ELSEVIER

Journal of the Neurological Sciences 262 (2007) 122 – 130

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Carbon monoxide intoxication: An updated review

Leon D. Prockop *, Rossitza I. Chichkova

Department of Neurology, College of Medicine, University of South Florida, USA

Available online 27 August 2007

Abstract

Carbon monoxide (CO), a highly toxic gas produced by incomplete combustion of hydrocarbons, is a relatively common cause of human injury. Human toxicity is often overlooked because CO is tasteless and odorless and its clinical symptoms and signs are non specific. The brain and the heart may be severely affected after CO exposure with carboxyhemoglobin (COHb) levels exceeding 20%. Damage occurs because the affinity of hemoglobin for CO is 210 times higher than for O_2. Hypoxic brain damage predominates in the cerebral cortex, cerebral white matter and basal ganglia, especially in the globus pallidus. Diagnosis requires clinical acumen and a high index of suspicion, combined with epidemiological data, clinical examination, analysis of ambient air CO and patient COHb levels; also required are cardiology evaluation including ECG as well as neurological evaluation including brain imaging (CT and/or MRI, MR spectroscopy), and neuropsychological testing. Although immediate O_2 breathing is sometimes an adequate treatment, hyperbaric oxygen therapy (HBO) is favored. Subsequently, only symptomatic therapy is available for the long-term sequelae of CO poisoning.

Keywords: Carbon monoxide (CO); Carboxyhemoglobin (COHb); Hyperbaric oxygen (HBO); Brain damage; Cardiac damage; Neurotoxicity; CT; MRI

1. Introduction

Carbon monoxide (CO) intoxication is one of the most common types of poisoning in the modern world, and the leading cause of death by poisoning in the Unites States. CO is a tasteless, odorless, non-irritating but highly toxic gas. Because of these properties and because it lacks a unique clinical signature, CO is difficult to detect and can mimic other common disorders. Therefore, the true incidence of CO poisoning is unknown and many cases probably go unrecognized. CO has been termed "the unnoticed poison of the 21st century" [1]. An environmental CO exposure is suggested when more than one person and animals are affected; when there is a history of fire, presence of fireplace or combustion appliances, or with occupational exposure; and by the occurrence of symptoms in relation to a possible exposure [2].

CO is a by-product of the incomplete combustion of hydrocarbons. Common sources include motor vehicle exhaust gases in a poorly ventilated garage or in areas in close proximity to garages; combustion appliances, *e.g.* heating units, in which partial combustion of oils, coal, wood, kerosene and other fuels generate CO. A common scenario is that of a heating unit used only occasionally and not well maintained. Retrograde flow can occur in residential, occupational or institutional settings in the presence of pressure problems, chimney or equipment malfunction. CO poisoning with immediate deaths may occur during a building fire or from fuel powered generators and heaters, especially in poorly ventilated spaces [3]. The latter causes are frequently reported during winter storms, hurricanes, earthquakes or other disasters after a power outage has occurred.

There are also endogenous sources of CO, such as during the heme degradation to bile pigments, catalyzed by heme oxygenases [4]. Constitutive and inducible isoforms (HO-l, HO-2) of the enzyme are known. Endogenously produced CO serves as a signaling molecule involved in multiple cellular functions, such as inflammation, proliferation, and apoptosis. CO, like nitric oxide, is a recently defined gaseous neurotransmitter in the central nervous system (CNS).

2. History

The ancient Greeks and Romans used CO to execute criminals. The deaths of two Byzantine emperors was related

* Corresponding author. Box 55, 12901 Bruce B. Downs Blvd., Tampa, FL 33612, USA.

E-mail address: lprockop@health.usf.edu (L.D. Prockop).

0022-510X/$ - see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.jns.2007.06.037

to CO produced by the burning of coal in braziers, the usual method of indoor heating during that epoch [5]. CO was first prepared by the French chemist de Lassone in 1776. Because it burned with a blue flame, he mistakenly thought it to be hydrogen. In 1880, William Cruikshank identified it as a compound containing carbon and oxygen. In the middle of the 19th century, Claude Bernard recognized that CO causes hypoxia by interaction with hemoglobin (Hb). He poisoned dogs with the gas, noticing the scarlet appearance of their blood. Towards the end of the 19th century, Haldane demonstrated that a high partial pressure of O_2 can counteract the interaction between Hb and CO despite the high affinity for this interaction. In World War II, wood was used widely as fuel and caused many cases of acute or chronic CO poisoning [6].

3. Biochemistry, physiopathology, and pathology

CO binds rapidly to Hb, leading to the formation of carboxyhemoglobin (COHb). The oxygen carrying capacity of the blood decreases, causing tissue hypoxia. COHb is red which explains the "cherry-like" discoloration of victims. CO diffuses from the alveoli to the blood in the pulmonary capillaries across the alveolo-capillary membrane that is composed of pulmonary epithelium, the capillary endothelium and their fused basement membrane. CO is taken up by the Hb at such a high rate that the partial pressure of CO in the capillaries stays very low. Therefore, the CO transfer is diffusion-limited. The affinity of hemoglobin for CO is 210 times its affinity for O_2. CO easily displaces oxygen from hemoglobin. On the other hand, COHb liberates CO very slowly. In the presence of COHb, the dissociation curve of the remaining HbO_2 shifts to the left further decreasing the amount of the oxygen released. The amount of COHb formed depends on the duration of exposure to CO, the concentration of CO in the inspired air and the alveolar ventilation. Even though CO is toxic to the cytochromes, this mechanism plays a minor role in clinical CO poisoning, since the amount of CO required to poison cytochromes is 1000 times higher than the lethal dose. CO binds to intracellular myoglobin in the myocardium and impairs the oxygen supply to the mitochondria. This negatively affects the oxidative phosphorylation and consequently, the energy source of heart muscle. Patients with underlying cardiac conditions are at risk for death from arrhythmias and fatal heart attacks can occur. However, chest pain as a symptom of myocardial ischemia can occur without underlying coronary artery disease. For example, 2 weeks after accidental exposure to CO, 34% of a group of Swiss soldiers had chest pain [7].

Henry et al. [8] studied mortality risk in patients with moderate to severe CO poisoning. In those at low risk for cardiovascular diseases, 37% suffered acute myocardial injury and 38% were dead within 7.6 years. The mortality rate was three times higher than the US expected mortality by age and sex [8].

