

Treatment of Late Neurologic Sequelae of Carbon Monoxide Poisoning with Hyperbaric Oxygenation: a Case Series

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ABSTRACT

Severe neurologic impairment may occur as a result of carbon monoxide (CO) poisoning, even after apparent recovery from the acute event. In four cases of late neurologic sequelae, significant improvement occurred with hyperbaric oxygenation therapy (HBOT). Improvement in brain metabolism shown by single photon emission computerized tomography (SPECT) paralleled the clinical response to HBOT. More aggressive use of HBOT for the acute injury might prevent these late sequelae.

Pathophysiology of Carbon Monoxide Intoxication

Carbon monoxide (CO) causes more accidental and intentional deaths than any other form of poisoning worldwide. This odorless, colorless gas binds to hemoglobin 240 times more strongly than does oxygen. The CO also shifts the oxyhemoglobin dissociation curve to the left, resulting in profound tissue hypoxia. Additionally, as Ball demonstrated in 1951,¹ cytochromes bind carbon monoxide preferentially to oxygen by a ratio of greater than 9:1, causing impairment of cellular respiration.² The binding of CO to myoglobin also causes myocardial and skeletal muscle dysfunction.³ Chronic low-level exposure often remains undetected as damage accumulates.⁴

More than 30% of patients with acute CO poisoning may experience delayed onset of neuropsychiatric symptoms. There is evidence that even low-level chronic exposure may cause varying degrees of neuropsychiatric impairment.^{5,6} Manifestations include drowsiness, dementia, movement disorders, aphasia, agnosia, apraxia, apathy, depression, disorientation, hallucinations, incontinence, and seizures. Parkinsonian features include bradykinesia and cogwheel rigidity.^{5,7,8} Delayed unexpected death from progressive cerebral anoxia and edema after acute exposure may occur.^{7,8} Onset may be weeks, months, or years after an acute episode, and a relapsing course should be anticipated.⁹

Firefighters, especially if they smoke, are at enhanced risk of CO poisoning. In our experience, firefighters who are aware of a personality change in a coworker say, "He ate too much smoke."

The pathologic hallmark of acute CO damage is bilateral necrosis of the globus pallidus. Other affected areas include the

cerebral cortex, hippocampus, cerebellum, and substantia nigra.^{3,10} Patients with globus pallidus necrosis have been known to survive, but a more accurate prognostic sign is that of changes in the white matter in the cortex. In 1980, Sawada et al.¹¹ showed that abnormal findings on the initial computerized tomographic (CT) scan were correlated with a poor neurologic outcome and progressive pathology over a period of a year, including ventricular enlargement, cortical atrophy, low density areas in the globus pallidus, lesions of the white matter with demyelination of the "spongy" cerebral cortex, and necrotic lesions of the hippocampus. Damage to the vestibular and auditory apparatus, anywhere from the peripheral organs to the eighth cranial nerve and brain nuclei, has been reported.¹¹

The Use of Hyperbaric Oxygenation

Delivery of oxygen under higher than atmospheric pressure, hyperbaric oxygenation therapy (HBOT), greatly increases the amount of oxygen that can be dissolved in plasma, thereby improving tissue oxygenation. At 3 atmospheres absolute (ATA), dissolved oxygen can supply the body's basal oxygen requirements with normal cardiac output in the absence of functional hemoglobin.¹² HBOT also reduces the half-life of COHb; induces cerebral vasoconstriction, with reduction in cerebral edema; and results in more rapid dissociation of CO from respiratory cytochromes.³ In a rat model, HBOT was shown to prevent CO-induced lipid peroxidation in brain¹³ and to prevent reperfusion injury by blocking adhesion of leukocytes to the microvasculature.¹⁴

