognitive sequelae after the inhalation of normobaric oxygen, as compared with no supplemental oxygen therapy.[18] However, since normobaric oxygen is safe, readily available, and inexpensive, it should be provided until the carboxyhemoglobin level is less than 5%.

Evaluation of the poisoned patient should emphasize the adequacy of ventilation and perfusion, the neurologic examination, and the exposure history (duration, source, and whether others were

exposed). The measurement of arterial blood gases by co-oximetry provides information about the adequacy of gas exchange, metabolic acidosis, and carboxyhemoglobin and should be performed in poisoned patients if clinically indicated. However, measurement of venous carboxyhemoglobin levels is adequate for diagnostic purposes.[27] Carboxyhemoglobin levels depend on multiple factors, including the magnitude of exposure, the degree of alveolar ventilation, the blood volume, and metabolic activity,[14] but in adult men at rest, the levels are determined predominantly by the ambient carbon monoxide level and the duration of exposure.[28] A carboxyhemoglobin level greater than 3% in nonsmokers or greater than 10% in smokers confirms exposure to carbon monoxide, but the level does not correlate with the presence or absence of initial symptoms[29] or with later outcomes,[18] which may be more attributable to inflammatory aspects of poisoning than to hypoxia.

Carbon monoxide poisoning can exacerbate angina[30] and cause cardiac injury,[31] even in persons with normal coronary arteries.[32] Therefore, poisoned patients should undergo a cardiovascular investigation, including electrocardiography and measurement of cardiac enzymes. If cardiac injury is present, a cardiology consultation is indicated.[31]

For cases of intentional carbon monoxide poisoning, laboratory toxicologic investigations should be performed for the detection of alcohol, benzodiazepines, narcotics, amphetamines, or other such agents. Emergency department personnel should facilitate access to mental health resources.

USE OF HYPERBARIC OXYGEN

Health care providers in the emergency department should consider using hyperbaric oxygen for treating poisoned patients.[2,14,17,18,33-35] Hyperbaric-oxygen therapy is defined as the breathing of 100% oxygen by patients within hyperbaric chambers compressed to greater than 1.4 atm of absolute pressure.[33] Clinicians who use carboxyhemoglobin levels as criteria for whether hyperbaric oxygen should be administered should consider that the level on presentation may underestimate earlier levels because of carboxyhemoglobin elimination over time, which is hastened by the application of supplemental oxygen by emergency medical personnel before arrival at the emergency department.[2,14,26,28]

The role of hyperbaric oxygen in the management of carbon monoxide poisoning remains controversial, although both physiological data and some randomized-trial data suggest a potential benefit.[17,35,36] Hyperbaric-oxygen therapy elevates arterial and tissue oxygen tensions, promoting carbon monoxide elimination,[2,14] and also increases adenosine triphosphate production[37] and reduces oxidative stress and inflammation.[14]

Among published randomized clinical trials of hyperbaric oxygen,[17,35,36,38,39] only one satisfied all Consolidated Standards for the Reporting of Trials (CONSORT) guidelines,[40] including double-blinding, enrollment of all eligible patients, a priori definitions of outcomes, and high rates of follow-up.[17] This single-center, prospective trial showed that the incidence of cognitive sequelae was lower among patients who underwent three hyperbaric-oxygen sessions (an initial session of 150 minutes, followed by two sessions of 120 minutes each, separated by an interval of 6 to 12 hours) within 24 hours after acute carbon monoxide poisoning than among patients treated with normobaric oxygen (25% vs. 46%, $P=0.007$ and $P=0.03$ after adjustment for cerebellar dysfunction and stratification variables). In addition, the use of hyperbaric oxygen reduced the rate of cognitive sequelae at 12 months (18%, vs. 33% with normobaric oxygen; $P=0.04$).[17] However, this trial did not clearly identify subgroups of patients in whom hyperbaric oxygen was appreciably more or less beneficial. A post hoc analysis of 86 patients suggested an interaction between the apolipoprotein genotype and the use of hyperbaric oxygen. In patients lacking the apolipoprotein E4 allele, hyperbaric oxygen reduced the rate of cognitive sequelae at 6 weeks, whereas in patients who had the E4 allele (which is present in 30% of the general population), the use of hyperbaric oxygen did not reduce the rate of cognitive sequelae.[34]