After CO exposure, angina attacks, arrhythmias, and increased level of cardiac enzymes frequently occur. This has led to a search for morphological changes that could be attributed to CO, especially because the myocardium binds more CO than skeletal muscle. Ultramicroscopic lesions have been reported but the relative roles of general tissue hypoxia and specific CO toxicity are unknown [9]. In addition to COHb, the binding of CO to cytochromes is also significant and is thought to be responsible for cytotoxicity. Combined ultra structural and cytochemical studies have enabled differentiation between toxic, hypoxic, and mixed alteration. The marked decrease in cytochrome oxidase in experimental studies suggests a direct toxic effect [9].

Myocardial injury with ischemic ECG changes and elevated cardiac biomarkers were found in 37% of 230 patients with moderate to severe CO poisoning with 5% in-hospital mortality [10]. Therefore, patients admitted to the hospital with CO poisoning should have a baseline ECG and serial cardiac enzymes.

Recent investigations suggest other mechanisms of CO-mediated toxicity. One hypothesis is that CO-induced tissue hypoxia may be followed by reoxygenation injury to the CNS. Hyperoxygenation facilitates the production of partially reduced oxygen species, which in turn can oxidize essential proteins and nucleic acids, resulting in typical reperfusion injury. In addition, CO exposure has been shown to cause lipid peroxygenation, *i.e.* degradation of unsaturated fatty acids leading to reversible demyelination of CNS lipids. CO exposure also creates substantial oxidative stress on cells, with production of oxygen radicals resulting from the conversion of xanthine dehydrogenase to xanthine oxidase [11]. Myocardial fiber necrosis was described in a 26 year old patient with accidental CO poisoning and blood concentration of COHb of 46.6% [12]. Electron microscopy of left ventricular biopsies of a 25 year old woman with functional evidence of cardiac failure after acute CO poisoning and otherwise normal myocardial perfusion showed slight ultrastructural changes in the myocytes, large glycogen deposits and swollen mitochondria. The above changes have been though to be signs of impaired energy metabolism of the myocardial cells [13]. In rat heart, CO causes vasodilatation and increased coronary flow that are not mediated by simple hypoxia [14]. CO exposure in the fetal period in rats causes myocyte hyperplasia and cardiomegaly. This cellular response is sustained through the early neonatal period in animals exposed to CO both *in utero* and in the post-partum [15]. Although hemorrhages and areas of necrosis in the heart, mostly in the septum and the papillary muscles were described with CO poisoning as early as 1865 [16] only few human cases of acute, fatal CO intoxication, with small foci of coagulation necrosis have been reported [17].

Disturbances of brain function predominate in acute CO intoxication. Delayed neurological effects also occur [18]. Tissue hypoxia is the end result of intoxication with CO and with many other physical and chemical agents. Some brain regions are sensitive to hypoxic damage including the cerebral cortex, particularly its second and third layers; the white matter, the basal nuclei, and Purkinje cells of the cerebellum.

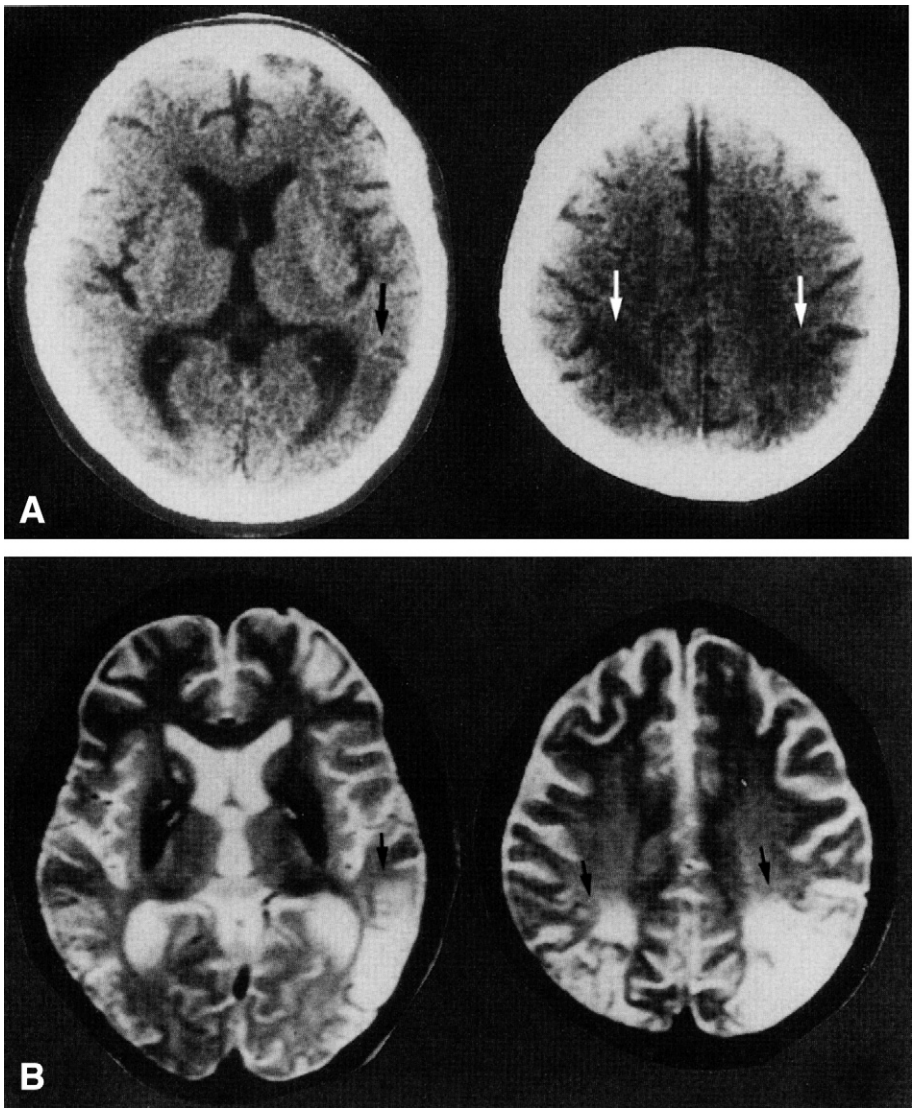

Fig. 1. Brain CT and MRI scans in the same patient. (A) CT findings. The arrows show low-density areas. (B) T2-weighted MRI cortical areas are more affected than the subcortical areas from Murata et al. [20].

