Carbon Monoxide and Other Tissue Poisons

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Abstract

Hyperbaric oxygenation (HBO) is a recognized treatment for carbon monoxide (CO) poisoning and has a supplemental role in the treatment of some other tissue poisons. Basic mechanisms, diagnosis, and management of carbon monoxide (CO) poisoning are discussed including controversies in the use of HBO for CO poisoning. Guidelines for the use of both normobaric oxygen (NBO) and HBO are discussed. HBO is more effective than NBO for the prevention of delayed neurological sequelae. HBO is also useful in the management of poisons other than CO: cyanide, hydrogen sulfide, carbon tetrachloride, and methemoglobinemias.

Keywords

Carbon monoxide poisoning • Carbon tetrachloride poisoning • Carboxyhemoglobin (COHb) • Carboxymyoglobin (COMb) • Cyanide poisoning • Hydrogen sulfide poisoning • Hyperbaric oxygen therapy (HBO) • Hypoxia • Methemoglobinemias • Normobaric oxygen (NBO) • Tissue poisons

Classification of Tissue Poisons

This chapter deals mainly with the role of hyperbaric oxygenation (HBO) in the treatment of carbon monoxide (CO) poisoning; several other tissue poisons that have been treated with HBO are also discussed. Classification of these poisons by their mode of action is presented in Table 13.1.

Carbon Monoxide Poisoning

Historical Aspects of CO Poisoning

Human beings have been exposed to CO ever since they have made fire inside sheltered caves. In 300 BC, Aristotle stated that "coal fumes lead to heavy head and death." Obviously, this was a reference to CO poisoning. Claude Bernard showed in 1857 that CO produces hypoxia by reversible combination with hemoglobin (Bernard 1857); and in 1865, Klebs described clinical and pathologic findings in rats exposed to CO (Klebs 1865). The classical bilateral lesions of the globus pallidus and diffuse subcortical demyelination were described and correlated with psychic akinesia in 1924 (Pineas 1924). Connection of CO poisoning with parkinsonism was described a couple of years later (Grinker 1926).

In 1895, Haldane showed that rats survived CO poisoning when placed in oxygen at a pressure of 2 atm (Haldane 1895). The effectiveness of hyperbaric oxygen (HBO) in experimental CO poisoning in dogs and guinea pigs was demonstrated in 1942 (End and Long 1942). In 1960, HBO was first used successfully in treating human cases of CO poisoning (Smith and Sharp 1960).

Biochemical and Physical Aspects of CO

This subject has been dealt with in detail by Jain (1990), and it will be briefly reviewed here with more recent findings.

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Table 13.1 Classification of tissue poisons where HBO has been used successfully

1. Action by combination with cytochrome α3 oxidase and P-450
– Carbon monoxide
– Hydrogen sulfide
2. Hepatotoxic free radical formation mediated by P-450
– Carbon tetrachloride
3. Drug-induced methemoglobinemias
– Nitrites
– Nitrobenzene

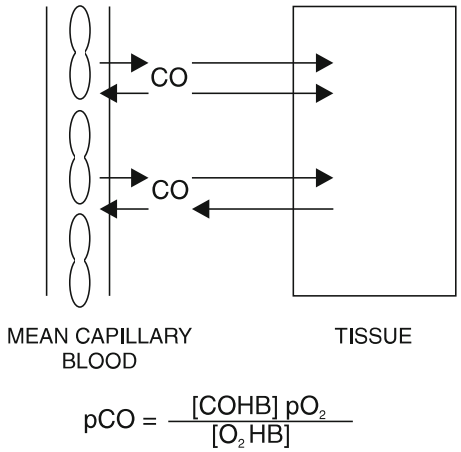

Fig. 13.1 Mean tissue CO tension is equal to the mean CO tension in capillary blood. CO tension in mean capillary blood depends on the parameters listed in the Haldane equation depicted in this figure. Modified from Coburn 1970

CO Body Stores

Most of the body deposits of CO are found in the blood chemically bound to Hb. However, 10–15 % of the total body content of CO is located in extracellular space, probably in combination with myoglobin (Mb). The combination of Hb with CO is governed by Haldane's law. Accordingly, when a solution containing Hb is saturated with a gas mixture containing oxygen and CO_2, the relative proportions of the Hb that combine with the two gases are proportional to the relative partial pressures of the two gases (Fig. 13.1), allowing for the fact that the affinity of the CO for Hb is 240 times greater than that of O_2. This is expressed by the equation:

$$\frac{\text{COHb}}{\text{O}_2\text{Hb}} = K \times \frac{\text{pC} =_2}{\text{pO}_2}$$

where K is 240.

The rate of formation of COMb can also be expressed by the Haldane equation, except that the estimated value of the constant K is then 40. Apparently Mb is involved in the oxygen transport mechanism and is ready to deliver oxygen when needed. Examination of O_2Hb and O_2Mb dissociation curves reveals that, at pO_2 less than 60 mmHg, O_2 has greater affinity for Mb than for Hb.

Table 13.2 Biochemical effects of carbon monoxide

1. Effects on the blood
– Increase of the carboxyhemoglobin level
– Shift to the left of the oxygen dissociation curve
– Rise of the lactate level
2. Action at the cellular level
– Inhibition of cytochrome α3 oxidase and P-450

Biochemical Effects of CO on Living Organisms

Carbon monoxide inhibits oxygen transport, availability, and utilization; its biochemical effects are summarized in Table 13.2. CO lowers the oxygen saturation in direct proportion to the COHb concentration, thus blocking oxygen transport from the lungs to the tissues. The binding of one or more CO molecules to Hb also induces an allosteric modification in the remaining heme group, distorting the oxygen dissociation curve and shifting it to the left. Tissue anoxia is thus far greater than would result from the loss of oxygen-carrying capacity alone. A concentration of 0.06 % of CO in the air is enough to block one-half of the Hb available for oxygen transport. The manner of CO combination with Hb differs appreciably from that of oxygen at high levels of CO saturation but is virtually the same at low levels of CO saturation.

Important factors that influence the accumulation of COHb are pH, pCO_2, temperature, and 2,3-DPG (diphosphoglycerate). The affinity of oxygen for the Hb is strongly influenced by 2,3-DPG, which is located inside the red blood cells (RBC). When 2,3-DPG levels rise, for example, in anaerobic glycolysis, hypoxia, anemia, and at high altitudes, affinity of the oxygen for Hb is reduced.

Inhibition of the Utilization of Oxygen by CO

Until recently it was believed that the sole effect of CO was to produce COHb, which blocks oxygen transfer to the cells. Warburg had already demonstrated in 1926 that CO competes with oxygen for the reduced form of cytochrome a3 oxidase, which is the terminal enzyme of the cellular respiratory chain. The possibility that CO is directly cytotoxic is borne out by in vitro demonstration of CO interactions with non-Hb hemoproteins. Reduced cytochrome a3 (cytochrome c oxidase) and cytochrome P-450 bind sufficient CO to inhibit their function in vitro. The possibility that CO inhibits mitochondrial electron transport in vivo is interesting because of the close relationship between the respiratory chain function and the

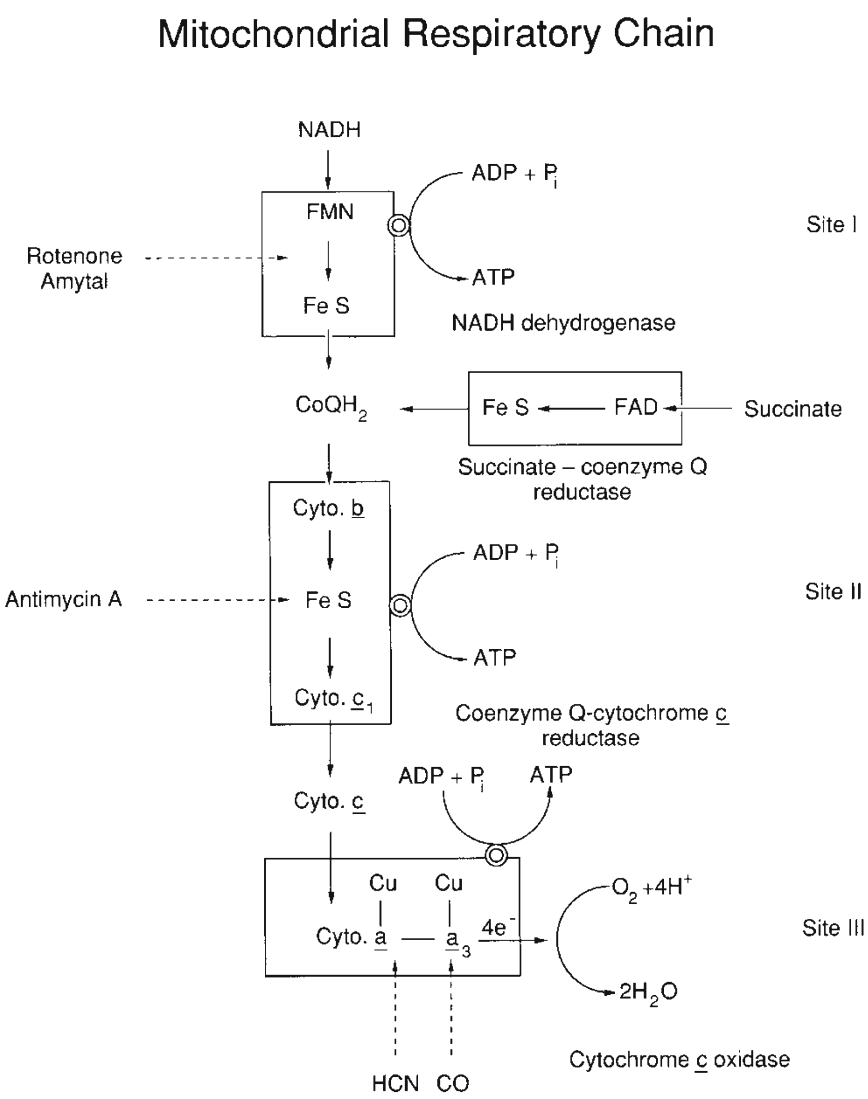

Fig. 13.2 The mitochondrial respiratory chain indicating sequence of electron transport, three sites of energy coupling (oxidative phosphorylation), and location of action of CO

cellular energy metabolism (Fig. 13.2). These basic mechanisms have been confirmed (Chance et al. 1970).

CO combines with cytochrome a3 oxidase, and cytochrome P-450, thus blocking cellular oxidation and causing cellular hypoxia. Organs with high metabolic rate, such as the heart and brain, are particularly affected by CO. Cytochrome prefers oxygen to CO by a factor of 9:1, and this may explain the disparity between COHb levels and the clinical effects. This also explains the beneficial effect of HBO therapy. CO alters brain metabolism in vivo independently of the COHb-related decreases in oxygen delivery.

In conclusion, it can be stated that CO poisoning is highly complex, and a great deal more is involved than simple production of COHb. Formation of carboxycytochrome oxidase has been postulated to act as a toxin by blocking cellular use of oxygen. The half-life of CO bound with cytochrome a3 oxidase is not known. More research is needed to determine this value, as it may be an important factor in the genesis of late sequelae of CO poisoning, and it may also provide a rational basis for determining the duration of treatment by oxygen therapy.

Epidemiology of CO Poisoning

Each year 50,000 persons visit emergency departments for CO poisoning in the United States. More than 4000 persons die annually from CO poisoning and in addition to this, CO accounts for more than half of the ~12,000 annual fire-associated deaths. In Korea, the incidence of CO poisoning in households using charcoal briquettes for heating and cooking was 5.4–8.4 % as shown in a survey of four major cities (Cho et al. 1986). There are no figures available for a much larger number of sufferers from occult CO poisoning.