A Cochrane review of six trials, including two published only in abstract form, did not support the use of hyperbaric oxygen for patients with carbon monoxide poisoning.[41] However, the reviewed trials were heterogeneous with respect to the methods used and differed in the selection of patients, dosing of hyperbaric oxygen and normobaric oxygen, and long-term outcome measures; lack of follow-up was a limitation in some trials. Because the trial described above[17] showed a significant benefit of hyperbaric oxygen, and because of the methodologic limitations of the trials in which a benefit was not shown, the review's conclusions have been controversial.

LONG-TERM MANAGEMENT

Patients with carbon monoxide poisoning should be followed medically after discharge. The extent and rate of recovery after poisoning are variable, and recovery is often complicated by the development of sequelae, which can persist after exposure or develop weeks after poisoning[2] and which can be permanent.

Specific therapy for sequelae after carbon monoxide poisoning is not available. Clinical experience suggests that patients with sequelae should have their symptoms treated, through cognitive, psychiatric, vocational, speech, occupational, and physical rehabilitation, although data on the effects of these interventions in patients with carbon monoxide–related sequelae are lacking. Patients with persistent headaches may benefit from evaluation by a headache specialist.

PREVENTION

Governmental air-quality limits for exposure to carbon monoxide are intended to keep carboxyhemoglobin levels in nonsmokers below 3%.[42] Carboxyhemoglobin levels of 3% or more can adversely affect high-risk groups such as the elderly, pregnant women, fetuses, infants, and patients with cardiovascular or respiratory diseases.

Accidental carbon monoxide poisoning is preventable. Carbon monoxide alarms are designed to go off at exposure levels that would result in carboxyhemoglobin levels exceeding 10%.[43]

Steps such as avoiding the operation of combustion engines indoors and performing periodic furnace inspections can prevent many cases of carbon monoxide poisoning, as can proper use of alternative heating and cooking sources and generators after natural disasters. A helpful online resource for the prevention of carbon monoxide poisoning is available from the Centers for Disease Control and Prevention (www.cdc.gov/co/).