Attempts have been made to relate this "selective vulnerability" to the cause of the hypoxia, but the nature and distribution of the lesions appear to depend on the severity, suddenness, and duration of the oxygen deprivation, as well as on its mechanism (hypoxemia or ischemia) rather than on its cause. Regions with relatively poor vascularization and "watershed" areas between two sources of blood supply, such as the globus pallidus, may be more vulnerable, especially during periods of hypotension. The effects of hypoxia on the brain, therefore, do not reflect it cause and neither the character of the lesions nor the areas affected are regarded as pathognomonic for CO.

The neuropathology of CO toxicity has been well described in postmortem studies [19] and includes, in acute cases, petechial hemorrhages of the white matter involving in particular the corpus callosum; in cases surviving more than 48 h there is multifocal necrosis involving globus pallidus, hippocampus, pars reticularis of the substantia nigra, laminar necrosis of the cortex and loss of Purkinje cells in the cerebellum, along with white matter lesions. The typical pallidum lesions are well-defined, bilateral globus pallidus macroscopic infarctions, usually asymmetrical, extending anteriorly, superiorly, or into the internal capsule. Occasionally, only a small linear focus of necrosis is found at the junction of the internal capsule and the internal nucleus of the globus pallidus. CO intoxication usually spares the hypothalamus, walls of the third ventricle, thalamus, striatum, and brainstem. Myelin damage is constant and ranges from discrete, perivascular foci in the corpus callosum, the internal–external capsule and the optic tracts usually seen in comatose patients who died within 1 week, to extensive periventricular demyelination and axonal destruction observed in comatose subjects with longer survival, sometimes leading to formation of plaques of demyelination. A distinct constellation of brain and MRI abnormalities appears premortem and in those surviving an exposure. It includes globus pallidus lesions, white matter changes, and diffuse low-density lesions throughout the brain.

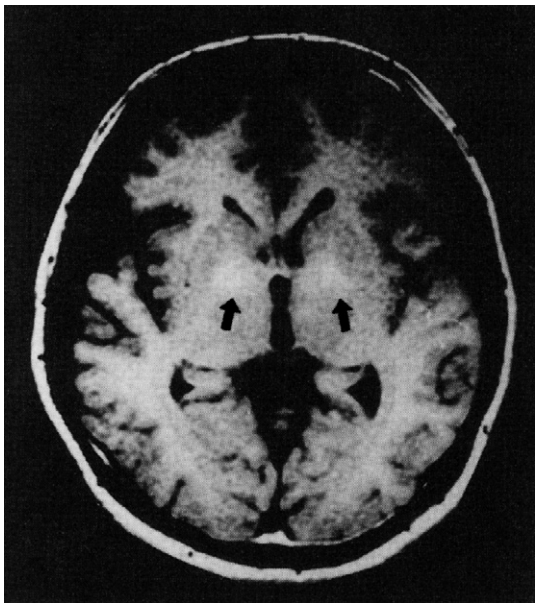

Fig. 2. T1-weighted MRI. High-signal regions are seen in the globus pallidus bilaterally (arrows) from Murata et al. [20].

In general, CT and MRI neuroimaging findings reflect the neuropathologic changes described by Lapresle and Fardeau [19] (Figs. 1–3). Previously unreported neuropathological findings include the MRI findings of thalamic lesions [22].

4. Clinical findings

Because of their high metabolic rate, the brain and the heart are most susceptible to CO toxicity. The clinical symptoms of CO poisoning are often non-specific and can mimic a variety of common disorders. The severity ranges from mild flu-like symptoms to coma and death. About 50% of exposed people may develop weakness, nausea, confusion, and shortness of breath. Less frequently, abdominal pain, visual changes, chest pain and loss of consciousness occur. Tachycardia and tachypnea develop to compensate from cellular hypoxia and cardiac output increases initially. Responses to cellular hypoxia vary depending on the premorbid condition of victims; those with underlying lung and heart disease will have little tolerance to even mild hypoxia. Hypoxia leads to increased intracranial pressure and cerebral edema which is partly responsible for decreased level of consciousness, seizures and coma. The classic cherry-red discoloration of the skin and cyanosis are rarely seen [19]. Varying degrees of cognitive impairment have been reported [23].

Table 1 lists some of the symptoms and signs of CO intoxication. Headache is one of the most common presenting features of CO poisoning: it occurs in 84% of the victims [24] and has been described as predominantly

Table 1
Signs and symptoms of carbon monoxide intoxication

1. Headache	8. Difficulty in coordinating
2. Dizziness	9. Difficulty in breathing
3. Irritability	10. Chest pain
4. Confusion/memory loss	11. Cerebral edema
5. Disorientation	12. Convulsions/seizures
6. Nausea and vomiting	13. Coma
7. Nausea and vomiting	14. Death

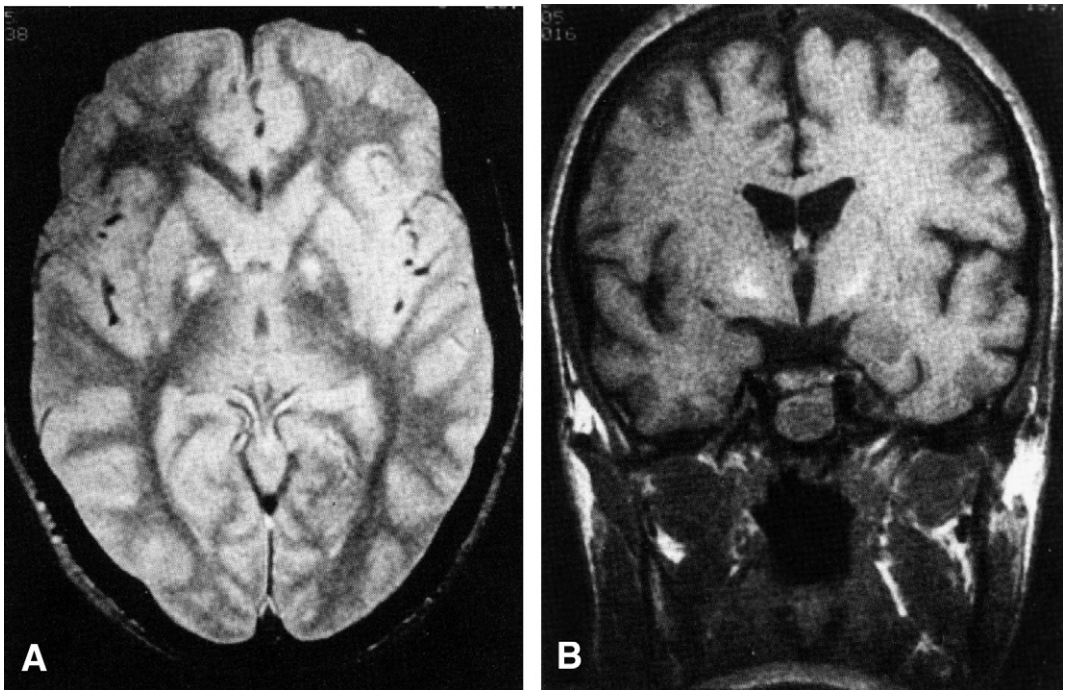

Fig. 3. (A) Proton density brain MRI, transaxial view, shows bilateral hemorrhage in the globus pallidus. (B) T1-weighted brain MRI, coronal view from Tom et al. [21].

