

*Editorials***HYPERBARIC-OXYGEN THERAPY FOR ACUTE CARBON MONOXIDE POISONING**

CARBON monoxide appears to be the leading cause of injury and death due to poisoning worldwide.<sup>1</sup> A colorless, odorless, tasteless gas, carbon monoxide is produced by the incomplete combustion of any carbon-containing fuel. Prevention of carbon monoxide poisoning requires public education on the safe operation of appliances, heaters, fireplaces, and internal-combustion engines, as well as increased emphasis on the installation of carbon monoxide alarms.<sup>1</sup> Despite the ubiquitous presence of carbon monoxide in our environment, its known threat to public health, and more than a century of scientific investigation, the mechanisms of injury and methods of treating carbon monoxide poisoning are poorly understood.

The affinity of hemoglobin for carbon monoxide, with which it forms carboxyhemoglobin, is more than 200 times as great as its affinity for oxygen. Tissue hypoxia is therefore a primary insult, but carboxyhemoglobin values correlate poorly with the most frequent effect, so-called delayed neurologic injuries. Between 23 and 47 percent of patients have impairments of concentration, attention, language, learning, memory, or motor function, or have depression, dementia, or psychosis that develops between 2 and 28 days after poisoning.<sup>1-6</sup> The pathogenesis of and risk factors for the delayed neurologic syndrome remain unknown. Mechanisms of carbon monoxide-mediated encephalopathy implicated by basic studies are oxidative stress related in part to cellular uptake of carbon monoxide, toxic effects from excessive release of excitatory amino acid neurotransmitters, and a cascade of inflammatory changes.<sup>7-9</sup>

Treatment of carbon monoxide poisoning has focused on providing the patient with supplemental oxygen to hasten the dissociation of carbon monoxide from hemoglobin and to improve oxygenation of tissue. These goals provided the initial motivation for using hyperbaric oxygen, and its efficacy has been investigated in four previous reports on randomized clinical trials.<sup>4-6,10</sup> In this issue of the *Journal*, Weaver et al.<sup>11</sup> report on the latest and most carefully controlled investigation of hyperbaric-oxygen therapy for acute carbon monoxide poisoning. Among the strengths of this trial are its large size, its use of a sham-treatment control group with blinding of both patients and investigators to the treatment-group assignment, its selection of seriously poisoned patients representative of those encountered in emergency departments, its employment

of treatment regimens similar to those in common use, its very high rates of follow-up evaluation, and its explicit definitions of cognitive sequelae. Weaver et al. found that hyperbaric-oxygen treatment significantly reduces the incidence of carbon monoxide-induced delayed neurologic sequelae. The assessment of the primary end point (identification of patients in whom cognitive sequelae developed) took place 6 weeks after poisoning, but evaluations at 6 and 12 months also showed a large benefit of hyperbaric-oxygen therapy. These findings lend further support to the use of hyperbaric oxygen, particularly because neurologic manifestations may persist for variable intervals after carbon monoxide poisoning.

Impediments to the use of hyperbaric-oxygen therapy include the limited availability of facilities and the risk of adverse effects. Weaver et al. found that for every six patients treated, one case of delayed neurologic sequelae could be avoided.<sup>11</sup> This result offers a strong motivation for treatment, given the functional impairments that may occur. The risk involved in transporting patients from an acute care setting to the hyperbaric chamber will always be cause for concern. Weaver et al. did not comment on this point, but others have failed to find that complications occurred due to the transport of patients.<sup>12</sup> Adverse effects from hyperbaric oxygen are generally mild. The most severe complication, oxygen-induced convulsions, has an incidence of 1 in 10,000 patients in large series,<sup>13</sup> and none occurred in the study by Weaver et al. Convulsions are usually well managed with the reduction of oxygen tension in the inspired gas and the administration of anticonvulsant agents.