Table 13.3 Causes of CO poisoning

1. Endogenous
Hemolytic anemias (rise of COHb to 4–6 %)
2. Exogenous
A. Natural environments
– Microbial activity in plant life
B. Artificial
– Automobile exhaust
– Defective domestic appliances for heating and cooking
– Industrial plant exhausts
– Mining accidents
– Fires
C. Indirect
– Poisoning by methylene chloride (paint-stripping solvent) due to its conversion to CO in vivo
D. Cigarette smoking
– Active smoking
– Passive smoking

Causes of CO Poisoning

CO is present universally, but clinically manifest poisoning occurs only when critical levels are exceeded. Various causes for this are listed in Table 13.3. Endogenous CO is unimportant because the values seldom exceed 3 % COHb. The most important sources of CO poisoning are exogenous.

Sources of CO Poisoning

The commonest source of CO poisoning in industrialized urban areas of Western countries is automobile exhausts. They contain 6–10 % CO and are responsible for 90 % of the CO content of the atmosphere of a city. Frequently such fatal poisoning occurs in a closed garage with the car engine running, a common method of suicide. There are ~2300 such suicides annually in the USA.

At busy city intersections, CO concentrations as high as 0.03 % have been measured. A pedestrian on a street with heavy automobile traffic is exposed to CO. A concentration of 20–40 mg/mL can raise COHb 1.5–2-fold within 1 h. Jogging in this environment increases the CO intake and further raises the COHb. Persons doing manual work on streets with heavy automobile traffic can suffer a rise of COHb to toxic levels. Jogging in Central Park in New York City can be more dangerous than walking or just standing around. Smoking in such environments further aggravates CO intoxication and COHb levels of 13 % can be reached.

After the garage, the kitchen is the most dangerous place and a frequent site of CO poisoning. Cooking gas usually contains 4–14 % CO. If not burned properly (as in a defective oven or stove), CO can leak into the room. Other sources of danger in the house are space-heating systems, such as a gas boiler. In Korea, household appliances are the commonest source of CO poisoning, open wood or coal-burning furnaces being the most frequent culprits.

Even though natural gas has been substituted for coal gas, 1000 persons still die annually in England and Wales as a result of CO poisoning from this source. Although natural gas burns more efficiently and cleanly than other forms of fuel, it is also the most potentially lethal if combustion is incomplete and is responsible for most of the deaths from domestic CO poisoning in the US. Incomplete combustion of other fuels such as charcoal and wood can also release CO, which can be trapped inside the building if the chimney is clogged. CO poisoning is more likely to occur in houses that are insulated and airtight to conserve energy.

Exhausts of many industrial plants, mills, and workshops contain CO. Risks are particularly high in blast furnaces and coal mines. Explosives can emit as much as 60 % CO. Smoke contains CO, and smoke inhalation injury is usually associated with CO intoxication. Wood and paper fires contain 12 % CO. Firefighters are particularly at risk from CO poisoning. COHb levels of 50 % have been found in those dying within 12 h of receiving burns, implicating CO as the main culprit.

Pathophysiology of CO Poisoning

CO Binding to Myoglobin

It has been known for decades that death from CO poisoning is caused by hypoxia resulting from displacement of oxygen from the Hb. The mechanism of this, however, is not straightforward. Oxygen is stored in myoglobin and this is made possible by the crooked angle at which oxygen binds to the protein. CO, which prefers to sit upright, competes with for space with oxygen in this molecular shuttle. When myoglobin's structures forces CO to lie on its side, it is excluded. This classical view has been challenged by the use of spectroscopic techniques which provide evidence that a nearly perpendicular CO fits comfortably in myoglobin and that forced bending has little to do with CO exclusion. The reason is more likely that the unbound CO is pinned on its side near the binding site and little binding takes place.

Both CO and oxygen bind to an iron atom in the middle of the ring-shaped portion of myoglobin known as the heme group. Heme when isolated in experiments, binds to CO 10,000 times as strongly as it does to oxygen but when embedded in myoglobin, it binds only 20–30 times as strongly as oxygen. This led the belief that protein must be doing something to suppress CO relative to oxygen.

CO-Induced Hypoxia

Although the toxic effect of CO is postulated to be at the cellular level, by formation of carboxycytochrome oxidase, CO poisoning is primarily a hypoxic lesion caused by the replacement of OHb by COHb. Studies comparing the effect in dogs of anoxia induced by 0.5 % CO ventilation with that induced by breathing low oxygen mixtures found no significant differences in oxygen consumption or oxygen extraction in the two sets of animals who were subjected to equal reduction of arterial OHb, although the mode of desaturation was CO poisoning in one group.

The term CO-hypoxia implies that there is inhibition of oxygen transport from the blood to the tissues. Tissue oxygen tension may be decreased directly through a reduction in oxygen content by a lowered arterial oxygen tension, as well as through the presence of COHb. The oxygen dissociation curve is shifted to the left. The clinical effects of CO are usually attributed to tissue hypoxia, but they do not always correlate with COHb levels. Because CO combines with extravascular proteins such as myoglobin, its combination with cytochrome C-oxidase and cytochrome P-450 has been considered possibly to cause cellular hypoxia by inhibiting the mitochondrial respiratory chain.

Effects of CO on Various Systems of the Body

CO involves most parts of the body, but the areas most affected are those with high blood flow and high oxygen requirement, such as the brain and the heart. The effects of CO on various systems are presented in Table 13.4.

Table 13.4 Effect of CO on various systems of the body

Cardiovascular system
• Precipitation of myocardial ischemia in patients with angina
• ECG abnormalities
• Cardiomyopathy as an acute effect and cardiomegaly as a chronic effect
• Hypertension and atherosclerosis as chronic effects
Elements of the blood and hemorrheology
• Increased platelet aggregation
• Lower RBC deformability
• Increased plasma viscosity and hematocrit
• Erythrocytosis as a chronic effect
Nervous system
• Brain: cerebral edema, focal necrosis
• Peripheral nerves: neuropathy and delayed motor conduction velocity
Special senses
• Visual system: retinopathy and visual impairment
• Auditory system: hearing loss due to hypoxia of the cochlear nerve
Lungs
• Pulmonary edema
Muscles
• Myonecrosis, compartment syndrome
Exercise physiology
• Decrease of physical work capacity and V2 max
Liver
• Impaired function due to inhibition of cytochrome P-450
Kidneys
• Impairment of renal function, renal shutdown
• Endocrines
• Impairment of hypophysis, hypothalamus, and suprarenals
Bone and joints
• Degenerative changes, hypertrophy of bone marrow
• Skin
• Erythema and blisters
Reproductive system
• Impaired menstruation and fertility in women
• Impotence in men
• Fetal toxicity with low conceptus weight and growth retardation

Cardiovascular System

The heart is particularly vulnerable to CO poisoning, because CO binds to cardiac muscle three times as much as to skeletal muscle. Studies on isolated animal hearts have shown that CO may have a direct toxic effect on the heart regardless of the formation of COHb. At levels of 1–4 % COHb, myocardial blood flow is higher, but no adverse effects are demonstrated. If the perfusion medium of an isolated rat heart muscle is gassed with 10 % CO, there is a 40 % increase in coronary blood flow, which is likely to be due to vasodilatation secondary to anoxia. Increase in myocardial blood flow occurs mostly without an increase in COHb levels.

Angina patients are particularly susceptible to CO exposure. The onset of angina during physical exertion can be accelerated by elevating COHb levels to the 5–9 % range. CO precipitates ischemia by reducing oxygen delivery to the myocardium. Changes in ECG have been shown to occur in workers chronically exposed to CO when COHb levels reach 20–30 %. These changes are reversible after withdrawal from exposure to CO. Various abnormalities in the ECG reported in CO poisoning are summarized in Table 13.5. Depression of the S-T segment is the most common ECG finding in these cases and may precede myocardial infarction resulting from exposure to CO. Conduction abnormalities may be the result of anoxia or a direct toxic effect of CO on hemorrhages into the conducting system of

Table 13.5 ECG abnormalities due to CO poisoning

1. Arrhythmias, extrasystoles, atrial fibrillation
2. Low voltage
3. Depression of S–T segment
4. Prolongation of ventricular complex, particularly the Q–T interval
5. Conduction defects
– Increased P–R interval
– A–V block
– Branch bundle block

the heart. Abnormalities of the motion of the left ventricular wall, as shown by echocardiography, are frequently seen in CO poisoning, and these correlate with a high incidence of papillary muscle lesions in fatal cases.

In a study on 9046 patients with CO poisoning and 36,183 controls, the overall risks for developing peripheral arterial disease were 1.85-fold in the patients with CO poisoning compared with the comparison cohort after adjusting for age, sex, and comorbidities (Chen et al. 2015). Oxidative stress caused by toxicological free radicals results in endothelial cell damage, inflammatory reactions, and subsequent atherogenic processes in peripheral artery circulative systems.

Hemorheological Effects of CO

Viscosity of the whole blood as well as of the plasma increases after inhalation of 400 ppm of CO. An increase in COHb levels also decreases the deformability of erythrocytes, thus impairing the microcirculation.

Effect of CO on Blood Lactate

Levels of COHb over 5 % have been shown to raise blood lactate levels. This is presumed to be an effect of hypoxia. Severity of CO poisoning depends on the duration of exposure rather than on COHb levels alone. Severe poisoning associated with long exposure is accompanied by high blood lactate and pyruvate levels.

Effect of CO on the Lungs

Pulmonary edema is present in 36 % of patients with CO poisoning and is considered to be caused by hypoxia. X-rays of the lungs show a characteristic ground-glass appearance. Perihaler haze and intra-alveolar edema may also be present. Vomiting in an unconscious patient may lead to aspiration pneumonia.

Exercise Capacity

Endurance and VO_2 max decrease as the COHb levels rise. Fatigue and reduced exercise capacity may also be caused by the accumulation of lactate resulting from exposure to CO. Lactate levels over 4 mmol hinder physical training.

Sleep

Sleep is severely disturbed by CO, without a detectable effect on the respiratory frequency and pulmonary ventilation. The aortic body receptors mediating circulatory reflexes are more sensitive to CO than the carotid body receptors mediating respiratory reflexes. Disruption of sleep could result from afferent discharges from aortic receptors in response to CO or low oxygen content. Anoxia is known to abolish REM sleep.

Effect on Pregnancy

Studies of the effects of CO inhalation on the conceptus weight in gravid rats lead to the following conclusions:

- Continuous CO inhalation lowered the conceptus weight on days 14 and 20 of pregnancy.
- The effect was more pronounced in the group exposed to cigarette smoke (CO plus nicotine) than the group exposed to CO alone.
- CO affects the fetus more adversely during the last trimester of pregnancy, which is the phase of rapid growth.

Experimental studies in neonatal animals have shown that acute exposure to CO can alter neurotransmitter function in the brain and that some of the effects persist for several weeks. Exposure of neonatal rats to CO has also been shown to produce hyperactivity that persisted for up to 3 months of age.

Musculoskeletal System

Compartment syndromes of the lower extremities may be caused by necrosis and swelling of the muscles.

Skin

Cutaneous blisters occur in CO poisoning. It seems possible that necrobiosis in eccrine glands starts early, but that the epidermal basal cells, notably at the papillary apices, suffer the same change only after temporary pressure anoxia and reactive hyperemia.

Gastrointestinal System

Extensive bowel ischemia with infarction has been reported in fatal cases of CO poisoning.

Effects on the Peripheral Nervous System

Peripheral neuropathy can be caused by CO poisoning. Possible causes include anoxia, the toxic effect of CO on the nerves, and positional compression of the nerves during the comatose stage.