AREAS OF UNCERTAINTY

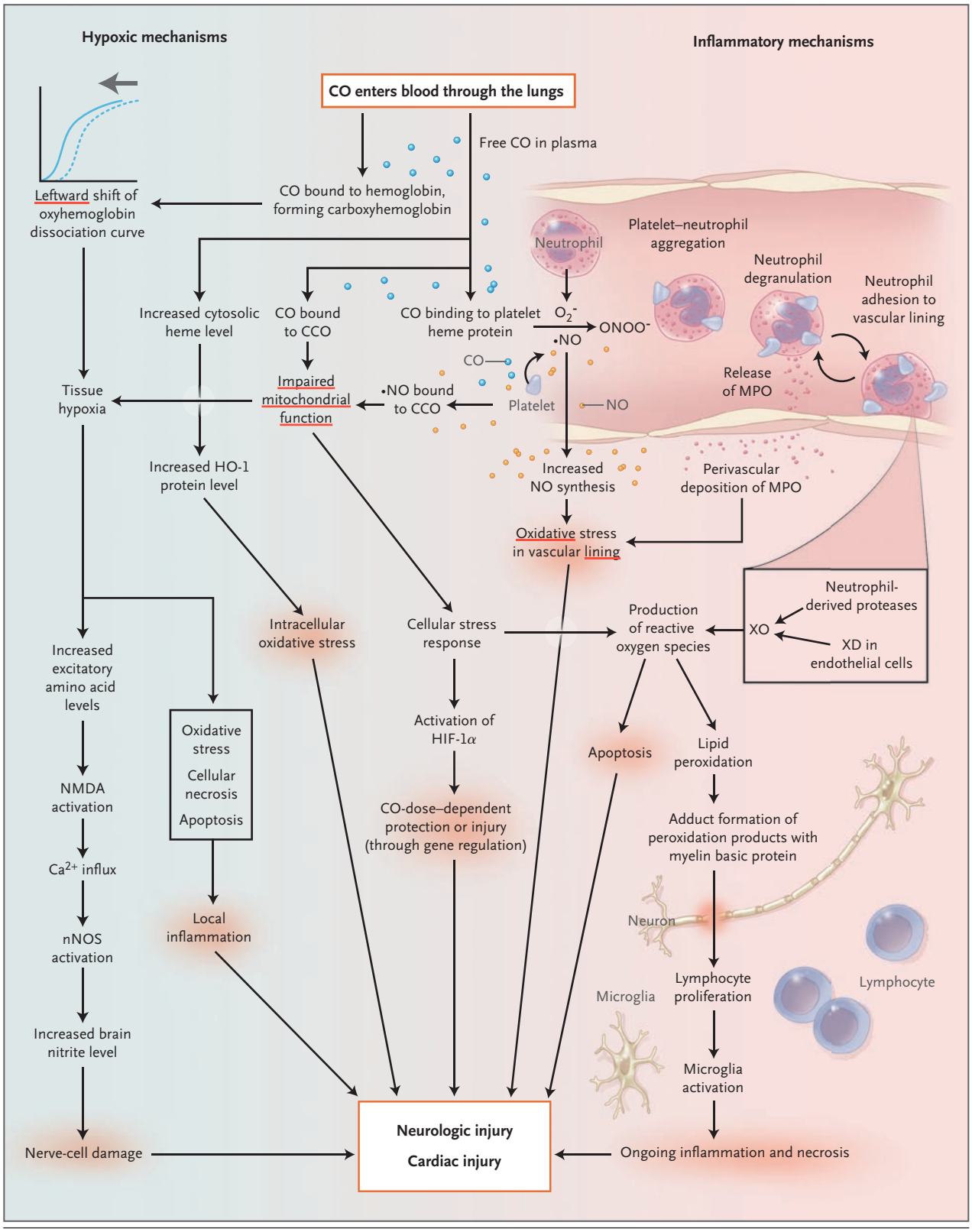
SEQUELAE

Although carbon monoxide poisoning can cause myriad neurologic and neuropsychological problems, the incidence of sequelae after carbon monoxide poisoning is not clearly known. Prospective studies of patients treated with normobaric oxygen showed that 34% reported symptoms such as headaches or memory problems at 4 weeks[38] and 46% had neuropsychological sequelae at 6 weeks.[17] However, among all poisoned patients, the number in whom carbon monoxide-related sequelae will develop is unknown. Studies of long-term outcomes in poisoned patients have not typically involved nonpoisoned, matched controls, nor have they included information about functional and cognitive status before poisoning occurred; rather, such information is inferred from educational level, scholastic performance, vocation, IQ testing, and collateral interviews after poisoning.

A patient's initial presentation does not predict later outcomes with certainty, but particular variables known at the time of poisoning are predictive of risks for subsequent sequelae.[17,18] In one study, patients who were 36 years of age or older or who had been exposed to carbon monoxide for at least 24 hours, who did not receive hyperbaric

Figure 2 (facing page). Pathophysiological Mechanisms of Carbon Monoxide Poisoning.