frontal, dull, sharp, continuous, throbbing, and intermittent in patients with a mean COHb level of 21.3% (± 9.3%). There is no clear correlation between pain intensity and COHb levels [25]. Some have reported tightness across the forehead at COHb levels of 10–20%, throbbing in the temples at 20–30%, and severe headache at 30–40% [26]. Headaches, generalized weakness, fatigue and sleepiness, are part of the vague symptomatology observed in subjects with COHb levels below 20%. Headache is a frequent complaint not only with acute but with chronic CO poisoning. Dizziness is a frequent companion of headache and can be seen in about 92% of CO victims of CO poisoning. In one report, 76% of 38 victims reported weakness with COHb levels > 30–40% [3].

A delayed neuropsychiatric syndrome may occur in patients from 3 days up to 240 days after acute CO exposure. Even those victims without neurological and psychiatric symptoms immediately after an exposure accident may demonstrate features of delayed impairment ranging from subtle abnormalities such as personality changes or mild cognitive deficit to severe dementia, psychosis, Parkinsonism, incontinence or other [18,27].

CO encephalopathy may cause a number of behavioral functional impairments including alterations in attention, executive function, verbal fluency, motor abilities, visuospatial skills, learning, short-term memory, and mood and social adjustment. Formal neuropsychological testing usually confirms these impairments [28].

5. Diagnosis

Diagnosis of CO poisoning requires a high level of suspicion. Epidemiological history with information about other affected individuals or pets as well as circumstances suggestive of possible exposure is of paramount importance.

Ambient air CO levels should be obtained as soon as possible after the exposure. Because the half-life of COHb is 4–5 h, a victim's COHb level should also be obtained as soon as possible. Normal level for non-smokers is < 2% and for smokers 5–13%. The Expert Panel on Air Quality Standard of the World Health Organization (WHO) in 1994 reported that blood COHb levels between 2.5% and 4% decrease in the short-term maximal exercise duration in young healthy men. Decrease exercise duration because of increased chest pain and in patients with ischemic heart occurred at levels from 2.7% to 4.1%. Levels between 2% and 20% can cause effects on visual perception levels, audition, motor, and sensory-motor functions, and behavior. Therefore, ambient air CO levels which produce blood COHb levels below 2.5% are recommended. The COHb levels depend not only upon the CO level in ambient air but also on the duration of exposure. According to WHO guidelines, exposures to levels of ambient air CO_2 in parts per million (ppm) should conform to the following durations of exposure: 87.1 ppm (100 mg/m^3) for 15 min; 52.3 ppm (60 mg/m^3) for 30 min; 26.1 ppm (30 mg/m^3) for 60 min; 8.7 ppm (10 mg/m^3) for 8 min. [29]. Any exposure to ambient air with CO levels greater than 100 ppm is dangerous to human health [28,30].

Physicians who deal with CO intoxication should be aware that pulse oximetry is a colorimetric method, unreliable for the diagnosis of CO intoxication since it can not distinguish oxyhemoglobin from COHb. Therefore, pulse oximeters overestimate arterial oxygenation in patients with severe CO poisoning. Accurate assessment of arterial oxygenation in patients with severe CO poisoning can currently be performed only by analysis of arterial blood with a laboratory CO-oximetry. High-flow oxygen should be administered to all patients suspected of significant CO exposure until direct measurement of CO levels can be performed, regardless of pulse oximetry readings [31].

For clinical purposes, automated spectrophotometer CO-oximeter device are recommended. Spectrophotometers measures light intensity as a function of color and can differentiate the different wavelengths of oxyhemoglobin and COHb with an acceptable accuracy for COHb saturation levels above 5%; they can simultaneously estimate total Hb and percentages of oxyhemoglobin and COHb. Gas chromatography, a more sensitive method, can be utilized for low-level exposure and for post-mortem blood samples [32].

Cardiac function must be monitored closely by ECG, 2D-ECHO, and cardiac enzymes. The heart, like the brain, is very sensitive to hypoxic injury. Patients with underlying cardiac disorders, whose reserves are impaired at baseline, are at higher risk compared to normal individuals. Cardiac arrest and sudden cardiac death can be expected. Chest pain, due to myocardial ischemia or infarction is a consequence of decreased oxygen supply to the cardiac muscle. Features of ischemia as well as other abnormalities, such as tachycardia, bradycardia, atrial and ventricular fibrillation, premature ventricular contractions, conduction abnormalities and others can be easily detected on ECG. Non-invasive devices that can be used to screen firefighters and victims can estimate the COHb levels in the exhaled alveolar breath have been suggested [31]. A non-invasive, high-resolution method of measuring COHb fraction using expiratory gas analysis in patients without evidence for pulmonary edema or atelectasis has been found to have accuracy equivalent to that of CO-oximetry [33].

Very high levels of S100B protein, a structural astroglial protein, have been found in patients who died from CO poisoning; elevated levels occur in unconscious patients, and normal levels in those without loss of consciousness. It was proposed that the S100B protein levels could be used as a biochemical marker of brain injury in CO poisoning [34]. However, Rasmussen et al. [35] failed to find significant increase in blood concentrations of neuron-specific enolase and of S-100 protein there was no correlation with level of consciousness in CO poisoning [35]. Scintigraphy studies of the heart with 99mTc have been proposed as method of choice for evaluation of heart injury in patients after acute CO intoxication [36].

Diffusion weighted images (DWI) in brain MRI show white matter high signal intensities consistent with restricted diffusion in acute CO poisoning. Follow-up MRI performed 16 days later reveals disappearance of white matter lesions, suggesting the white matter can be more sensitive than gray matter to hypoxia in the acute phase [37].