Effects on the Visual System

Measurable decreases in sensitivity to light and adaptation to darkness have been shown to result from low levels of CO exposure. These alterations persist even after elimination of COHb from the blood, indicating that a significant amount of CO may be retained in the tissues. Retinal hemorrhages have been observed on ophthalmoscopy of patients with acute CO poisoning. Retinal venous engorgement and peripupillary hemorrhages resemble those seen in hypoxia. CO retinopathy has been recorded as an acute effect of CO poisoning leading to visual impairment.

Effect on the Auditory System

Hearing loss of a central type caused by anoxia from CO poisoning is only partially reversible. The loss of auditory threshold activity is pronounced at the level of the auditory cortex; the relative vulnerability of the central auditory pathway has been demonstrated. Vestibular function is more frequently involved than the auditory function. Recovery from hearing loss is uncommon; this is the result of hypoxia of the cochlear nerve and the brain stem nuclei.

Effect on the Central Nervous System

The most important lesions of CO poisoning are in the central nervous system (CNS). This subject has been discussed in detail elsewhere (Jain 2016).

Neuropathology

Of the cells of the CNS, the astrocytes are more sensitive than neurons to the effects of CO. The critical lesions in CO poisoning are in the brain. There are three stages in the evolution of the brain lesions:

1. In immediate death after CO poisoning, there are petechial hemorrhages throughout the brain, but no cerebral edema
2. In patients who die within hours or days after poisoning, cerebral edema is present. There is necrosis of the globus pallidus and substantia nigra.
3. In patients who die days or weeks later from delayed sequelae of CO poisoning, edema has usually disappeared.

Degenerative and demyelinative changes are usually seen.

Necrosis of the globus pallidus in a patient is revealed by CT scan as a low-density area. The corpus callosum, hippocampus, and substantia nigra may also be affected. In the late stages, there is cerebral atrophy, which is also demonstrated by CT scan; this usually correlates with poor neurological recovery. White matter damage is considered to be significant in the pathogenesis of parkinsonism in patients with CO poisoning.

Pathophysiology

The tendency for effects on certain areas of the brain such as the globus pallidus and substantia nigra has been considered to be caused by a hypoxic effect of CO. Clinical instances of "pure hypoxia" are rare, and many investigators consider CO intoxication to represent cerebral hypoxia aggravated by relative ischemia, as the lesions are similar to those induced by other forms of hypoxia and/or ischemia. It was shown 80 years ago that CO damages the blood–brain barrier, particularly in the cerebral white matter, where the venous drainage pattern predisposes to focal edema similar to that seen in multiple sclerosis (Putnam et al. 1931). This may lead to hypoxia and set up the cycle of hypoxia–edema–hypoxia. Delayed neurological deterioration can occur following anoxia from other causes and can explain similar deterioration after CO poisoning, in the absence of elevated levels of COHb.

The mechanism of delayed neurological toxicity is based on several reactions triggered by increased calcium concentrations in the cell, which persist long enough to produce alterations in cell function and delayed neurological damage. White matter demyelination is believed to be responsible for delayed neuropsychiatric syndrome.

Harmful effects of an acute nonlethal CO exposure do not cease with a decrease in COHb concentration. The decreased cytochrome oxidase activity may later on be mediated by a loss of mitochondria because of lipid peroxidation, rather than by specific inhibitory effects of CO. A similar mechanism would explain the acid proteinase activity in the glial cell fraction within 24 h of reoxygenation.

CO may alter the oxidative metabolism of the brain independently of a COHb-related decrease in oxygen delivery. Binding of CO to cytochrome oxidase in the brain cortex is

a possible explanation of a nonhypoxic mechanism of CO toxicity. Mitochondria may contribute to CO-mediated neuronal damage during reoxygenation after severe CO intoxication. CO-mediated brain injury is a type of post-ischemic reperfusion phenomenon and xanthine-oxidase-derived reactive oxygen species may be responsible for lipid peroxidation. These explanations are offered for a number of poorly understood clinical observations regarding CO poisoning, particularly the neuropsychological effects at concentrations below 5 %. Delayed amnesia induced by CO exposure in experimental animals may result from delayed neuronal death in the hippocampus and dysfunction of the acetylcholinergic neurons in the frontal cortex, the striatum, and/or the hippocampus. In animal studies it has been shown that *N*-methyl-D-aspartate (NMDA) receptor/ion channel complex is involved in the mechanism of CO-induced neurodegeneration, and that glycine binding site antagonists and NMDA-antagonists may have neuroprotective properties. In spite of various explanations that have been offered, nothing is known with certainty about the pathomechanism of CO poisoning. Recognition of CO a putative neural messenger that interacts with the enzyme guanylyl cyclase may provide an important clue to the pathomechanism of CO toxicity. Endogenously formed CO arises from the enzymatic degradation of heme oxygenase and acts as a neuromodulator. In addition to its physiological role, CO that arises subsequent to the appearance of heme oxygenase-1 may underlie various pathological states.

Relative cerebral hyperperfusion has been observed during CO-hypoxia and is considered to be due to a fall in the P50 (PO_2 at 50 % saturation of non-CO bound sites on hemoglobin) rather than a direct tissue effect of CO. Cerebral blood flow has been shown to increase in anesthetized animals exposed to 1 % CO, despite a fall of mean arterial blood pressure. In the presence of tissue hypoxia with undiminished plasma PO_2, the brain vasculature allows greater flow of blood while the microvasculature adjusts to reduce the diffusion distance for O_2.

Clinical Features of CO Poisoning

Signs and symptoms of CO poisoning are nonspecific and involve most of the body systems. They vary according to the COHb levels, as presented in Table 13.6. The clinical signs and symptoms depend on both the dose of CO and the duration of exposure. COHb levels do not necessarily correlate with the severity of clinical effects.

Neuropsychological Sequelae of CO Poisoning

The neurological sequelae of CO poisoning as reported in the literature are summarized in Table 13.7. There is some disparity in the results of the studies summarized here. However, psychological impairment can be detected at COHb levels between 2.5 and 5 % by appropriate tests.

Higher levels of COHb during acute exposure may lead to impairment of consciousness, coma, and convulsions. Most of the neurological manifestations of CO poisoning

Table 13.6 Degree of severity of CO poisoning, COHb levels, and clinical features

Severity	COHb level	Clinical
Occult	>5 %	No apparent symptoms
		Psychological deficits on testing
	5–10 %	Decreased exercise tolerance in patients with chronic obstructive pulmonary disease
		Decreased threshold for angina and claudication in patients with atherosclerosis. Increased threshold for visual stimuli
Mild	10–20 %	Dyspnea on vigorous exertion headaches, dizziness
		Impairment of higher cerebral function
		Decreased visual acuity
Moderate	20–30 %	Severe headache, irritability, impaired judgment
		Visual disturbances, nausea, dizziness, increased respiratory rate
		Cardiac disturbances, muscle weakness
	30–40 %	Vomiting, reduced awareness
		Fainting on exertion
		Mental confusion
Severe	40–50 %	Collapse
		Convulsions
		Paralysis
	50–60 %	Coma, frequently fatal within a few minutes
	Over	Immediately fatal

Table 13.7 Neuropsychological sequelae of CO poisoning

Authors and year	Subjects	COHb level or CO/ppm	Effects
Lilienthal and Fugitt (1946)	Humans	5–10 % COHb	Impairment in the FFT test
Trouton and Eysenck (1961)	Humans	5–10 % COHb	Impairment of the precision of control
			Multiple limb incoordination
Schulte (1963)	Humans	2–5 % COHb	Decrease in cognition and psychomotor ability
			Increase in the number of errors and the completion time in arithmetic tests, t-crossing test, and visual discrimination tests
Beard and Wertheim (1967)	Humans	90 min at 50 ppm shorter time at 250 ppm (=COHb of 4–5 %)	Impaired ability to discriminate short
	Rats	100 ppm for 11 min	Disruption of ability to judge time (assessed by differential reinforcement at a low rate of response)
Mikulka et al. (1973)	Humans	125–250 ppm briefly (COHb 6.6 %)	No effect on time estimation
			No disruption of tracking
Gliner et al. (1983)	Humans	100 ppm for 2.5 h controls (room air)	Decreased arousal and interest with fatigue resulting in decrease in performance
Schrot et al. (1984)	Rats	500 ppm—90 min (40 % COHb)	Disruption of the rate at which the rats acquired a chain of response
		850 ppm—90 min (50 % COHb)	
		1200 ppm—90 min (60 % COHb)	
Schaad et al. (1983)	Humans	COHb 20 %	No impairment on a tracking simulator device
Yastrebov et al. (1987)	Humans	900 ± 20 mg/m^3 for 10 min (COHb of 10 to +0.5 %)	Impairment in a two-dimensional compensatory tracking task combined with mental arithmetic. Symptoms of mild CO intoxication at COHb levels of 10 %

are late sequelae (listed in Table 13.8); these late sequelae are also referred to as "secondary syndromes." The complications may develop a few days to 3 weeks after exposure to CO, and as late as 2 years after apparently complete recovery from acute CO poisoning. Neuropsychiatric symptoms are prominent in the late sequelae. The incidence of secondary syndromes varies from 10 to 40 %. Patients poisoned by CO and treated by oxygen still developed late sequelae but such sequelae are rare in patients treated by HBO therapy.

In the largest reported series of 2360 victims of CO poisoning, delayed neurological sequelae were diagnosed in 11.8 % of those admitted to hospital and 2.75 % of the total group (Choi 1983). The lucid interval before appearance of neurological symptoms was 2–40 days (mean, 22.4 days). The most frequent symptoms were mental deterioration, urinary incontinence, gait disturbance, and mutism. The most frequent signs were masked face, glabellar sign, grasp reflex, increased muscle tone, short-step gait, and retropulsion. Most of these signs indicate parkinsonism. There were no important contributing factors except anoxia and age. Previous associated disease did not hasten the development of sequelae. Of the 36 patients followed for 2 years, 75 % recovered within 1 year.

Table 13.8 Delayed neuropsychological sequelae of CO poisoning

- Akinetic mutism
- Apallic syndrome
- Apraxia, ideomotor as well as constructional
- Ataxia
- Convulsive disorders
- Cortical blindness
- Deafness (neural)
- Delirium
- Dementia
- Depression
- Diminished IQ
- Dysgraphia
- Gilles de la Tourette syndrome
- Headaches
- Memory disturbances
- Movement disorders, parkinsonism, choreoathetosis
- Optic neuritis
- Peripheral neuropathy
- Personality change
- Psychoses
- Symptoms resembling those of multiple sclerosis
- Temporospatial disorientation
- Urinary incontinence
- Visual agnosia

Clinical Diagnosis of CO Poisoning

Few symptoms of CO poisoning occur at COHb concentrations of <10 %. The presence of symptoms and history of exposure to CO and the circumstances in which the patient is found should lead to strong suspicion of CO poisoning. Therapy may be started before the laboratory investigations are completed.

Pitfalls in the Clinical Diagnosis of CO Poisoning

The following points should be taken into consideration in making a diagnosis of CO poisoning:

1. Clinical signs and symptoms of CO poisoning do not always correspond to COHb levels.
2. The cherry red color of the skin and the lips, usually considered to be a classical sign, is not present when the COHb levels are below 40 % and there is cyanosis caused by respiratory depression. In practice this sign is rarely seen.
3. Some of the symptoms are aggravated by preexisting disease, such as intermittent claudication.
4. Tachypnea is frequently absent, because the carotid body is presumably responsive to the oxygen partial pressures rather than the oxygen content.
5. Examples of frequent misdiagnosis of CO poisoning are psychiatric illness, migraine headaches, stroke, acute alcohol intoxication or delirium tremens, heart disease, and food poisoning.
6. CO poisoning in infants is a frequently missed diagnosis. When unexplained neurological symptoms occur in an infant who has been a passenger in a car, COHb determinations should be made and CO poisoning should be considered in the differential diagnosis.
7. A bit of detective work may be required to locate the source of carbon monoxide poisoning. A simple tool based on the CH^2OPD^2 mnemonic (Community, Home, Hobbies, Occupation, Personal habits, Diet and Drugs) is helpful in obtaining an environmental exposure history.