Carbon monoxide (CO) diffuses quickly into the blood by way of the lungs and causes injury and an adaptive response that continue after carboxyhemoglobin levels have returned to normal. CO causes hypoxemia through the formation of carboxyhemoglobin and a leftward shift of the oxyhemoglobin dissociation curve.[2] CO binds to heme proteins such as cytochrome *c* oxidase (CCO), impairing mitochondrial function[9] and thereby contributing to hypoxia. Brain hypoxia elevates levels of excitatory amino acids, increasing brain nitrite levels and causing subsequent injury.[10] Brain hypoxia causes oxidative stress, necrosis, and apoptosis,[11] contributing to inflammation and injury. CO also causes inflammation by increasing levels of cytosolic heme and the heme oxygenase-1 (HO-1) protein, resulting in intracellular oxidative stress.[12] CO binds to platelet heme proteins, causing the release of nitric oxide (•NO).[13] Excess •NO produces peroxynitrite ($ONOO^-$),[13] impairing mitochondrial function,[14] which contributes to hypoxia. CO causes platelet-to-neutrophil aggregation and neutrophil degranulation,[13] involving the release or production of myeloperoxidase (MPO), proteases, and reactive oxygen species[13] — which cause oxidative stress, lipid peroxidation,[13] and apoptosis.[11] Proteases interact with xanthine dehydrogenase (XD) in endothelial cells, forming xanthine oxidase (XO), which inhibits endogenous mechanisms against oxidative stress.[13] Lipid-peroxidation products form adducts with myelin basic protein, altering its structure, triggering a lymphocytic immunologic response, increasing microglia activation and activity, and causing neuropathologic effects.[14] Finally, CO induces cellular stress responses such as the activation of hypoxia-inducible factor 1α (HIF-1α),[15] which can induce gene regulation. This gene regulation can be protective[5] or can result in injury, depending on the CO dose and on host factors, which remain largely unknown. NMDA denotes *N*-methyl-D-aspartate, and nNOS neuronal nitric oxide synthase.



oxygen,[18] or who had cerebellar abnormalities on presentation[17] had an increased risk of cognitive sequelae at 6 weeks as compared with those without these characteristics. In another study, patients with dizziness before hospital admission or headaches at the time of admission had an increased risk of minor neurologic problems 1 month after poisoning.[44] Given the role of inflammation in carbon monoxide–associated injury (Fig. 2), levels of inflammatory markers might predict the risk of sequelae, but this possibility requires further study.

Information about sequelae beyond the first year after poisoning is limited.[17-19] In one cohort, approximately 6 years after poisoning, 19% of patients had cognitive problems[45] and 37% had abnormal neurologic evaluations.[46]

In patients without a history of carbon monoxide poisoning, abnormalities found on neuroimaging that are consistent with those reported after carbon monoxide poisoning — such as hippocampal atrophy[47] or white-matter hyperintensities[48] — are associated with an increased risk of early cognitive decline. It is unknown whether patients with carbon monoxide poisoning who have such abnormalities are also at increased risk for early cognitive decline or Alzheimer's disease.