T2-weighted brain MRI shows increased signal intensity bilaterally in the putamen and the caudate nucleus, as well as high signal intensity in the globus pallidus [38]. Initially, unilateral low attenuation areas in the right putamen, globus pallidus and thalamus were observed in the CT of a patient after CO exposure, followed by transient bilateral appearance of lesions on subsequent CT examination. Hemorrhagic infarction of the right putamen, and ischemic lesions in both thalami were visualized on MRI 2 weeks later [39]. Diffusion-weighted MRI in a case of CO poisoning revealed pallidoreticular damage and delayed leukoencephalopathy characterized by restricted water diffusion pattern in the early stage. DWI brain MRI imaging is more sensitive than brain CT and is useful for early identification of the effects of acute CO poisoning [40].

Brain MRI changes after CO poisoning are variable and reflect the neuropathological lesions. Most unconscious patients present with abnormalities of globus pallidus or the entire lentiform nucleus (globus pallidus and putamen), putamen alone, caudate nucleus, thalamus, periventricular and subcortical white matter, cerebral cortex hippocampus and cerebellum. Brain MRI may appear to be normal in some victims who have suffered CO brain damage [41]. Previously unreported brain MRI findings in CO poisoning included bilateral diffuse high signal in the centrum semiovale and bilateral high intensity lesions in the anterior thalami [42]. Extensive bilateral cerebellar white matter signal change, with sparing of the overlying cortex, consistent with demyelination was reported 6 years after CO poisoning [43].

In a study of patients with severe CO intoxication, coma on admission and normobaric 100% oxygen, persistent changes on the MRI were found 1 to 10 years after exposure, independently of the neuropsychiatric findings. T2-weighted and FLAIR images showed bilateral symmetric hyperintensity of the white matter, more often involving the centrum semiovale, with relative sparing of the temporal lobes and anterior parts of the frontal lobes, along with atrophy of the cerebral cortex, cerebellar hemispheres, vermis, corpus callosum as well as T1-hypointensities and T2 and FLAIR hyperintensities in globus pallidus [44].

Kim and colleagues studied the delayed effects of CO on the cerebral white mater 25–95 days after the exposure with initial recovery followed by relapse of neuropsychiatric symptoms. T2-weighted imaged, DWI and FLAIR sequences demonstrate bilateral, diffuse and confluent lesions in the periventricular white matter and centrum semiovale, more prominent changes were present in the frontal lobes than elsewhere [45,46]. The effects of CO poisoning in acute stages can be evaluated by DWI sequences on brain MRI. A restricted water diffusion pattern in globus pallidus and substantia nigra can be seen [47].

Cerebral edema occurs early. Clinical status and outcome correlate with diffuse white matter changes [48]. Long-term (25 years) after CO exposure, MRI has demonstrated symmetrical globus pallidus and white matter changes in most patients. Temporal, parietal and occipital lobes are usually affected with asymmetrical cortical and subcortical lesions [49,50].

Magnetic resonance spectroscopy (MRS) examines brain metabolites. The major resonances of MRS are *N*-acetyl aspartate (NAA), choline (Cho), and creatine (Cr). NAA is located within neurons and is a specific neuronal and axonal marker. Choline is part of the membrane constituent phosphatidylcholine. Based on previous studies of demyelinating brains, Cho increases are due to an increase in phosphatidylcholine due to demyelination or gliosis. NAA decreases in demyelinated white matter presumably represent axonal and neuronal loss [51]. MRS provides evidence for CO-induced brain damage including decreased NAA found in the basal ganglia and elsewhere [23].

Proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive method that can provide biochemical information about brain tissues. In early CO poisoning ^{1}H MRS studies showed a persistent increase in choline related to progressive demyelination. In irreversibly injury, lactate appears and NAA decreases [52] ^{1}H MRS studies of frontal lobe white matter revealed increase in the choline-containing compounds, and reductions of NAA in all cases [53]. Normalization of the findings was found in a subclinical case. In two cases with akinetic mutism increased lactate was noted to persist. These results indicate the ^{1}H MRS is a useful indicator in the clinical evaluation of patients with the interval form of CO poisoning when compared to MRI, EEG and *N*-isopropyl–p^{123}idoamphetamine SPECT [54].

Kamada et al. [55] reported that MRS in patients with delayed sequelae of carbon monoxide (CO) exposure precisely reflects the severity of symptoms. With severe clinical presentation, marked lowering of NAA/Cr ratio and slightly increased Cho/Cr ratio is noted with subsequent return of NAA and Cho/Cr ratio to normal with clinical improvement. Proton MRS appears to be superior to conventional radiological examinations in CO poisoning [55].

Brain CT, MRI and MRS as well as neuropsychological testing are useful tools in diagnosis of CO toxicity and its severity. In addition, positron emission tomography (PET) and single photon emission tomography (SPECT) may provide additional information [56,57].

6. Treatment

Tissue hypoxia is the major outcome of CO intoxication: therefore based on chemical and pathophysiological data, O_2 is the "natural antidote" [58]. Since the clinical signs and symptoms of CO toxicity are nonspecific, all suspected victims should be treated with O_2 inhalation immediately after blood is drawn for COHb content. Furthermore, there is wide variation in individual responses to similar levels of CO exposure,

ranging from death to a Parkinsonian syndrome to mild or moderate intellectual impairment [23]. Therefore, immediately after securing the airway and adequate ventilation, administration of normobaric oxygen (NBO) is the corner stone of therapy, reducing the half-life of COHb from a mean of 5 h (range, 2–7 h) to about 1 h. Hyperbaric oxygen therapy (HBO) at 2.5 atm reduces it to 20 min and also has other benefits, at least in animal models. For example in rat brains, it prevents lipid peroxidation and leukocyte adherence to brain microvascular endothelium while accelerating regeneration of inactivated cytochrome oxidase. Therefore, usually at 2.5 to 3 ATA for 90 to 120 min, it is considered the treatment of choice for those who present with syncope, coma, or seizure, and focal neurological deficit or COHb > 25% (15% in pregnancy) [59–63].

In theory, NBO should be the treatment of the last severely poisoned patients, reserving HBO for severe intoxications. However, there are problems with this policy: 1) COHb levels do not correlate with the clinical severity of CO poisoning. 2) There is not universally accepted severity scale of CO poisoning, although loss of consciousness and neurologic deficits generally indicate severe poisoning. 3) All victims of CO poisoning are at risk for delayed neuropsychological sequelae. Therefore, in general the following approach is appropriate: 1) Patients with presumed CO poisoning should be placed on 100% oxygen. 2) Patients with severe poisoning must receive HBO regardless of COHb level. 3) Pregnant women must be treated with HBO irrespective of signs and symptoms. 4) In patients with lesser degrees of poisoning, careful evaluation is advised before deciding that 100% NBO for > 6 h is the adequate therapy [58]. Administration of more than one course of HBO is those who remain in coma remains controversial.