Occult CO Poisoning

This is a syndrome of headache, fatigue, dizziness, paresthesias, chest pains, palpitation, and visual disturbances associated with chronic CO exposure. Headache and dizziness are early symptoms of CO poisoning and occur at COHb concentrations of 10 % or more. Among patients taken to an emergency department during the winter heating season with complaints of headache or dizziness, 3–5 % have COHb levels in excess of 10 %. They are usually unaware of exposure to toxic levels of CO in their home prior to the visit to the emergency department. In patients who present with ill-defined symptoms and no history of CO exposure, CO poisoning must be considered when two or more patients are similarly or simultaneously sick.

Laboratory Diagnosis of CO Poisoning

Various laboratory procedures that may be used in the diagnosis of CO poisoning are as follows:

1. Determination of CO in the blood
   (a) Direct measurement of the COHb levels
   (b) Measurement of CO released from the blood
   (c) Measurement of CO content of the exhaled air
2. Arterial blood gases and lactic acid levels
3. Screening tests for drug intoxication and alcohol intoxication
4. Biochemistry
   (a) Enzymes: creatine kinase, lactate dehydrogenase, SGOT, SGPT
   (b) Serum glucose
5. Complete blood count
6. Electroencephalogram
7. Electrocardiogram
8. Brain imaging: CT scan, MRI, SPECT/PET
9. Magnetic resonance spectroscopy
10. Neuropsychological testing

COHb Measurement. This is the most commonly used investigation. Measurement is done spectrophotometrically, offering an accurate and rapid determination of the patient's COHb levels. An instrument like the CIBA Corning 2500-CO oximeter determines various selected wavelengths from 520 to 640 nm, and the following hemoglobin derivatives are measured: oxyhemoglobin (O_2Hb), deoxyhemoglobin (HHb), carboxyhemoglobin (COHb), and methemoglobin (MetHb).

Determination of CO Released from the Blood. Several methods are available for releasing CO from samples of blood. CO is then measured by gas chromatography. The amount of CO in the blood sample is calculated from the ratio of the CO content to the full CO capacity of the same sample.

CO Measurement in Exhaled Air. This can be measured by gas chromatography. A bag can be used to collect exhaled air and CO is determined by a flame ionization detector after catalytic hydration with methane. The values are given as parts per million (ppm) in the range of 0–500.

Clinical Significance of Monitoring Blood COHb. The following recommendations are based on various studies of monitoring of COHb in patients with acute CO poisoning:

1. Blood COHb greater than 10 % has diagnostic significance and, COHb > 30 % should be considered serious.
2. Clinical manifestations should be primary and COHb secondary when judging the degree of CO poisoning.
3. Treatment should be continued even when COHb levels have returned to normal, if the clinical symptoms are still present.
4. COHb sampling need not be continued when the patient has been away from the toxic environment for more than 8 h.
5. Monitoring of COHb is useful in making a differential diagnosis and in the event of death, a definitive diagnosis.

Pitfalls in the Diagnosis of CO Poisoning from COHb Level Determinations. COHb levels may be normal when first obtained and not reflect the true insult. This is likely to happen when:

- There is delay in obtaining samples following cessation of exposure to CO.
- Oxygen is administered before blood samples are withdrawn.
- COHb is calculated from oxygen partial pressures using a slide-rule nomogram.

Arterial pO_2 may be normal in the presence of CO if the patient is not dyspneic. The calculated oxyhemoglobin saturation may be grossly wrong in this case.

Changes in Blood Chemistry. Increased levels of lactate, pyruvate, and glucose are influenced by the duration of exposure to CO and are more pronounced after prolonged acute exposure than after a short exposure. Hyperglycemia may occur as a result of hormonal stress response. Blood lactate and COHb levels both correlate with the changes of consciousness in CO poisoning and are useful for defining indications for HBO treatment (Icme et al. 2014).

Electroencephalographic Changes. Various EEG abnormalities noticed in CO poisoning are diffuse abnormalities (continuous theta or delta activity) and low voltage activity accompanied by intervals of spiking or silence, as well as rhythmic bursts of slow waves. Topographic quantitative EEG methods may have promise in the study of acute and long-term effects of CO poisoning. Longitudinal and quantitative EEG recording after acute CO poisoning may show the following:

1. Elevated Absolute Power of all EEG frequencies with the most marked voltage increases occurring in the alpha-theta range.
2. Sharply defined regional increases in the absolute power of delta activity over the posterior temporal–parietal–occipital cortex bilaterally.
3. Increased relative power of the alpha wave that is most marked over the prefrontal cortex.
4. Decreased relative power of the alpha wave that is most marked over the prefrontal cortex.
5. Pronounced decreases in interhemispheric coherence for most frequency bands.

The multimodality evoked potentials have proved to be sensitive indicators in the evaluation of brain dysfunction and in the prognosis of acute CO poisoning and development of delayed encephalopathy. Pattern shift visual evoked potential (PSVEP) N75 and P100 latencies are not a sensitive screening tool for treatment decision making in a group of acutely CO poisoned patients.

Neuropsychological Testing. It has long been known that CO poisoning has a spectrum of effects on cognitive functioning. Neuropsychological impairments in CO-poisoned subjects include memory, intellectual, executive, and visuospatial defects. Various psychological tests have been designed for patients with CO poisoning. One neuropsychological screening battery for use in assessment of such patients consists of six tests: general orientation, digit span, trail making, digit symbols, aphasia, and block design (Messier and Myers 1991). These tests can be administered in an emergency by a nonpsychologist in 20 min. There is a strong correlation between abnormalities detected on psychometric testing and COHb levels. The former measures actual neurological disability and is a better index of severity of CO poisoning.

CO poisoning is significantly associated with impairment of context-aided memory, with the degree of pretreatment impairment predicting the number of HBO treatments judged to be necessary on the basis of clinical monitoring of the patient. In patients with poisoning of moderate severity, pretreatment performance in context-aided memory improved after the first HBO treatment. The memory measure used in this study appears to have considerable potential usefulness in the clinical assessment of the severity of CO poisoning in patients treated in an emergency setting.

Brain Imaging Studies

Various brain imaging studies have been found to be useful in assessing the brain involvement in CO poisoning. These are described in the following pages and a comparison of the value of various techniques is presented in Table 13.9.

CT Scan. The CT scan is the most widely used neuroimaging method for patients with CO poisoning. Common CT findings

Table 13.9 Comparative value of brain imaging studies in CO poisoning

	CT	MRI	SPECT/PET
Basal ganglia lesions	+	++	
White matter lesions	+	+++	
Both white and gray matter	+	++	+++
Cerebral edema	+	++	
Cerebral perfusion	+	+	+++
Predicting late sequelae	+	++	+++
Assessing response to HBO	+	++	+++

are symmetrical low-density abnormalities of the basal ganglia and diffuse low-density lesions of the white matter. The globus pallidus lucencies may be unilateral and white matter involvement may show marked asymmetry. Postcontrast CT offers an advantage when noncontrast CT is normal in CO poisoning. Acute transient hydrocephalus has been observed in acute CO poisoning but it may resolve in a few weeks. In the interval form of CO poisoning, low-density lesions bilaterally in the frontal regions, centrum semiovale, and pallidum have been correlated with demyelination of white matter of the corresponding parts at autopsy. An initial normal CT scan in a comatose patient does not rule out CO poisoning. Serial CT scanning showed no low-density lesions of the frontal lobes and basal ganglia until 3 days after exposure to CO.

Magnetic Resonance Imaging (MRI). Most of the knowledge of MRI findings in CO poisoning is based on case studies of patients in the subacute or chronic phase following exposure. MRI studies in the acute phase of CO poisoning show that, although the globus pallidus is the commonest site of abnormality in the brain, the effects are widespread.

In patients with CO poisoning, MRI can demonstrate bilateral edematous lesions in the globus pallidus and it is considered to be a more sensitive examination than serial CT in acute CO poisoning. Although the severity of white matter lesions correlates with the prognosis in acute CO poisoning, it does not always correspond to the neurological outcome in the subacute stage.

MRI has been used less often in cases of delayed encephalopathy after CO poisoning. The main finding in such cases is a reversible demyelinating process of the cerebral white matter. Lesions of the anterior thalami, which may be missed on CT scan, can be demonstrated by MRI. A spectrum of MRI changes has been seen even years after relatively mild CO poisoning. Patients with severe CO intoxication may develop persistent cerebral changes independently of their neuropsychiatric findings in the chronic stage, which may present with characteristic MRI findings. Diffusion tensor MRI is a promising technique to characterize and track delayed encephalopathy after acute carbon monoxide poisoning.

Positron Emission Tomography (PET). PET studies in acute CO poisoning show a severe decrease in rCBF, rOER, and rCMRO in the striatum and the thalamus, even in patients treated with HBO. These changes are temporary and the values return to normal in patients without clinical sequelae or only transient neurological disturbances. PET findings remain abnormal in patients with severe and permanent sequelae.

Single Photon Emission Computed Tomography (SPECT). This can provide imaging of cerebral perfusion. Diffuse hypoperfusion has been shown in both the gray and the white matter of the cerebral cortex in CO poisoning. SPECT is helpful in documenting the increase in cerebral perfusion along with clinical improvement as a result of HBO treatment. Cerebral vascular changes may be the possible cause of hypoperfusion in patients with CO poisoning and there is a good correlation between the clinical outcome and the findings of SPECT. SPECT can be used for predicting and evaluating the outcome of delayed neurological sequelae after CO poisoning. In comparison to traditional brain imaging techniques, 99 mTc-HMPAO brain imaging with fanbeam SPECT in combination with surface 3D display is a better tool for early detection of regional cerebral anomalies in acute CO poisoning. HMPAO-SPECT has been used in the management of patients with acute and delayed neurological sequelae of CO poisoning and found to be helpful in identifying potentially recoverable brain tissue and the response to HBO (see Chap. 20). The case history and SPECT scans of one of the patients are reproduced in Chap. 20.

Magnetic Resonance Spectroscopy (MRS). MRS is a noninvasive method that provides information about brain metabolites such as *N*-acetyl aspartate, choline, and creatine. MRS can reflect the severity of delayed sequelae of CO poisoning precisely. Increase in choline in the frontal lobes indicates progressive demyelination. Appearance of lactate and decrease in *N*-acetyl aspartate reflect the point at which neuron injury becomes irreversible. These findings have been correlated with those of MRI and SPECT. It may be a useful method to determine neuron viability and prognosis in CO poisoning. The combination of proton MRS and diffusion tensor imaging is useful for monitoring the changes in brain damage and the clinical symptoms of patients with delayed encephalopathy after CO poisoning and response to HBO treatment.

General Management of CO Poisoning

General guidelines for the management of CO poisoning are presented in Table 13.10. Once the patient is removed from CO environments, CO slowly dissociates from the Hb and is eliminated. The half-life of the COHb is presented in Table 13.11.

Table 13.10 Guidelines for the management of CO poisoning

1. Remove patient from the site of exposure
2. Immediately administer oxygen, if possible after taking a blood sample for COHb
3. Endotracheal intubation in comatose patients to facilitate ventilation
4. Removal of patient to HBO facility when indicated
5. General supportive treatment: for cerebral edema, acid–base imbalance, etc.
6. Keep patient calm and avoid physical exertion by the patient

Table 13.11 Half-life of COHb

	Pressure	Time
Air	1 ATA	5 h 20 min
100 % oxygen	1 ATA	1 h 20 min
100 % oxygen	3 ATA	23 min

At atmospheric pressure in fresh air, the circulating half-life of CO is 5 h 20 min. This time decreases to 23 min with HBO at 3 ATA. These half-lives are not constant, as they depend on a number of variable factors. They are particularly inaccurate when COHb levels are high. The objectives of treatment in CO poisoning are as follows:

- To hasten elimination of CO
- To counteract hypoxia
- To counteract direct tissue toxicity.