The efficacy of HBOT in acute carbon monoxide intoxication was first demonstrated in 1942 by End and Long.¹⁵ In 1977, a lawsuit resulted in a \$3.8 million judgment for failure to use HBOT in a patient with severe carbon monoxide intoxication, who was left with a permanent mental disability. The patient had been transferred to the nearest hospital that had a hyperbaric chamber, but the admitting house staff was not aware that the hospital offered this treatment.¹⁶ A number of reports showed benefits of HBOT, but it has been considered controversial because of the lack of definitive randomized controlled trials (RCTs).³ A Cochrane Systematic Review of six randomized trials involving 1,997 patients showed a favorable odds ratio of 0.78 (95% CI, 0.54-1.12) for symptoms and signs 4-6 weeks after HBOT. But it concluded, apparently because the benefit fell slightly short of statistical significance, that there was "no evidence to support use of

hyperbaric oxygen for treatment of patients with carbon monoxide poisoning.” It recognized the existence of conflicting results and methodologic flaws in all studies.¹⁷ The most recent trial was stopped after the third of four scheduled interim analyses because cognitive sequelae at 6 weeks were less frequent in the HBOT group ($P=.007$).¹⁸ This study, which involved only three sessions of HBOT in a 24-hour period, “shifts the balance of evidence to support HBO over normobaric oxygen,” according to an analysis by the American College of Physicians Journal Club.¹⁹

In the acute episode it is standard to administer HBOT only when the COHb is above 25% and symptoms, especially impaired consciousness, are evident, or possibly if abnormalities are seen on electrocardiogram or magnetic resonance imaging (MRI).²⁰

Our interest in HBOT for CO poisoning began in 1978, when a patient was brought to us, having been in a coma-like state for more than 12 years after a suicide attempt. As previously reported,^{21,22} this patient recovered a nearly normal level of functioning, with minimal cognitive defects, after some 350 sessions of HBOT, in conjunction with physical and occupational therapy.^{21,22}

Our facility in Florida has treated approximately 15 patients in Florida for long-term neurologic consequences of acute or chronic CO inhalation, mostly the former. In Taipei, Taiwan, one of us (AKCN) has treated dozens of such patients with HBOT. Patients were referred to us for salvage therapy, as no additional “standard” therapy was deemed appropriate or beneficial for their condition. Nearly all patients experience some degree of improvement, even from deficits of long duration, as documented in the records of the patient who had been in a comatose state for 12 years. Each patient was treated according to the clinician’s best judgment, rather than a research protocol. A monoplace chamber pressurized with 100% oxygen was used, at pressures of 1.5 to 1.75 ATA, as we were treating chronic brain injury, not acute CO intoxication.

Case Reports

These four cases are representative of patients referred to our practice with neurologic impairment from acute or chronic CO intoxication. Pre- and post-treatment single photon emission computerized tomographic (SPECT) scans are available for three of them.

Case 1. A 29-year-old woman had been exposed to CO from an exhaust leak in her vehicle for 3 months. She at first complained of memory loss and migraines. At that time, motor skills were intact, and several physicians had referred her for psychiatric evaluation. When she began falling asleep in the vehicle, it was discovered that the exhaust pipe had separated from the manifold. She was referred to us after the diagnosis of CO poisoning was made. She was found to have poor coordination, confusion, and difficulty in problem solving. Two one-hour sessions of HBOT at a pressure of 1.75 ATA were administered daily, for a total of 69 treatments. Her symptoms and signs resolved completely, and marked improvements were seen in her post-treatment functional brain imaging (Figure 1).

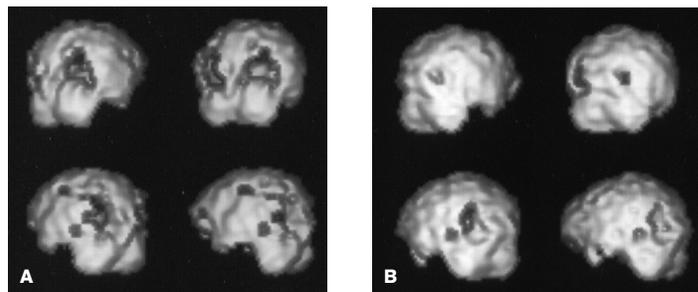


Figure 1. A. 3-D Reconstruction Images from Pre-HBOT SPECT Scan in Case #1. **B.** Images from Post-HBOT SPECT Scan. These scans demonstrate significant decrease in the areas of nonfunction in both cerebral hemispheres as shown by the smaller and less numerous defects in the post- compared with the pre-treatment study.