There are a number of practical considerations since not all treatment facilities, *e.g.* hospital ERs, can measure COHb and/or administer HBO. For example, in one recent study, only 44% of acute care hospitals had the capability of measuring COHb [64].

HBO is 100% oxygen at two to three times the atmospheric pressure at sea level. The oxygen tension in the arteries increases to about 2000 mm Hg and that of the tissues — to almost 400 mm Hg. The pressure is expressed in multiples of the atmospheric pressure, which is 1 at sea level. At sea level, the blood oxygen concentration is 0.3 ml/dl. At 100% oxygen at ambient (normobaric) pressure, the amount of the dissolved oxygen in the blood increases five fold to 1.5 ml/dl. At 3 atm, the dissolved-oxygen content reaches 6 ml/dl. HBO decreases the bubble formation in the blood and replaces inert gases with oxygen, which is rapidly taken up and utilized by the tissues. HBO can be bactericidal, bacteriostatic or suppress toxin production increasing tissues resistance against infections. HBO is more effective that normobaric oxygen in promoting collagen formation and angiogenesis and thus can facilitate wound healing. HBO inhibits neutrophil adherence to the walls of the ischemic vessels, which decreased the free radical production, vasoconstriction and tissue destruction.

HBO is commonly delivered in a monoplace chamber, or less often in a multi-occupant chamber. The duration of a single treatment for CO poisoning is about 45 min. HBO with oxygen pressures of up to 3 atm for a maximum of 120 min is safe. Adverse effects include reversible myopia, cataract, tracheobronchial symptoms, self-limited seizures and barotraumas to the middle ear, cranial sinuses, rarely teeth or lungs. Claustrophobia can be an issue in monoplace chambers. Despite the conflicting results from the literature regarding the effect of the HBO *versus* normobaric oxygen, Tibbles and Edelsberg [63] concluded that patients with severe carbon monoxide poisoning should receive at least one HBO treatment at 2.5 to 3.0 atm because this therapy is the fastest method of treatment of the potentially reversible life-threatening effects.

The treatment of a patient with CO poisoning should not be based solely on the COHb levels. The clinical manifestations, COHb levels and, importantly, the patient's underlying medical history should be taken into account. In patients with suspected CO poisoning, 100% oxygen should be given immediately by a mask. The goal is to raise the PaO_2 levels, decrease the half-life of CO, and facilitate its dissociation from hemoglobin, thus allowing oxygen to attach to the freed binding sites. Strict bed rest should be provided, since it decreases oxygen demand and consumption. Patients with respiratory distress and decreased level of consciousness should be intubated and ventilated. Chest radiograph, blood lactate levels and arterial blood gases should be performed in the emergency department.

Headache improved prior to hyperbaric oxygen treatment in 72%, resolving entirely in 21% of those with residual headache, pain improved with hyperbaric oxygen in 97%, resolving entirely in 44% [25]. Even though the deaths from CO poisoning have decreased in the United States in the recent years, the total burden, including fatal and non-fatal cases has not significantly changed [65].

Juurlink et al. [66] analyzed available data from six randomized controlled trials involving non-pregnant adults acutely poisoned with CO. At one month follow-up after treatment, symptoms possible related to carbon monoxide poisoning were present in 34.2% of those treated with HBO, compared with 37.2% treated with NBO. They find not evidence that unselected use of HBO in the treatment of acute CO poisoning reduces the frequency of neurological symptoms at 1 month. Because of insufficient evidence, they recommend further research for defining the role of HBO in treatment of carbon monoxide poisoning.

Five years later, the same group examines the evidence for the effectiveness of the HBO for prevention of neurological sequelae in patients with acute carbon monoxide poisoning. Four out of six trials find no benefit of HBO for the reduction of neurologic sequelae, while two other do not. The authors conclude that the existing randomized trials have not been able to establish reduction of neurological sequelae with the administration of HBO to patients with carbon monoxide poisoning [68–71]. In a recent study,

Weaver et al. [72] concluded that HBO is indicated for patients with acute CO poisoning who are ≥ 36 years of age, or have exposure intervals ≥ 24 h, or in patients with loss of consciousness, or with higher COHb levels.

Close monitoring of the serum pH and lactic acid levels is required, since the anaerobic metabolism in the presence of tissue hypoxia generates lactic acidosis. Acidosis below pH of 7.15 should be treated with sodium bicarbonate. Caution has to be exercised with the administration of sodium bicarbonate because carbon dioxide, a by-product of its metabolism, could lead to respiratory acidosis and has to be eliminated by proper ventilation.

Because prevention is the best treatment, our society should be on high alert in attempt to prevent cases of CO poisoning.

References

[1] Proceedings Satellite Meeting IUTOX VIIIth Internationazl Congress of Toxicology. “Carbon monoxide: the unnoticed poison of the 21st Century” 1998. Université de Bourgogne, France.

[2] Wikipedia contributors. Carbon Monoxide. Wikipedia, The free encyclopedia;http://en.wikipedia.org/windex.php?title=Carbon_monoxide.

[3] Abelsohn A, Sanborn MD, Jessiman BJ, Weir E. Identifying and managing adverse environmental health effects: 6. Carbon monoxide poisoning. CMAJ 2002;166(13):1685–90.

[4] Ryter SW, Alam J, Choi AM. Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. Physiol Rev 2006;86 (2):583–650.

[5] Lascaratos JG, Marketos SG. The carbon monoxide poisoning of two Byzantine emperors. J Toxicol Clin Toxicol 1998;36(1-2):103–7.

[6] Tvedt B, Kjuus H. Chronic CO poisoning. Use of generator gas during the Second World War and recent research. Tidsskr Nor Laegeforen 1997;117(17):2454–7.

[7] Henz S, Maeder M. Prospective study of accidental carbon monoxide poisoning in 38 Swiss soldiers. Swiss Med Wkly 2005;135(27-28):398–408.

[8] Henry CR, Satran D, Lindgren B, Adkinson C, Nicholson CI, Henry TD. Myocardial injury and long-term mortality following moderate to severe carbon monoxide poisoning. JAMA 2006;295(4):398–402.

[9] Somogyi E, Balogh I, Rubanyi G, Sotonyi P, Szegedi L. New findings concerning the pathogenesis of acute carbon monoxide (CO) poisoning. Am J Forensic Med Pathol 1981;2(1):31–9.