A flow chart as a guide for handling patients with CO poisoning is shown in Fig. 13.3. HBO therapy is the most important factor in treatment, but the following adjunctive measures should be considered:

- Treatment of cerebral edema. HBO therapy itself is effective against cerebral edema, but the use of steroids and mannitol may be helpful.
- Cellular protection. Mg2+ can be used; the usual dose is 20–30 mmol/day.
- Fluid and electrolyte balance should be carefully maintained and overhydration, which may aggravate cerebral edema and pulmonary complications, should be avoided. Acidosis should not be corrected pharmacologically, as slight acidosis aids in the delivery of oxygen to the tissues by shifting the oxygen dissociation curve to the right. HBO usually limits the metabolic acidosis associated with CO poisoning.
- Management of cardiac arrhythmias. Cardiac arrhythmias are a common complication of CO poisoning. They may subside with reversal of tissue hypoxia but may require pharmacological management.
- Preclinical studies show that the novel synergism of hydroxocobalamin (B12) with ascorbic acid has the potential to extract CO through conversion to CO_2, independently of high-flow or high-pressure O_2 (Roderique et al. 2015). This results in a clinically significant off-gassing of CO_2 at levels five to eight times greater than those of controls, a clinically significant reduction in COHgb half-life, and evidence of increased brain oxygenation. Reduced B12 has major potential as an injectable antidote for CO toxicity.

Rationale for Oxygen Therapy (NBO or HBO) for CO Poisoning

Hyperoxygenation enhances oxygen transfer into the anoxic tissues. At normal concentrations of tissue oxygen it should physically dilute the CO and possibly halt the movement of CO from Hb to Mb and cytochrome enzymes. Hyperoxygenation may be achieved by breathing 100 % oxygen either at atmospheric pressure (normobaric) or under hyperbaric conditions. HBO is more effective than NBO. HBO accomplishes the following therapeutic goals in CO poisoning:

- Immediate saturation of plasma with enough oxygen to sustain life and to counteract tissue hypoxia in spite of high levels of COHb.
- It causes a rapid reduction of CO in the blood by mass action of O_2. In the equation "$HbO2 + CO = HbCO + O_2$," an increase in either oxygen or CO results in a comparable increase in the corresponding compound with hemoglobin.
- It assists in driving CO away from cytochrome oxidase and in restoration of function. The increase in oxygen tension in plasma and not simply an increase in dissolved oxygen is responsible for the efficacy of HBO.
- HBO reduces cerebral edema.
- Brain lipid peroxidation caused by CO is prevented by 100 % oxygen at 3 ATA.
- HBO prevents immune-mediated delayed neurologic dysfunction following exposure.

Although breathing NBO hastens the removal of COHb, HBO hastens COHb elimination and favorably modulates inflammatory processes initiated by CO poisoning, an effect not observed with breathing NBO (Weaver 2014). HBO inhibits leukocyte adhesion to injured microvasculature, and reduces brain inflammation caused by the CO-induced adduct formation of myelin basic protein. Based upon three supportive randomized clinical trials in humans and considerable evidence from animal studies, HBO should be considered for all cases of acute symptomatic CO poisoning. HBO is indicated for CO poisoning complicated by concomitant cyanide poisoning, as happens often in smoke inhalation.

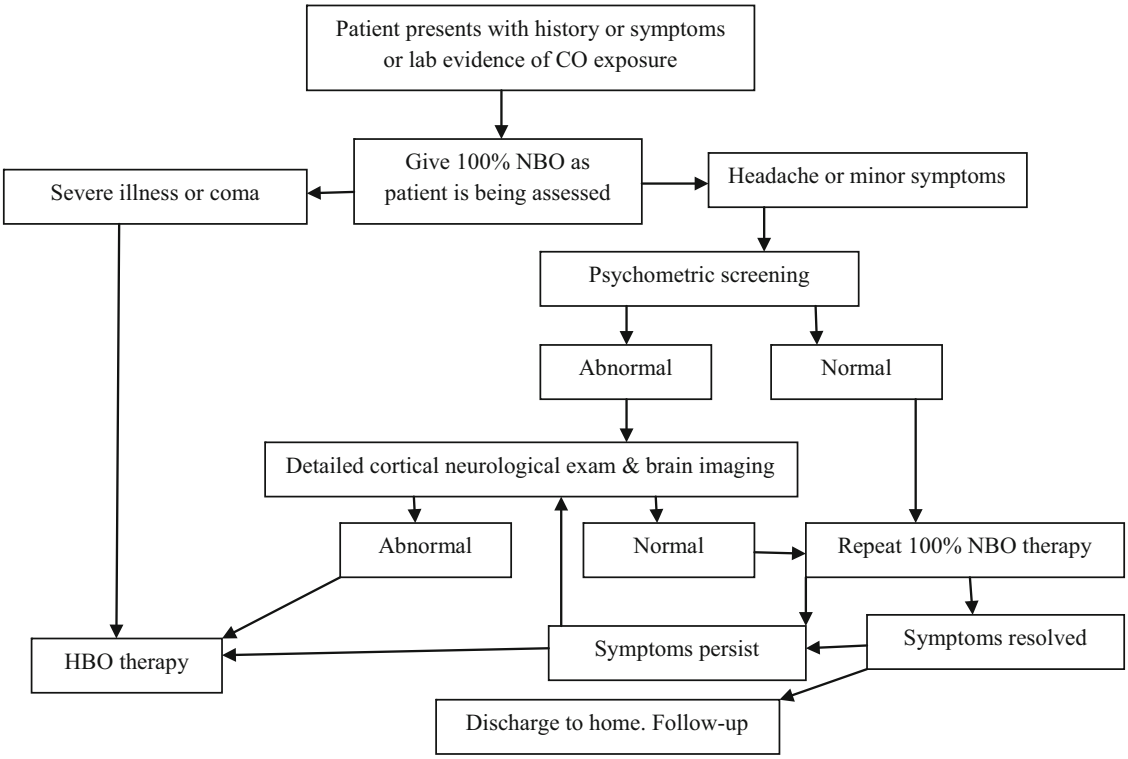

Fig. 13.3 Flow chart to guide treatment of carbon monoxide poisoning

HBO improves mitochondrial function. Mitochondrial complex IV (mtCIV) inhibition, along with COHb-induced hypoxia, may influence acute clinical symptoms and outcome in acute CO poisoning. To evaluate mitochondrial aspect of treatment efficacy, a study has correlated intoxication severity and symptoms with mitochondrial function and oxidative stress (lipid peroxidation) in 60 poisoned patients and determined recovery depending on either NBO or HBO therapy in a 3-month follow-up (Garrabou et al. 2011). Results show that mtCIV is a good biomarker of recovery from acute CO poisoning, efficacy of treatment, as well as development of delayed neurological sequelae, and favor HBO therapy as the treatment of choice.

Experimental Evidence

The results of some experimental studies of the use of HBO in CO poisoning are presented in Table 13.12.

Clinical Use of HBO in CO Poisoning

Guidelines for the use of HBO versus NBO are given in Table 13.13. Some open clinical studies of CO poisoning treated by HBO are presented in Table 13.14. HBO, if available, should be used at COHb levels of 25 % or above, but the clinical picture of the patient with a history of CO exposure is the deciding factor for the initiation of HBO therapy, and the COHb levels should be a secondary consideration. Because of the cost and limited availability of hyperbaric chambers, a decision regarding transfer of the patient to a hyperbaric facility is not always easy, particularly when the patient is critically ill. If possible, the patient should be transferred to a multiplace chamber with facilities for critical care and suitably qualified personnel. During transport to such a facility, the patient should receive 100 % oxygen, using a mask, and care should be taken that the patient does not rebreathe the exhaled air. The argument that NBO is always satisfactory for severe CO poisoning can no longer be sustained. A pO_2 of 1800 mmHg achieved by HBO is definitely more effective than the maximal pO_2 of 760 mmHg attainable by normobaric 100 % oxygen. In practice, it is much lower than this, since few oxygen masks exist that are suitable for administering oxygen to achieve a pO_2 above 600 mmHg.

The Undersea and Hyperbaric Medical Society of USA recommends HBO therapy for patients suffering from serious CO poisoning as manifested by transient or prolonged unconsciousness, abnormal neurologic signs, cardiovascular dysfunction, or severe acidosis or patients who are 36 years

Table 13.12 Experimental studies on the effect of HBO on carbon monoxide poisoning

Authors and year	Experimental subjects	Mode of oxygen therapy	Results
End and Long (1942)	Dogs and guinea pigs	HBO 3 ATA, 100 % oxygen	HBO more effective than normobaric oxygen in eliminating CO from the body
Pace et al. (1950)	Human volunteers	HBO 2 ATA	Rate of diminution of CO accelerated
Ogawa et al. (1974)	Dogs	HBO	Hemoconcentration (20 % decrease of blood volume reversed by HBO)
Koyama (1976)	Dogs	Half of the animals treated by conventional methods and the other half by HBO 2 ATA	COHb determination and biochemical studies showed that HBO was more effective than the conventional methods
Sasaki (1975)	Dogs	HBO	Acceleration of the half-clearance time of COHb
			Proposed procedure for HBO therapy based on it:
			1. For severe CO poisoning, HBO at 2.8 ATA for 20 min followed by 1.9 ATA for 57 min
			2. For moderate CO poisoning, 2.8 ATA oxygen for 20 min followed by 1.9 ATA for 46 min
			3. For light CO poisoning, 2.8 ATA oxygen for 20 min followed by 1.9 ATA for 30 min
Jiang and Tyssebotn (1997)	Rats with occluded left carotid artery	NBO in one group versus HBO in the other, normoxic animals as controls	1. Compared to the normoxic treatments, the HBO, but not the NBO, significantly reduced the mortality and the neurologic morbidity
			2. HBO was also significantly better than NBO in increasing surviving time and survival rate
			3. The results support the value of HBO in improving short-term outcome of acute CO poisoning in this rat model

Table 13.13 Hyperbaric oxygen (HBO) versus normobaric oxygen

Hyperbaric facilities available	COHb > 25 %	HBO
	COHb < 25 %	HBO if symptoms, NBO if none
No hyperbaric facilities	COHb > 40 % no symptoms	NBO
	COHb < 40 % with symptoms	Referral to HBO center

of age or older, were exposed for 24 h or more (including intermittent exposures), or have a carboxyhemoglobin level of 25 % or more. Results of the latest study on this topic show that the indications of HBO therapy for CO poisoning are still not universally recognized (Mutluoglu et al. 2016). HBO therapy protocols used at European hyperbaric centers vary significantly, suggesting a need for more education regarding the published guidelines.

Clinical Trials of HBO in CO Poisoning

Clinical trials of HBO in CO poisoning are listed in Table 13.15. These are discussed in more detail later.