VARIABILITY AMONG PATIENTS

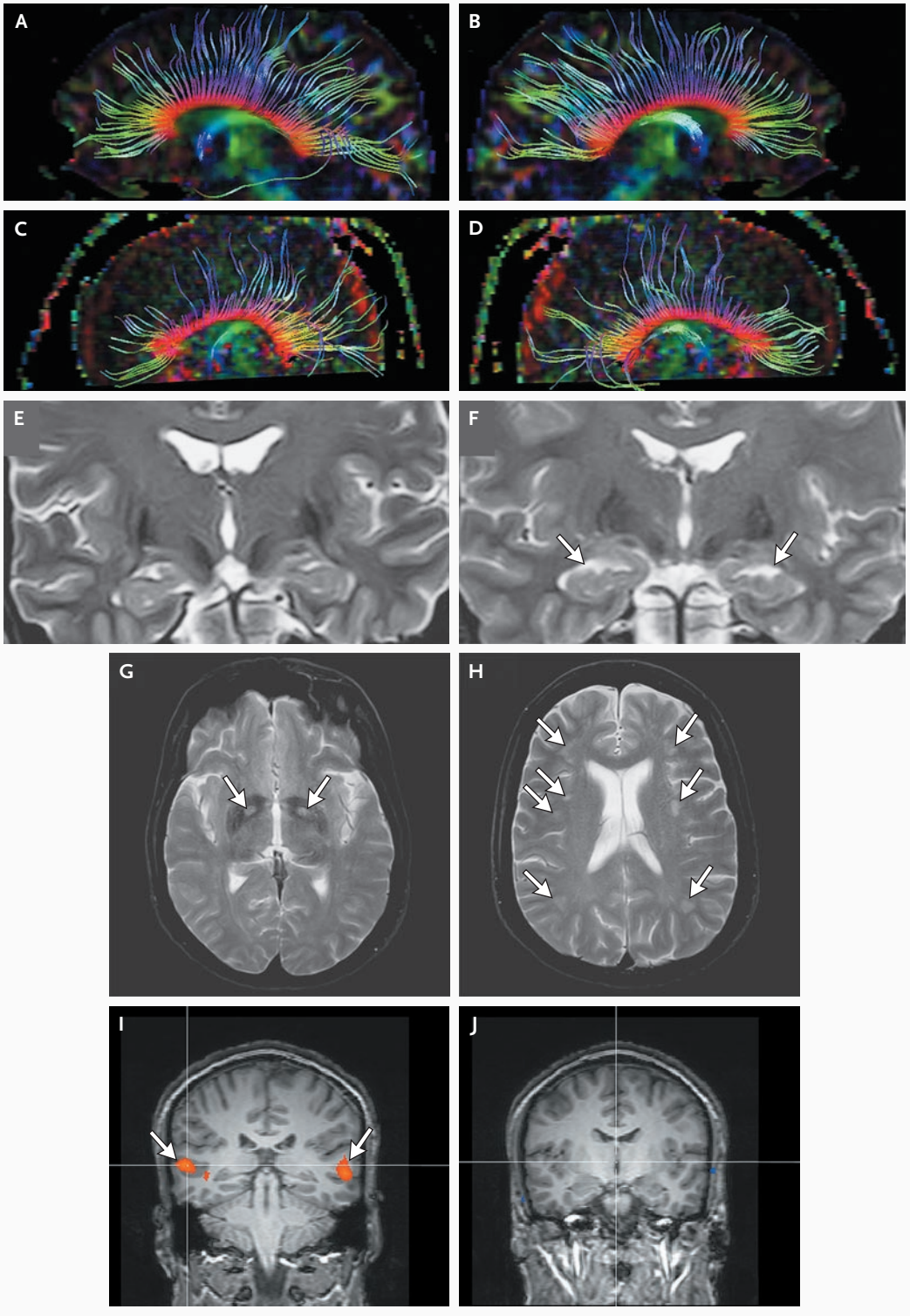
Responses to carbon monoxide exposures are variable. Exposed children often become symptomatic earlier, and recover faster, than similarly exposed adults, because of their lesser blood volume and increased minute ventilation per unit of body mass as compared with adults. Prospective studies of children exposed to carbon monoxide have reported variable rates of sequelae.[49,50] The unborn fetus is highly susceptible to the adverse effects of carbon monoxide. The period required to eliminate carbon monoxide is prolonged for fetal blood as compared with adult blood, and maternal poisoning and hypoxemia contribute to fetal hypoxia.[51] Fetal mortality exceeds 50% in cases of severe poisoning.[52] Hyperbaric-oxygen therapy should be considered in women with acute carbon monoxide poisoning,[17] including pregnant women, and in particular if the fetus shows signs of distress.[51] The role of hyperbaric oxygen in treating a fetus with carbon monoxide poisoning remains unclear, although there has been at least one case report of a favorable outcome.[51]

Figure 3 (facing page). Findings on Brain MRI after Carbon Monoxide Poisoning.

Carbon monoxide–related brain damage, which may be seen in poisoned patients presenting with sequelae, is shown here. The images were obtained with the use of highly sensitive 3-T MRI, which is not universally available, according to specific protocols; typical clinical 1.5-T scans would generally depict less damage. White-matter fiber tracks are revealed on diffusion tensor imaging in a 21-year-old normal volunteer (Panels A and B) and in an age-matched patient with a history of carbon monoxide poisoning (Panels C and D). Each image is a fractional anisotropy map obtained by acquiring data in 32 diffusion directions. The average variances of the fractional anisotropy values and the apparent diffusion coefficient values of the corpus callosum differed significantly more in the patient with carbon monoxide poisoning than in the normal subject. Panels E and F show coronal T_2-weighted images of the hippocampus in a normal volunteer and in a patient after carbon monoxide poisoning, respectively. Hippocampal atrophy (Panel F, arrows) was found in the patient. In a patient with carbon monoxide poisoning, abnormally increased T_2 signals are revealed on axial T_2-weighted images of the globus pallidus (Panel G, arrows) and on spin-echo imaging of subcortical structures (Panel H, arrows). The results of auditory functional MRI after carbon monoxide poisoning in a patient with previously normal auditory acuity shows normal activation after auditory stimulation of the right ear (Panel I, arrows) and no activation after auditory stimulation of the left ear (Panel J). This pattern is consistent with normal auditory processing on one side (the right, in this case) but suppression of processing on the other side, presumably in relation to brain injury from carbon monoxide poisoning.