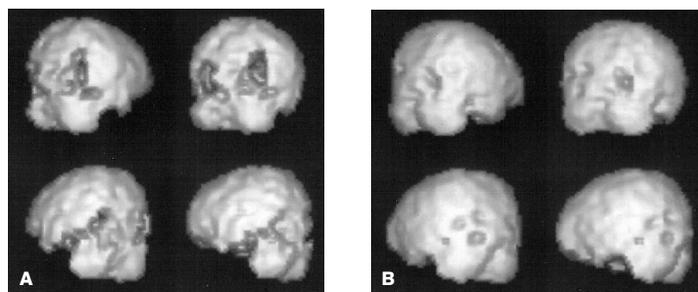


Figure 2. A. 3-D Reconstruction Images from Pre-HBOT SPECT Scan in Case #2. **B.** Images from Post-HBOT SPECT Scan. The markedly abnormal baseline scan shows large bilateral occipital lobe and moderate left parieto-occipital areas of absent localization. After treatment, there is marked improvement in all abnormal regions, with only small patchy areas of reduced localization within the areas of previous significant abnormality.

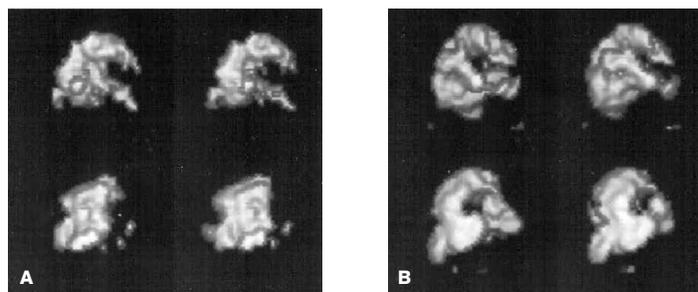


Figure 3. A. 3-D Reconstruction Images from Pre-HBOT SPECT Scan in Case #3. **B.** Images from Post-HBOT SPECT Scan. Severely abnormal scan with numerous large areas of absent localization, with some improvement in most areas after HBOT.

Case 2. An 11-year-old boy was one of a family of five that had suffered severe CO intoxication due to a faulty furnace 4 years previously. Normobaric oxygen had been given for four or five hours before the COHb level was measured and determined to be 12.3%. The patient was thus not considered to be a candidate for HBOT at the time. He later developed seizures, severe headaches, and difficulty concentrating. His school performance deteriorated. Following 22 twice-daily HBOT sessions at 1.5 ATA, seizure activity ceased, his headaches diminished greatly, and his schoolwork improved, as did his SPECT scans (Figure 2). The other family members were also treated, and all improved.

Case 3. A 75-year-old man suffered acute CO poisoning when his car was inadvertently left running in the enclosed garage attached to his home. After he received normobaric oxygen, his COHb level was normal. He was discharged from the emergency room asymptomatic, and was told that he had fully recovered. Two weeks later, he became comatose. When he emerged from the coma, he was almost completely aphasic, showed personality changes, and required gastrostomy tube feedings. His neurologic abnormalities persisted for 3.5 months, at which time he was referred for HBOT. His SPECT scan showed diffuse cerebral deficits, especially in the frontal lobe, and also involvement of the basal ganglia. After about 80 sessions of HBOT at 1.5 ATA, his cognitive and social functioning improved substantially, and he could speak coherently. His SPECT scans also improved (Figure 3).

Case 4. A 19-year-old male pre-law student from Buenos Aires was showering when a fire was started in his home by a natural gas-burning heater. The flames were extinguished, but as a result of inhaling the smoke and fumes, the patient became confused, then stuporous. An anoxic encephalopathy was diagnosed. With time he improved, but his intelligence had regressed to that of a 12-year-old child. He was referred to our center for HBOT 14 months after the incident. CT scanning showed rather diffuse white matter lesions and a mild degree of cortical atrophy. SPECT scan showed markedly decreased localization in both cerebral hemispheres, worse on the right, and in the right basal ganglia. The patient had spasticity in all extremities and the masseters. Although formal psychological testing was not performed, it was apparent that his responses were childlike and immature, and that he was not able to speak in complete sentences. Following the third session of HBOT at 1.5 ATA, the patient's spasticity was notably diminished, and he was more affable. During the course of treatment, he improved progressively and became self-sufficient in ambulation, eating, and toileting. Because he had a limited visa, only 14 treatments were given. He was advised to breathe 6 liters/min of normobaric oxygen for 30 minutes twice daily on his return home. He continued to improve in balance, gait, and cognition, and was able to return to his pre-law studies within 3 months.