A trial of normobaric and hyperbaric oxygen for acute CO intoxication carried out in 629 adults who had been poisoned at home in the 13 h preceding admission to hospital (Raphael et al. 1989). It was a randomized study with grouping based on whether or not there was initial loss of consciousness. In those without any loss of consciousness HBO was compared with normobaric oxygen (NBO) treatments, with no difference being noticed in the recovery rate. Those who had an episode of loss of consciousness were treated either by a single session of 2 h of HBO at 2 ATA followed by 4 h of NBO, or by 4 h of NBO with two sessions of HBO 6–12 h apart. Two sessions of HBO were shown to have no advantage over a single session. The authors concluded that those who do not sustain initial loss of consciousness should be

Table 13.14 Open clinical studies of HBO in CO poisoning

Authors and year	No. of patients	Pressure	Results
Smith et al. (1962)	22	2 ATA	All recovered
Sluitjer (1963)	40	3 ATA	Group I: conscious or drowsy. 21 patients. Excellent results
			Group II: comatose with neurological abnormalities. 10 patients. Two died, 7 recovered fully and one had severe neurological sequelae
			Group III: Attempted suicide with combination of CO and barbiturates. Nine patients. Cardiorespiratory depression mainly with little localizing neurological signs. All recovered completely
Goulon et al. (1969)	302	2 ATA	Mortality when treatment started before 6 h was 13.5 %, and when after 6 h 30.1 %
Heyndrickx et al. (1970)	11	3 ATA	Clinical improvement more than in another 11 patients treated by NBO
Kienlen et al. (1974)	370	2–3 ATA	93.7 % of the patients recovered
Adamiec et al. (1975)	44	2.5 ATA	80 % showed good recovery
Yun and Cho (1983)	2242	?	98.2 recovered
Mathieu et al. (1985)	203	?	Mortality 1.7 %; incidence of secondary syndromes, 4 %: rest recovered
Norkool and Kirkpatrick (1985)	115	?	88 % recovered fully
Colignon and Lamy (1986)	111	83 ATA	0.5 % died in emergency room; 3.3 % admitted to ICU; rest 96.2 % had minor symptoms and recovered completely
Tirpitz and Bakyara (1988)	276	2–2.5 ATA	4 deaths. Rest recovered. Many treated and released to home the same day
Sloan et al. (1989)	297	3 ATA	Extremely ill patients with mortality of 6 %. Rest recovered
Abramovich et al. (1997)	24	2.8 ATA	20 (84 %) recovered consciousness during one treatment, 3 required a second treatment, and one who arrived in deep coma died

treated by NBO regardless of the COHb levels. The authors did not deny the usefulness of HBO in those with loss of consciousness, but stated that two sessions of HBO had no advantage over a single session. The methodology in the study is questionable.

A randomized study compared the effects of NBO versus HBO therapy in patients with moderate CO poisoning (Ducassé et al. 1995). In conscious patients without neurological impairment, one HBO treatment at 2.5 ATA for 0.5 h, within the first 2 h after admission, had the following advantages:

- Faster recuperation from symptoms such as headache and nausea.
- Quicker elimination of CO during the first 2 h. After 12 h, there was no difference in blood COHb levels between the two groups.
- Fewer EEG abnormalities after 3 weeks in the group treated with HBO.
- Recovery of the cerebral vasomotor response in the group treated with HBO, as shown using the acetazolamide test.

In a longitudinal study of 100 consecutive patients, the frequency of neuropsychiatric sequelae among patients who received oxygen at atmospheric pressure was 63 %, among those who received one HBO treatment it was 46 %, and in those who received two or more HBO treatments it was 13 % (Gorman et al. 1992). The frequency of sequelae was greater if HBO treatment was delayed. In a prospective randomized clinical study, delayed neuropsychiatric sequelae were found to be less frequent with HBO treatment as compared with normobaric oxygen administration (Thom 1992). These authors recommend that HBO should be used in the initial treatment of all patients with CO poisoning, regardless of the severity of their initial clinical manifestations. It is difficult to compare the results of different reported studies, because the patient conditions differed widely and the HBO technique used also varied. The overall results of HBO therapy, however, were favorable. Some patients in critically ill condition died from other complications, and in some other cases the HBO therapy was instituted too late to be lifesaving.

Table 13.15 Clinical trials of HBO in CO poisoning

Authors and year	Study design	HBO pressure	Results
Annane et al. 2011	Randomized, not blinded 2 trials	Trial 1: 1 session HBO 2 ATA versus NBO if transient loss of consciousness	Trial 1: HBO was nonsuperior to NBO
		Trial 2: 2 sessions HBO versus 1 session HBO if initial coma	Trial 2: patients with 2 HBO sessions had worse outcomes than those with 1 HBO session
Weaver et al. (2002)	Double-blind, randomized trial to study the effect of HBO on cognitive sequelae of acute CO poisoning	HBO (2–3 ATA)	3 HBO treatments within a 24-h period reduced the risk of cognitive sequelae 6 weeks and 12 months after
	Control with normobaric oxygen + air		
Scheinkestel et al. (1999)	Randomized controlled double-blind trial and sham treatments in a multiplace hyperbaric chamber. Neuropsychological assessments	HBO (2.8 ATA/1 h) or 100 % oxygen	Both groups received high doses of oxygen but HBO therapy did not benefit
Thom et al. (1995)	Prospective, randomized study in patients with mild to moderate CO poisoning who presented within 6 h. Incidence of delayed neurological sequelae (DNS) compared between groups treated with oxygen or HBO	Normobaric 100 % oxygen or HBO (2.8 ATA for 30 min + 2 ATA for 90 min)	HBO treatment decreased the incidence of DNS after CO poisoning
Ducassé et al. (1995)	Randomized study in acute CO poisoning: normobaric oxygen (NBO) versus hyperbaric oxygen	2 h treatment with normobaric oxygen or HBO (2.5 ATA)	Patients treated with HBO had a significant clinical improvement compared with patients treated with NBO
Raphael et al. (1989)	Randomization of patients with acute CO intoxication to normobaric or hyperbaric oxygen. Grouping based on whether or not there was initial loss of consciousness	Single session of HBO (2 ATA/2 h) followed by 4 h of NBO, or by 4 h of NBO with 2 sessions of HBO, 6–12 h apart	Better recovery with HBO treatment in those with initial loss of consciousness. There was no advantage of 2 sessions of HBO over a single session

The treatments may be carried out in a monoplace or a multiplace hyperbaric chamber. A large chamber with intensive care facilities is preferable in case of a critically ill patient. Various regimens have been used for the treatment of CO poisoning. The pressures used vary between 2 and 3 ATA. The most commonly used protocol is an initial 45 min of 100 % oxygen at 3 ATA followed by further treatment at 2 ATA for 2 h or until the COHb is less than 10 %. HBO is the treatment of choice in patients who lost consciousness during toxic exposure, who are comatose on admission to hospital and who have persisting neurological abnormalities (Wattel et al. 1996). Complications of HBO in comatose patients include rupture of the eardrum in about 10 % of the patients. Seizures may occur in patients with brain injury who are subjected to high HBO pressures. In a series of 300 consecutive CO-poisoned patients, there was one seizure at 2.45 ATA (0.3 %), nine seizures at 2.80 ATA (2 %), and six seizures at 3 ATA (Hampson et al. 1996). This difference is statistically significant and should be considered when selecting the HBO treatment pressure for CO poisoning. Concern has been expressed that patients with severe CO poisoning, who are intubated and mechanically ventilated, may not achieve adequate hyperbaric oxygenation in a multiplace chamber. In a review of 85 such patients, pO_2 greater than 760 mmHg was documented in 95 % of the patients (Hampson 1998). Such patients should not be excluded from HBO treatment for fear that adequate oxygenation cannot be achieved.

North American HBO facilities were surveyed to assess selection criteria applied for treatment of acute CO poisoning (Hampson et al. 1995). Responses were received from 85 % of the 208 facilities in the United States and Canada which treated a total of 2636 patients in 1992. A majority of facilities treat CO-exposed patients in coma (98 %), transient loss of consciousness (77 %), focal neurologic deficits (94 %), or abnormal psychometric testing (91 %), regardless of carboxyhemoglobin (COHb) level. Although 92 % would use HBO for a patient presenting with headache, nausea, and a COHb value of 40 %, only 62 % of facilities utilized a specified minimum COHb level as the sole criterion for HBO therapy of an asymptomatic patient. It was concluded that when COHb is used as an independent criterion to determine HBO treatment, the level utilized varies widely between institutions. The limitations of some clinical trials were lack of long-term follow-up. Most of these studies comparing HBO with NBO had significant methodological limitations that make it difficult to draw any conclusions about the efficacy of HBO.

As of April 2016, only two clinical trials of use of HBO in CO poisoning that were initiated in 2007 were in progress. The first of these is investigating important clinical outcomes of patients with acute CO poisoning randomized to receive either one or three HBO treatments and is expected to be completed by 2019 (ClinicalTrials.gov Identifier: NCT00465855). HBO will be given 3 ATA for 25 min breathing oxygen, 5 min air breathing, 25 min oxygen breathing, 5 min air breathing, pressure reduced to 2 ATA for 30 min breathing oxygen, 5 min air breathing, and 30 min oxygen breathing. For the second and third HBO sessions, the subject will breathe 100 % oxygen delivered at 2 ATA for 90 min with two 5-min air breathing periods. The second clinical study is a retrospective review of the principal investigator's experience using SPECT brain imaging and HBO therapy in the diagnosis and treatment of nonacute phases of CO poisoning (ClinicalTrials.gov Identifier: NCT00596180). The purpose is to see if the SPECT brain imaging is consistent with the clinical condition and cognitive testing on the patients with neuropsychiatric sequelae. It is expected to be completed by end of 2016.

HBO for CO Intoxication Secondary to Methylene Chloride Poisoning

Methylene chloride (dichlormethane) is converted to CO by cytochrome P450 after it enters the human body. Occupational exposure to dichloromethane is frequent and can result in both acute and chronic toxicity, affecting mostly the central nervous system, directly or through its metabolite, CO. In 1 of the earliest series of 12 cases of methylene chloride poisoning from a single exposure, 9 required HBO treatment and made a good recovery (Youn et al. 1989). The authors observed that CO derived from methylene chloride has an effective half-life 2.5 times that of exogenously inhaled CO. In the case of methylene chloride poisoning, tissue levels of CO continue to rise after exposure, whereas in CO poisoning, the CO levels begin to fall after the exposure is terminated. The practical implication of this observation is that patients with methylene chloride poisoning should be treated adequately with HBO and observed for 12–24 h after exposure. Bilateral hypoacusis developing after accidental exposure to methylene chloride has been reported to improve following 25 days treatment with HBO (Bonfiglioli et al. 2014).

Treatment of CO Poisoning in Pregnancy

In the past, pregnancy was considered to be a relative contraindication for the use of HBO, because of the possible toxic effects of oxygen on the fetus. Dangers of hyperoxic exposure to the fetus have been demonstrated in animals. However, these experimental exposures exceeded the time and pressures routinely used in clinical therapy. If 100 % oxygen given to pregnant women with CO intoxication, it should be prolonged to five times what the mother needs, because of the slow elimination of CO by the fetus. A 17-year-old pregnant woman with CO intoxication (COHb 47.2 %) at 37 weeks of gestation was treated by using HBO at 2.4 ATA for a 90-min treatment resulting in recovery and produced a healthy baby at full-term normal delivery (Van Hoesen et al. 1989). If the mother had been left untreated, considerable morbidity would have been anticipated for the mother as well as for the fetus. HBO treatment for acute CO poisoning in pregnant women is usually well tolerated without any hazards to the fetus or the mother. Results of the first prospective, multicenter study of acute CO poisoning in pregnancy showed that severe maternal CO toxicity was associated with significantly more adverse fetal cases when compared to mild maternal toxicity (Koren et al. 1991). Because fetal accumulation of CO is higher and its elimination slower than that in the maternal circulation, HBO decreases fetal hypoxia and improves outcome. Based on the available clinical evidence, the following recommendations are made for the treatment of CO poisoning during pregnancy:

- Administer HBO therapy if the maternal COHb level is above 20 % at any time during the exposure.
- Administer HBO therapy if the patient has suffered or demonstrated any neurological signs, regardless of the COHb level.
- Administer HBO therapy if signs of fetal distress are present, that is, fetal tachycardia, decreased beat-to-beat variability on the fetal monitor, or late decelerations, consistent with the COHb levels and exposure history.
- If the patient continues to demonstrate neurological signs or signs of fetal distress 12 h after initial treatment, additional HBO treatments may be indicated.
- Treatment requires HBO sessions of a longer duration for fetal CO elimination than in the nonpregnant patients (Friedman et al. 2015).