[10] Satran D, Henry CR, Adkinson C, Nicholson CI, Bracha Y, Henry TD. Cardiovascular manifestations of moderate to severe carbon monoxide poisoning. J Am Coll Cardiol 2005;3;45(9):1513–6.

[11] Ernst A, Zibrak JD. Current concepts: carbon monoxide poisoning. N Engl J Med 1998;339(22):1603–8.

[12] Kumazawa T, Watanabe-Suzuki K, Seno H, Ishii A, Suzuki O. A curious autopsy case of accidental carbon monoxide poisoning in a motor vehicle. Leg Med 2000;2(3):181–5 [Tokyo].

[13] Tritapepe L, Macchiarelli G, Rocco M, Scopinaro F, Schillaci O, Martuscelli E, et al. Functional and ultra structural evidence of myocardial stunning after acute carbon monoxide poisoning. Crit Care Med 1998;26(4):797–801.

[14] Lin H, McGrath JJ. Responses of the working rat heart to carbon monoxide. Physiol Behav 1989;46(1):81-4 2813558.

[15] Clubb Jr FJ, Penney DG, Baylerian MS, Bishop SP. Cardiomegaly due to myocyte hyperplasia in prenatal rats exposed to 200 ppm carbon monoxide. J Mol Cell Cardiol 1986;18(5):477–86.

[16] Anderson RF, Allensworth DC, DeGroot WJ. Myocardial toxicity from carbon monoxide poisoning. Ann Intern Med 1967;67 (6):1172–82.

[17] Fineschi V, Agricola E, Baroldi G, Bruni G, Cerretani D, Mondillo S, et al. Myocardial findings in fatal carbon monoxide poisoning: a human and experiment morphometric study. Int J Legal Med 2000;113(5): 276–82.

[18] Choi S. Delayed neurological sequelae in carbon monoxide intoxication. Arch Neurol 2000;57:1214–8.

[19] Lapresle J, Fardeau M. The central nervous system and carbon monoxide poisoning II. Anatomical study of brain lesions following intoxication with carbon monoxide (22 cases). In: Bour H, Ledingham IM, editors. Carbon monoxide poisoning, vol. 24. Prog Brain Res; 1967. p. 31–74.

[20] Murata S, Asaba H, Hiraishi K, et al. Magnetic resonance imaging findings on carbon monoxide intoxication. J Neuroimaging 1993;3:128–31.

[21] Tom T, Abedon S, Clark RI, Wong W. Neuroimaging characteristics in carbon monoxide toxicity. J Neuroimaging 1996;6:161–6.

[22] Ernst A, Zibrak JD. Carbon monoxide poisoning. N Engl J Med 1998;339(22):1603–8.

[23] Prockop LD. Carbon monoxide brain toxicity: clinical, magnetic resonance imaging, magnetic resonance spectroscopy, and neuropsychological effects in 9 people. J Neuroimaging 2005;15(2):144–9.

[24] Handa PK, Tai DY. Carbon monoxide poisoning: a five year review at Tan Tock Seng Hospital, Singapore. Ann Acad Med Singapore 2005;34(10):611–4.

[25] Hampson NB, Hampson LA. Characteristics of headache associated with acute carbon monoxide poisoning. Headache 2002;42(3):220–3.

[26] Choi IS. Carbon monoxide poisoning: systemic manifestations and complication. J Korean Med Sci 2001;16(3):253–61.

[27] Mimura K, Harada M, Sumiyoshi S, et al. Long-terms follow-up study on sequelae of carbon monoxide poisoning: serial investigation 33 years after poisoning. Seishin Shinkeigaku Zasshi 1999;101:592–618.

[28] White RF, Feldman RG, Proctor SP. Neurobehavioral effects of toxic exposure. In: White RF, editor. Clinical syndrome in adult neuropsychology. The practitioner’s handbook. New York: Elsevier; 1992. p. 1–51.

[29] Department of the Environment. Expert panel on air quality standard. London: HMSO; 1994.

[30] Townsend CL, Maynard RI. Effects on health of prolonged exposure to low concentrations of carbon monoxide. Occup Environ Med 2002;59 (10):708–11.

[31] Bozeman WP, Hampson NB. Pulse oximetry in CO poisoning — additional data. Chest 2000 Jan; 117(1):295-6 (Hampson NB Pulse oximetry in severe carbon monoxide poisoning. Chest 1998;114 (4):1036-41.

[32] Widdop B. Analysis of carbon monoxide. Ann Clin Biochem 2002;39 (pt 4):378–91.

[33] Sawano M, Mato T, Tsutsumi H. Bedside red cell volumetry by low-dose carboxyhaemoglobin dilution using expiratory gas analysis. Br J Anaesth 2006;96(2):186–94.

[34] Brvar M, Mozina H, Osredkar J, Mozina M, Noe M, Brucan A, et al. S100B protein in carbon monoxide poisoning: a pilot study. Resuscitation 2004;61(3):357–60.

[35] Rasmussen LS, Poulsen MG, Christiansen M, Jansen EC. Biochemical markers from brain damage after carbon monoxide poisoning. Acta Anaesthesiol Scand 2004;48(4):469–73.

[36] Hubalewska-Hola A, Pach D, Pach J, Sowa-Staszczak A, Winnik L, Huszno B. Clinical and scintigraphic (99mTc-MIBI SPECT) heart evaluation in young acutely carbon monoxide poisoned patents. Przegl Lek 2003;60(4):226–32.

[37] Sener RN. Acute carbon monoxide poisoning: diffusion MR imaging findings. AJNR Am J Neuroradiol 2003;24(7):1475–7.

[38] Ferrier D, Wallace CJ, Fletcher WA, Fong TC. Magnetic resonance features in carbon monoxide poisoning. Can Assoc Radiol J 1994;45 (6):466–8.

[39] Schils F, Cabay JE, Flandroy P, Dondelinger RF. Unusual CT and MRI appearance of carbon monoxide poisoning. JBR-BTR 1999;82 (1):13–5.