Discussion

Clinicians need a high level of awareness of CO poisoning as it is a common condition that is frequently misdiagnosed. CO poisoning can be mistaken for an influenza-like illness, a drug overdose, or a neurologic or psychiatric disease.

Emergency responders routinely treat victims of CO poisoning with normobaric oxygen. Although its use is clearly indicated, normobaric oxygen may reduce the COHb to a level that is considered acceptable, without removing all the bound excess CO from the tissues. Normal clinical findings and blood tests are no guarantee that serious neurologic sequelae will not develop.

The biochemical and immunologic effects mentioned above—lipid peroxidation¹¹ and leukocyte sequestration¹³—may play a role in the late tissue damage. Additionally, CO has been shown to injure the blood-brain barrier, causing focal edema.²³ However, the mechanism of the delayed injury, as well as the mechanism of action of HBOT in repairing the damage, remains speculative.

It is a reasonable premise that earlier treatment with HBOT, before tissue damage is established, could be efficacious, and that fewer HBOT sessions should be required to prevent central nervous system damage than to attempt to repair it. A better method of identifying patients most likely to suffer delayed effects would be highly desirable. In our opinion, functional brain imaging, either SPECT or PET (positron emission tomography), should be obtained before patients are discharged. Knowing the high incidence of late sequelae that can be devastating and permanent, the prudent clinician may wish to continue normobaric oxygen for some time, in the event that HBOT and/or functional brain imaging is not available.

As fixed neurologic deficits are generally believed to be irreversible, documentation of distinct improvement, even in the small number of patients described here and in our previous report, shows the need for further study and broader availability of empiric HBOT treatment. There are other reports that deficits attributed to CO poisoning improve with HBOT, and that improvements may continue even after therapy is discontinued.²⁴

In our opinion, further studies should focus on the question of optimal treatment pressures and schedules. Victims of CO poisoning should not be denied the opportunity to minimize their risk of brain damage, through the benign and physiologically sound treatment modality of HBOT, because of devotion to an impossible gold standard of an "adequate" RCT. Oxygen indeed has been described as the first of three "universal antidotes" that all emergency physicians should utilize aggressively. Oxygen is the "antidote" to hypoxia of any cause. (The other two universal antidotes are dextrose and naloxone.)²⁵ Nor should neurologically damaged patients be denied HBOT, as the brain's capacity for healing is greater than previously believed.

The appropriateness of the RCT must be considered in context. RCTs are most suitable for drugs, and impossible for procedures like joint replacements. They are, at best, difficult for HBOT, and not feasible for situations that may require a large number of treatments. The patient must spend significant periods of time in a special chamber and undergo pressurization and depressurization. Existing trials have been criticized for many reasons, including: exclusion of the sickest patients, who are most likely to benefit; inadequate length of follow-up, thus missing late complications; delays in starting treatment; difficulty blinding patients or examiners; and loss of inordinate numbers of patients to follow-up.¹⁷ Must patients facing the prospect of life-altering

brain damage wait for the proper multicenter RCT to be designed, funded, carried out, analyzed, and published? Is it sensible for the RCT be the gold standard even in circumstances when it is extremely difficult or impossible to perform? Should a poorly performed RCT—or the absence of an RCT—trump pathophysiology and clinical observation?²⁶ Few surgical procedures have been subjected to RCTs.

Conclusions

Current assessment and treatment of CO poisoning in the emergency department is grossly inadequate to prevent serious neurologic complications. HBOT speeds removal of CO from tissues and counters a number of its deleterious effects. Past studies have demonstrated efficacy of HBOT for reducing the incidence of neurologic sequelae, even though only three sessions of HBOT were used. Clinical experience such as that reported here shows that HBOT treatment late in the course of established impairments from CO can lead to clinical improvements. Improvement is documented by evidence of increased brain metabolism on functional brain imaging by SPECT after HBOT. Further study as well as wider availability of HBOT, particularly for persons such as firefighters who are at high occupational risk of CO poisoning, is warranted.

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