It is generally agreed that oxygen therapy should be offered in all cases of CO poisoning, especially if there are maternal symptoms during exposure (Bothuyne-Queste et al. 2014). In addition, a fetal echography directed on the cephalic pole and even a fetal MRI should also be done 3 weeks after exposure. A prospective single-center cohort study spanning 25 years (1983–2008) included all pregnant women living in the Nord-Pas-de-Calais region of France who received HBO for CO poisoning and who gave birth to a living child (Wattel et al. 2013). There were no significant psychomotor or height/weight sequelae in those exposed to HBO treatment. Therefore, no specific follow-up of the children is necessary if their neonatal status is normal.

Treatment of Smoke Inhalation

Smoke inhalation involves multiple toxicities and pulmonary insufficiency, as well as thermal and chemical injury. CO intoxication is the most immediate life-threatening disorder in such cases. As a practice guideline, the following patient groups in smoke inhalation injury should be directed by rescue personnel to an emergency service with a hyperbaric facility:

- Those who are unconscious
- Those who are responsive but combative
- Those not responding to verbal instructions or painful stimuli.

If the patient meets these criteria, 100 % oxygen is administered initially during transport to a hyperbaric emergency medical center. If the COHb is over 20 % and the surface burns are covered less than 20 % of the patient's body, the patient should be treated initially with HBO and then transferred to a burn center, unless the burn service is located in the hyperbaric facility itself. HBO is given at 2.8 ATA for 46 min using 100 % oxygen. Patients with surface burns more extensive than 10 % should be treated initially at a burn center.

Experimental pulmonary edema caused by smoke inhalation is lessened by HBO. This may be the explanation of benefit of HBO on respiratory insufficiency associated with smoke inhalation and CO poisoning. Administration of HBO 2.8 ATA for 45 min inhibits adhesion of circulating neutrophils subsequent to smoke inhalation in rats whether used in a prophylactic manner before smoke inhalation, or as treatment immediately after the smoke insult. However, the beneficial effect appears related to inhibition of neutrophil adhesion to the vasculature rather than prevention of CO poisoning.

Prevention and Treatment of Late Sequelae of CO Poisoning

Several reports indicate that the incidence of secondary syndromes is reduced by adequate treatment with HBO in the acute stage of CO poisoning. Empirical overtreatment has been used in the belief that it would prevent late sequelae. The half-life of CO bound with cytochrome a3 oxidase, which is the determining factor for late sequelae, is not known. Further research is required to evaluate the CO bound to cytochrome a3 oxidase, so that the necessary duration of HBO treatment can be determined more realistically. HBO has been used for the treatment of late sequelae of CO poisoning. Patients with severe CO poisoning who have abnormalities on brain imaging that persist after HBO treatment are more likely to develop neuropsychiatric sequelae. Cognitive deficits demonstrated at time of assessment have been successfully reversed by HBO, despite the delay between the exposure and treatment. Controlled clinical trials have shown that incidence of delayed neurologic sequelae (DNS) in a group of patients acutely poisoned with CO decreases with HBO but not NBO treatment. In patients with CO-induced akinetic mutism and cortical as well as subcortical lesions, improvement in rCBF correlated well with functional recovery after HBO treatment (Chen et al. 2016).

Controversies in the Use of HBO for CO Poisoning

Even those who recognize the value of HBO question its role in CO poisoning, because there are no definite correlations of clinical manifestations with COHb levels, and COHb levels are not a definite guide for therapy. There is a particularly poor correlation between carboxyhemoglobin levels and neurological presentation. Neurological effects are due to unmeasured tissue uptake of CO, which increases during hypoxia because of competition between CO and oxygen at the oxygen-binding sites on hemoproteins. The efficacy of HBO therapy cannot be ascribed to hastened dissociation of carboxyhemoglobin. Additional mechanisms of action of HBO found in studies in animals include:

- Improved mitochondrial oxidative metabolism
- Inhibition of lipid per oxidation
- Impairment of adherence of neutrophils to cerebral vasculature.

Randomized controlled trials have shown that HBO is the only effective therapy for acute CO poisoning if delayed neurologic sequelae are to be minimized. NBO should not be used between multiple HBO treatments, as this can contribute to oxygen toxicity.

Review of all the available evidence indicates that HBO has a definite place in the management of CO poisoning. COHb levels cannot be used as a guide for treatment as they do not correlate with the clinical severity of CO poisoning. The following approach is recommended for HBO treatment for CO poisoning:

- Patients with severe poisoning must receive HBO regardless of their COHb levels.
- Pregnant patients must be treated with HBO regardless of signs and symptoms.
- Administration of more than one course of HBO treatment to those who remain in coma remains controversial.

There is some controversy regarding the pressure of HBO. Use of pressures between 2.5 and 3 ATA seems appropriate for CO poisoning. Mg^{2+}, a physiological calcium antagonist, helps in the prevention of late sequelae of CO poisoning by blocking cellular calcium influx.

Cyanide Poisoning

Cyanide is one of the most rapidly acting and lethal poisons known. Cyanide exists as either a gas or as the liquid hydrogen cyanide (HCN), also known as prussic acid. It is one of the smallest organic molecules that can be detected: inhalation of as little as 100 mg of gas can cause instantaneous death. An oral dose of the sodium or potassium salt (lethal dose 300 mg) acts more slowly; symptoms may not appear for several minutes and death may not occur for 1 h. Cyanide poisoning is mostly suicidal, but exposure can occur in the electroplating industry, in laboratory procedures, and through smoke inhalation in fires. Propionitrile, a substituted aliphatic nitrile commonly used in manufacturing industry, is capable of generating cyanide. Cyanogenic glycosides are found in several plant species, including apricot kernels and bitter almonds. The iatrogenic source is sodium nitroprusside, which is used as a vasodilator and as a hypotensive agent. Cyanide is a metabolite of nitroprusside, and toxicity results from rapid infusion, prolonged use, or renal failure.

Pathophysiology

Cyanide combines with cytochrome-a3-oxidase and exhibits a great affinity for oxidized iron (Fe^{3+}). This complex inhibits the final step of oxidative phosphorylation and halts aerobic metabolism. The patient essentially suffocates from an inability to use oxygen.

Clinical Features of Cyanide Poisoning

Signs and symptoms of acute cyanide poisoning reflect cellular hypoxia and are often nonspecific. The central nervous system is the most sensitive target organ with initial stimulation followed by depression.

Laboratory Diagnosis

Blood cyanide levels are useful in confirming toxicity, but treatment has to be initiated before the results of this test are available. Changes in ECG and EEG are nonspecific.

Treatment

The basic treatment of cyanide poisoning is chemical (Cyanide Antidote Kit, Eli Lilly & Co). The object is to bind the cyanide in its harmless form as a stable cyanmethemoglobin by giving sodium nitrite. Cyanide is later liberated by dissociation of cyanmethemoglobin. To convert this to thiocyanate, a harmless substance, intravenous sodium thiosulfate is given. Theoretically, hydroxocobalamin is promising as antidote for cyanide poisoning because cobalt compounds have the ability to bind and detoxify cyanide. Limited data on human poisonings with cyanide salts suggest that hydroxocobalamin is an effective antidote; data from smoke inhalation are less clear-cut (Thompson and Marrs 2012). The rate of absorption may be greater with inhaled hydrogen cyanide and the recommended slow intravenous administration of hydroxocobalamin may severely limit its clinical effectiveness in these circumstances. Limitations of chemical treatment indicate the need for a supplemental approach and use of HBO has been explored for this indication. Acute cyanide poisoning in rats, combined administration of hydroxocobalamin and HBO has a beneficial and persistent effect on the disturbed cerebral metabolism due to cyanide intoxication (Hansen et al. 2013).

Rationale for Use of HBO in Cyanide Poisoning

Theoretically it appears unlikely that HBO would exert its effect in cyanide poisoning by competing with cyanide at a receptor site in cytochrome-a3-oxidase. Possible mechanisms for the positive effect of HBO are as follows:

- The equation "cytochrome oxidase + cyanide = cytochrome oxidase cyanide" is pushed to the left by high pO_2 levels.
- Increased detoxification of cyanide by elevated oxygen pressures.
- Sufficient cellular respiration may continue via cyanide insensitive pathways under hyperbaric conditions to counteract effects of hypoxia.

Animal experimental studies have shown HBO to be effective in cyanide poisoning. There are several anecdotal reports of patients with cyanide poisoning in whom HBO was useful for treatment.

Hydrogen Sulfide Poisoning

Hydrogen sulfide (H_2S) is a highly toxic, inflammable, colorless gas, readily recognized by its characteristic odor of "rotten eggs." The mechanism of toxicity is similar to that of cyanide and CO poisoning. Hydrogen sulfide is a mitochondrial toxin and inhibits cellular aerobic metabolism. Therapies for toxic exposures include removal from the contaminated environment, ventilation with 100 % oxygen, and nitrite therapy if

administered immediately after exposure. The rationale for the use of HBO in H_2S poisoning is that nitrates aid the conversion of hemoglobin to methemoglobin. The latter, by binding free sulfide ions, spares intracellular cytochrome oxidase.

In rats poisoned with LD75 hydrogen sulfide, pure oxygen at 1 ATA was effective in preventing death, but oxygen at 3 ATA was more effective (Bitterman et al. 1986). The best therapy was the combination of oxygen at 3 ATA with sodium nitrite. The clinical usefulness of HBO in H2S poisoning is based on the relief of cerebral edema and protection of the vital organs from hypoxia. Several case reports have shown that HBO treatment is successful in treating H_2S poisoning. Five patients with severe H_2S poisoning were treated successfully with HBO in combination with the use of nitrates (Hsu et al. 1987). Delayed neurologic toxicity from H_2S was treated successfully in a patient by using HBO 3 ATA for 90 min during the initial treatment with significant improvement (Pontani et al. 1998). Daily treatments at 2.4 ATA were continued and neurological deficits resolved completely in 3 days. HBO therapy was used successfully in the management of H_2S toxicity in patients who had not responded to NBO (Belley et al. 2005).

Carbon Tetrachloride Poisoning

Carbon tetrachloride (CCl_4) poisoning is not an uncommon occurrence in clinical practice. In moderate cases, the clinical course is benign. When severe hepatorenal injury occurs, the prognosis is grave because of hepatic insufficiency.

Although ischemic anoxia can damage the sinusoidal capillaries, the popular theory of CCl_4-induced hepatic injury is based on free radicals. CCl_4 exerts its toxicity through its metabolites, including the free radicals CCl_3 and CCl_3OO. Oxygen strongly inhibits the hepatic cytochrome P-450-mediated formation of CCl_3 from CCl_4 and promotes the conversion of CCl_3 to CCl_3OO. Both of these free radicals can injure the hepatocyte by lipoperoxidation and by binding covalently to the cell structures. Under conditions of hypoxia most of the free radicals are CCl_3, whereas under hyperoxia most are CCl_3OO. A reduced glutathione (GSH)-dependent mechanism can protect against CCl_3OO but not against CCl_3, so there is an advantage in using HBO in CCl_4 poisoning. HBO at 2 ATA given 6 h after administration of CCl_4 to rats has been shown to improve the survival rate and inhibit the in vivo conversion of CCl_4 to its volatile metabolites $CHCl_3$ and CO_2. The predominant effect is on CO_2, which is quantitatively the more significant metabolite. Most of the animal experimental studies show that the mortality of the HBO-treated animals is lowered and there is less impairment of the liver function tests. Conclusions of controlled studies of the effects of HBO on rats poisoned with CCl_4 are as follows:

- HBO improves survival from CCl_4 poisoning.
- The response rate is time related. There is a better survival rate in animals treated within 1 h of poisoning compared with those treated after 4 h.
- The improved survival with HBO is the result of decreased hepatotoxicity.