Neurologic abnormalities and a history of loss of consciousness are the primary clinical features used to define severe carbon monoxide poisoning. Objective laboratory tests have not been found to be useful.<sup>1</sup> Therefore, the post hoc analysis performed by Weaver et al. supports the continued recommendation of hyperbaric-oxygen therapy for patients with a base excess lower than  $-2$  mmol per liter, a carboxyhemoglobin level higher than 25 percent, or both. Notably, Weaver et al. identified abnormalities on cerebellar examination as a risk factor.<sup>11</sup> There is some concern that fetuses, neonates, and the elderly may have increased susceptibility to carbon monoxide poisoning; however, the risk of neurologic sequelae posed by extremes of age is not clear.

Determination of the optimal number of hyperbaric-oxygen treatments will require additional study, as will determination of the interval after poisoning after which therapy is no longer effective and the optimal treatment pressure. The majority of hyperbaric-oxygen treatment centers follow the dictum that all patients at high risk deserve a single treatment, but multiple treatments are typically reserved for those

who do not recover fully on completion of the first treatment.<sup>13</sup> Weaver et al. treated patients with hyperbaric oxygen three times within 24 hours — a protocol that was based on retrospective observations by Gorman et al.,<sup>3</sup> who found that the relapse rate for cognitive sequelae was lower in patients who were treated two or more times than it was in those treated only once.

With regard to the window for treatment, work by Goulon et al.<sup>2</sup> suggested that there is a six-hour interval of greatest opportunity for benefit from hyperbaric-oxygen therapy; however, the interval during which any therapeutic effect may be achieved remains unclear. Weaver et al. used an interval of 24 hours after exposure to carbon monoxide as an upper limit for inclusion of patients in the study, and the mean time between exposure and the initial treatment was 5.8 hours. Two previous investigations failed to find hyperbaric oxygen effective in preventing carbon monoxide-mediated brain injury; the mean time from poisoning to randomization and treatment ranged from 5.3 to 6.4 hours in different groups in one of these studies,<sup>4</sup> and was 7.3 hours in the other study.<sup>10</sup>

Further study will also be required in order to determine the optimal dose of hyperbaric oxygen — that is, the treatment pressure. Patients in the current study received oxygen at 3.0 atmospheres absolute, and two other randomized trials that found a benefit from hyperbaric oxygen used pressures of 2.5 and 2.8 atmospheres absolute.<sup>5,6</sup> Therefore, use of hyperbaric oxygen at a pressure between 2.5 and 3.0 atmospheres absolute seems appropriate. The optimal pressure cannot be determined until the mechanisms of injury and the therapeutic actions of hyperoxia are better defined. At the time of treatment, patients in the study by Weaver et al. had only nominal elevations of carboxyhemoglobin, indicating that the efficacy of hyperbaric-oxygen therapy cannot be ascribed to hastened dissociation of carboxyhemoglobin. Additional mechanisms of action of hyperbaric oxygen found in studies in animals include improved mitochondrial oxidative metabolism,<sup>14</sup> inhibition of lipid peroxidation,<sup>15</sup> and impairment of adherence of neutrophils to cerebral vasculature.<sup>16</sup> The mechanism of inhibition of neutrophil adherence and the dose of oxygen that is required are the same in rats and in humans.<sup>16,17</sup>

One might hope that the current study will inspire greater interest in the scientific investigation of hyperbaric-oxygen therapy. The Computer Retrieval of Information on Scientific Projects service of the National Institutes of Health (NIH) indicates that during the past 10 years, only 23 investigators at 14 academic institutions have received NIH funding for studies of the therapeutic aspects of hyperbaric oxygen.

Carbon monoxide is a health hazard that poses difficult diagnostic challenges. Carbon monoxide poi-

soning may cause cardiovascular compromise and, at times, respiratory arrest. Neither hyperbaric oxygen nor any other current therapy can be expected to prevent cognitive sequelae due to cellular injuries sustained at the time of exposure. The article by Weaver et al. provides a reliable foundation on which to base decisions regarding management.

STEPHEN R. THOM, M.D., PH.D.

University of Pennsylvania  
Philadelphia, PA 19104-6068

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## CONFLICTING DISPATCHES FROM THE TOBACCO WARS

**P**REVENTION and cessation are the two principal strategies in the battle against tobacco. Preven-