[40] Kinoshita T, Sugihara S, Matsusue E, Fujii S, Ametani M, Ogawa T. Pallidoreticular damage in acute carbon monoxide poisoning: diffusion-weighted MR imaging findings. AJNR Am J Neuroradiol 2005;26(7):1845–8.
[41] O'Donnell P, Buxton PJ, Pitkin A, Jarvis LJ. The magnetic resonance imaging appearances of the brain in acute carbon monoxide poisoning. Clin Radiol 2000;55(4):273–80.
[42] Tuchman RF, Moser FG, Moshe SL. Carbon monoxide poisoning: bilateral lesions in the thalamus on MR imaging of the brain. Pediatr Radiol 1990;20(6):478–9.
[43] Mascalchi M, Petruzi P, Zampa V. MRI of cerebellar white matter damage due to carbon monoxide poisoning: case report. Neuroradiology 1996;38(Suppl 1):S73–4.
[44] Durak AC, Coskun A, Yikilmaz A, Erdogan F, Mavili E, Guven M. Magnetic resonance imaging findings in chronic carbon monoxide intoxication. Acta Radiol 2005;46(3):322–7.
[45] Kim JH, Chang KH, Song IC, Kim KH, Kwon BJ, Kim HC, et al. Delayed encephalopathy of acute carbon monoxide intoxication: diffusivity of cerebral white lesions. AJNR Am J Neuroradiol 2003.
[46] Kawada N, Ochiai N, Kuzuhara S. Diffusion MRI in acute carbon monoxide poisoning. Intern Med 2004;43(7):639–40.
[47] Kinoshita T, Sugihara S, Matsusue E, Fujii S, Ametani M, Ogawa T. Pallidoreticular damage in acute carbon monoxide poisoning: diffusion-weighted MR imaging findings. AJNR Am J Neuroradiol 2005;26(7):1845–8.
[48] Schils F, Cabay JE, Flandroy P, Dondelinger RF. Unusual CT and MRI appearance of carbon monoxide poisoning. JBR-BTR 1999;83(1):13–5.
[49] Inagaki T, Ishino H, Seno H, Umegae N, Aoyama T. A long-term follow-up study of serial magnetic resonance images in patients with delayed encephalopathy after acute carbon monoxide poisoning. Psychiatry Clin Neurosci 1997;51(6):4213.
[50] Prockop LD, Naidu KA. Brain CT and MRI findings after carbon monoxide toxicity. J Neuroimaging 1999 Jul;9(3):175–81.
[51] Van Zijl PCM, Barker PB. Magnetic resonance spectroscopy and spectroscopic imaging for the study of brain metabolism. Ann NY Acad Sci 1997;820:75–96.
[52] Murata T, Itoh S, Koshino Y, et al. Serial proton magnetic resonance spectroscopy in a patient with the interval form of carbon monoxide poisoning. J Neurol Neurosurg Psychiatry 1995;58:100–3.
[53] Murata T, Itoh S, Koshino Y, et al. Serial proton magnetic resonance spectroscopy in a patient with the interval form of carbon monoxide poisoning. J Neurol Neurosurg Psychiatry 1995;58:100–3.
[54] Murata T, Kimura H, Kado H, Omori M, Onizuka J, Takahashi T, et al. Neuronal damage in the interval form of carbon monoxide determined by serial diffusion weighted magnetic resonance imaging plus 1H-magnetic resonance spectroscopy. J Neurol Neurosurg Psychiatry 2001;71(2):250–3.
[55] Kamada K, Houkin K, Aoki T, Koiwa M, Kashiwaba T, Iwasaki Y, et al. Cerebral metabolic changed in delayed carbon monoxide sequelae studied by proton MR spectroscopy. Neuroradiology 1994;36(2):104–6.
[56] Tengvar C, Johansson B, Sorensen J. Frontal lobe and cingulated cortical metabolic dysfunction in acquired akinetic mutism: a PET study of the interval form of carbon monoxide poisoning. Brain Inj 2004;18(6):615–25.
[57] Gale SD, Hoskins RO, Weaver LK, Bigler ED, Booth EJ, Blatter DD. MRI, quantitative MRI, SPECT, and neuropsychological findings following carbon monoxide poisoning. Brain Inj 1999;13(4):229–43.
[58] Elkharrat D. Indications of normobaric and hyperbaric oxygen therapy in acute CO intoxication. Proceedings satellite meeting IUTOX VIIIth international congress of toxicology Dijon France July 3–4; 1998.
[59] Tibbles PM, Perotta PL. Treatment of carbon monoxide poisoning: a critical review of human outcome studies comparing normobaric oxygen with hyperbaric oxygen. Ann Emerg Med 1994;24:269–76.
[60] Weaver LK, Hopkins RO, Larson-Lorh V, Howe S, Haberstock D. Double blind, controlled, prospective, randomized clinical trial (RCT) in patients with acute carbon monoxide (CO) poisoning: outcome of patients tested with normobaric oxygen or hyperbaric oxygen (HBO_2), an interim report. Undersea Hyperb Med 1995;22(suppl):14.
[61] Thom SR, Taber RI, Mediguren II, Clark JM, Hardy KR, Fisher AB. Delayed neuropsychological sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. Ann emerg Med 1995;25:479–86.
[62] Van Meter KW, Weiss L, Harch PE, et al. Should the pressure be off or on with use of oxygen in the treatment of carbon monoxide poisoned patients. Ann Emerg Med 1994;24:283–8.
[63] Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. N Engl J Med 1996;334:1642–8.
[64] Hampson NB, Scott KL, Zmaeff JL. Carboxyhemoglobin measurement by hospitals: Implications for the diagnosis of carbon monoxide poisoning. J Emerg Med 2006 Jul;31(1):13–6.
[65] Hampson NB. Trends in the incidence of carbon monoxide poisoning in the United States. Am J Emerg Med 2005;23(7):838–41.
[66] Juurlink DN, Stanbrook MB, McGuigan MA. Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database Syst Rev 2000(2): CD002041.
[67] Juurlink DN, Buckley NA, Stanbrook MB, Isbister GK, Bennett M, McGuigan MA. Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database Syst Rev 2005;(1):CD002041 Review.
[68] Muller NG, Gruber O. High-resolution magnetic resonance imaging reveals symmetric bitemporal cortical necrosis after carbon monoxide intoxication. J Neuroimaging 2001;11(3):322–5.
[69] Kesler SR, Hopkins RO, Blatter DD, Edge-Both H, Bigler ED. Verbal memory deficits associated with fornix atrophy in carbon monoxide poisoning. J Int Neuropsychol Soc 2001;7(5):640–6.
[70] Sohn YH, Jeong Y, Kim HS, Im JH, Kim JS. The brain lesion responsible for parkinsonism after carbon monoxide poisoning. Arch Neurol 2000;57(8):1214–8.
[71] Weaver LK, Valentine KJ, Hopkins RO. Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. Am J Respir Crit Care Med 2007 May 11 [Epub ahead of print].