HYPERBARIC-OXYGEN THERAPY

It is not clear which patients should receive hyperbaric-oxygen therapy. Additional uncertainties about this therapy include the optimal chamber pressure, the optimal number of hyperbaric-oxygen sessions, and the maximal interval after poisoning during which hyperbaric oxygen may still have a favorable effect. Case reports describe improvement of sequelae with a series of hyperbaric-oxygen sessions beginning days after poisoning,[53] although mechanisms of possible benefit are unknown, and most clinicians do not administer hyperbaric oxygen if more than 24 hours has elapsed since carbon monoxide poisoning.[54] A single-center, double-blind clinical trial (ClinicalTrials.gov number, NCT00465855) is under way to determine the effect of one or three hyperbaric-oxygen sessions on rates of cognitive sequelae at 6 weeks among accidentally poisoned patients presenting less than 24 hours after exposure.



OTHER THERAPY

Inflammation caused by carbon monoxide results in tissue injury. Whether antiinflammatory therapy or the use of other neuroprotective interventions, such as induced hypothermia, could improve outcomes after poisoning is unknown.

GUIDELINES

The Undersea and Hyperbaric Medical Society recommends hyperbaric-oxygen therapy for patients with serious carbon monoxide poisoning — as manifested by transient or prolonged unconsciousness, abnormal neurologic signs, cardiovascular dysfunction, or severe acidosis — or patients who are 36 years of age or older, were exposed for 24 hours or more (including intermittent exposures), or have a carboxyhemoglobin level of 25% or more.[33]

A Clinical Policies Subcommittee of the American College of Emergency Physicians states that hyperbaric oxygen "is a therapeutic option for [carbon monoxide–]poisoned patients; however, its use cannot be mandated. . . . No clinical variables, including carboxyhemoglobin levels, identify a subgroup of [carbon monoxide–]poisoned patients for whom [hyperbaric oxygen] is most likely to provide benefit or cause harm."[55] The subcommittee advocates a large, multicenter clinical trial with elements identical to those incorporated in a previous single-center trial.[17] My recommendations diverge from this policy statement in that I more strongly recommend that hyperbaric-oxygen therapy be considered for patients with carbon monoxide poisoning, on the basis of the available data, including biochemical studies, studies in animals, and at least one rigorous clinical trial.

CONCLUSIONS AND RECOMMENDATIONS

Patients who have had carbon monoxide poisoning, such as the patient in the vignette, should be treated immediately with normobaric oxygen (with a fraction of inspired oxygen as high as possible), which speeds up the excretion of carbon monoxide. The source of carbon monoxide should be identified and removed.

Carbon monoxide poisoning can result in permanent sequelae. Clinicians evaluating patients with acute poisoning should consider hyperbaric-oxygen therapy. Although some randomized trials did not show efficacy, in the most rigorous trial, the rate of cognitive sequelae at 6 weeks was 25%, a 46% reduction from the rate of sequelae among patients receiving normobaric oxygen.[17] Patients should be informed that they may not fully recover after poisoning, and they should be given referrals as appropriate for their sequelae.

The case of carbon monoxide poisoning described in the vignette was caused by a faulty home furnace. Patients should be educated to minimize the risks of carbon monoxide exposure, including by avoiding the operation of combustion engines indoors and performing periodic furnace inspections. Patients should also be encouraged to obtain, install, and heed carbon monoxide alarms.

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