Although the mechanism of the protective effect of HBO on the liver is not well understood, it has been used successfully in patients with CCl_4 poisoning. CCl_4 poisoning is rare these days as this toxic solvent is no longer used in the industry. However, when a case occurs there is no satisfactory conventional treatment. HBO has been shown to be useful, and free radical scavengers such as vitamin E seem to be effective only if given before or with HBO.

Methemoglobinemias

The reversible oxygenation and deoxygenation of Hb at physiological partial pressures of oxygen require that the heme iron of deoxyhemoglobin remain in the Fe^{2+} form. In methemoglobinemias iron is already oxidized to the Fe^{3+} form, rendering the molecule incapable of binding oxygen. When Hb is oxygenated during the process of respiration, an electron is transferred from the Fe^{+} atom to the bound oxygen molecule. Thus, in oxyhemoglobin, the iron possesses some of the characteristics of the Fe^{3+} state, whereas the oxygen takes on the characteristic of the superoxide (O_2^-) anion, which is a free radical.

Methemoglobinemia results from exposure to oxidizing substances such as nitrates or nitrites. Many drugs and chemicals have toxic effects on the Hb molecule and produce methemoglobinemia, e.g., nitrobenzene and nitrites. The methemoglobinemia is usually asymptomatic. As methemoglobin levels increase, patients show evidence of cellular hypoxia in all tissues. Death usually occurs when methemoglobin fractions approach 70 % of total hemoglobin. The diagnosis depends upon the demonstration of methemoglobin and the causative agent.

Treatment

Methylene blue remains an effective treatment for methemoglobinemia, but HBO can be a useful adjunct. Comparison of antagonism to the lethal effects of sodium nitrite displayed by various combinations of methylene blue, oxygen, and HBO shows that HBO is the most effective agent, with or without methylene blue. Patients with drug-induced methemoglobinemia (methemoglobin levels 50–70 %), who are admitted in a comatose state, recover following treatment

with HBO at 2.2 ATA as methemoglobin decreases at a rate of 5–8 % per hour of exposure to HBO. A patient, who was accidentally intoxicated with isobutyl nitrite by a threefold lethal dose, a blood exchange transfusion was performed under HBO and the patient recovered (Jansen et al. 2003). In a young male suffering from severe methemoglobinemia of 68 % after consumption of nitrites ('poppers') in association with considerable ethanol consumption, toluidine blue was administered as first-line antidotal therapy immediately followed by HBO therapy (Lindenmann et al. 2015). The result was enhanced reduction of methemoglobin, and rapid tissue reoxygenation by the oxygen dissolved in plasma, independent of the degree of methemoglobinemia.

Miscellaneous Poisons

Organophosphorus Compounds

Organophosphorus compounds have been used as pesticides and as chemical warfare nerve agents such as soman and sarin. The mechanism of toxicity of organophosphorus compounds is the inhibition of acetylcholinesterase, resulting in accumulation of acetylcholine and the continued stimulation of acetylcholine receptors. The management of poisoning with organophosphorous compounds consists of atropine sulfate and blood alkalinization with sodium bicarbonate and also magnesium sulfate as an adjunctive treatment. Neurotoxicity is a serious concern. Experiments on rabbits have shown that accumulated poisoning with paraoxon leads to development of hypoxia with a rapid fall in oxygen tension in the muscles and the venous blood, and a shift of the acid–base balance toward the uncompensated metabolic acidosis. HBO at 3 ATA for 2–4 h considerably prolongs the survival of the poisoned animals. Role of HBO in potential management of organophosphorus poisoning with neurotoxicity requires further investigation.

Conclusions: Poisoning Other Than with CO

There are only anecdotal reports of the use of HBO in cases of cyanide, hydrogen sulfide, and CCl_4 poisoning and methemoglobinemias; in situations like this one cannot have controlled studies. In a critical case HBO should be considered as a supplement to conventional methods. The liver is the target organ for injury caused by toxins that are activated by drug-metabolizing enzymes to reactive molecular intermediates. These intermediates cause cell injury by forming chemical bonds with cell proteins, nucleic acid, and lipids, and by altering the biological function of these molecules. The hepatocyte, in particular, is affected by toxic drug injury because it is the main site in the body where these toxins are activated. HBO has a marked effect on toxic liver damage by blocking the injury caused by toxins activated by oxidative biotransformation. HBO has no effect on damage caused by toxins that do not require biotransformation to induce liver damage. HBO may increase the hepatic necrosis induced by compounds which undergo oxidative biotransformation (e.g., thioacetamide, aflatoxin, dimethylnitrosamine), but this can be overcome and inhibited by prolonged hyperoxia.

References

Abramovich A, Shupak A, Ramon Y, Shoshani O, Bentur Y, Bar-Josef G, et al. Hyperbaric oxygen for carbon monoxide poisoning. Harefuah. 1997;132:21–4, 71.

Adamiec L, Kaminski B, Kwiatkowski H, et al. Hyperbaric oxygen in treatment of acute carbon monoxide poisoning. Anaesth Resusc Intensive Ther. 1975;3:305–13.

Annane D, Chadda K, Gajdos P, Jars-Guincestre MC, Chevret S, Raphael JC. Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials. Intensive Care Med. 2011;37:486–92.

Beard RR, Wertheim GA. Behavioral impairment associated with small doses of carbon monoxide. Am J Public Health. 1967;57:2012–22.

Belley R, Bernard N, Côté M, Paquet F, Poitras J. Hyperbaric oxygen therapy in the management of two cases of hydrogen sulfide toxicity from liquid manure. CJEM. 2005;7:257–61.

Bernard C. Lecons sur les effets des substances toxiques et medicamenteuses. Paris: Bailliere; 1857.

Bitterman N, Talmi Y, Lerman A, Melamed Y, Taitelman U. The effect of hyperbaric oxygen on acute experimental sulfide poisoning in the rat. Toxicol Appl Pharmacol. 1986;84:325–8.

Bonfiglioli R, Carnevali L, Di Lello M, Violante FS. Bilateral hearing loss after dichloromethane poisoning: a case report. Am J Ind Med. 2014;57:254–7.

Bothuyne-Queste E, Joriot S, Mathieu D, Mathieu-Nolf M, Favory R, Houfflin-Debarge V, et al. Ten practical issues concerning acute poisoning with carbon monoxide in pregnant women. J Gynecol Obstet Biol Reprod (Paris). 2014;43:281–7.

Chance B, Erecinska M, Wagner M. Mitochondrial responses to carbon monoxide toxicity. Ann NY Acad Sci. 1970;174:193–204.

Chen YG, Lin TY, Dai MS, Lin CL, Hung Y, Huang WS, et al. Risk of peripheral artery disease in patients with carbon monoxide poisoning: a population-based retrospective cohort study. Medicine (Baltimore). 2015;94:e1608.

Chen SY, Lin CC, Lin YT, Lo CP, Wang CH, Fan YM. Reversible changes of brain perfusion SPECT for carbon monoxide poisoning-induced severe akinetic mutism. Clin Nucl Med. 2016;41(5):e221–7.

Cho S-H, Lee DH, Yeun DR. Incidence of carbon monoxide intoxication. J Korean Med Assoc. 1986;29:1233–40.

Choi IS. Delayed neurologic sequelae in carbon monoxide intoxication. Arch Neurol. 1983;40:433–5.

Coburn RF. Endogenous carbon monoxide production. N Engl J Med. 1970;282:207–9.

Colignon M, Lamy M. Carbon monoxide poisoning and hyperbaric oxygen therapy. In: Schmutz J, editor. Proceedings of the 1st Swiss symposium on hyperbaric medicine. Basel: Foundation for Hyperbaric Medicine; 1986. p. 51–68.

Ducassé JL, Celsis P, Marc-Vergnes JP. Non-comatose patients with acute carbon monoxide poisoning: hyperbaric or normobaric oxygenation? Undersea Hyperb Med. 1995;22:9–15.

End E, Long CW. HBO in carbon monoxide poisoning. I. Effect on dogs and guinea pigs. J Ind Hyg Toxicol. 1942;24:302–6.

Friedman P, Guo XM, Stiller RJ, Laifer SA. Carbon monoxide exposure during pregnancy. Obstet Gynecol Surv. 2015;70:705–12.

Garrabou G, Inoriza JM, Morén C, Oliu G, Miró Ò, Martí MJ, et al. Mitochondrial injury in human acute carbon monoxide poisoning: the effect of oxygen treatment. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2011;29:32–51.

Gliner JA, Horvath SM, Mihevic PM. Carbon monoxide and human performance in a single and dual task methodology. Aviat Space Environ Med. 1983;54:714–7.

Gorman DF, Clayton D, Gilligan JE, Webb RK. A longitudinal study of 100 cases consecutive admissions for carbon monoxide poisoning to the Royal Adelaide Hospital. Anesth Intensive Care. 1992;20:311–6.

Goulon M, Barois A, Bapin M, Nouailhat F, Grosbuis S, Labrousse J. Intoxication oxycarbonée et anoxie aigue par inhalation de gaz de charbon et d'thydrocarbures. Ann Med Intern (Paris). 1969;120:335–49.

Grinker RR. Parkinsonism following carbon monoxide poisoning. J Neuro Ment Dis. 1926;6:18–28.

Haldane JS. The action of carbonic oxide on man. J Physiol. 1895;18:430.

Hampson NB. Treatment of mechanically ventilated patients poisoned with carbon monoxide: is "hyperbaric oxygenation" achieved. Undersea Hyperbaric Med 1998;25:17 (abstract).

Hampson NB, Dunford RG, Kramer CC, Norkool DM. Selection criteria utilized for hyperbaric oxygen treatment of carbon monoxide poisoning. J Emerg Med. 1995;13:227–31.

Hampson NB, Simonson SG, Kramer CC, Piantadosi CA. Central nervous system oxygen toxicity during hyperbaric treatment of patients with carbon monoxide poisoning. Undersea Hyperb Med. 1996;23:215–9.

Hansen MB, Olsen NV, Hyldegaard O. Combined administration of hyperbaric oxygen and hydroxocobalamin improves cerebral metabolism after acute cyanide poisoning in rats. J Appl Physiol (1985) 2013;115:1254–61.

Heyndrickx A, Scheiris C, Vercruysse A, Okkerse E. Gas chromatographic determination of carbon monoxide in blood and the hyperbaric oxygen treatment in carbon monoxide poisoning cases. J Pharm Belg. 1970;25(3):247–58.

Hsu P, Li HW, Lin YT. Acute hydrogen sulfide poisoning treated with hyperbaric oxygen. J Hyperbaric Med. 1987;2:215–21.

Icme F, Kozaci N, Ay MO, Avci A, Gumusay U, Yilmaz M, et al. The relationship between blood lactate, carboxy-hemoglobin and clinical status in CO poisoning. Eur Rev Med Pharmacol Sci. 2014;18:393–7.

Jain KK. Carbon monoxide poisoning. Green: St. Louis; 1990.

Jain KK. Carbon monoxide poisoning: neurologic aspects. In: Greenamyre JT, editor. Medlink neurology. San Diego: MedLink Corporation; 2016.

Jansen T, Barnung S, Mortensen CR, Jansen EC. Isobutyl-nitrite-induced methemoglobinemia; treatment with an exchange blood transfusion during hyperbaric oxygenation. Acta Anaesthesiol Scand. 2003;47:1300–1.

Jiang J, Tyssebotn I. Normobaric and hyperbaric oxygen treatment of acute carbon monoxide poisoning in rats. Undersea Hyperb Med. 1997;24:107–16.

Kienlen J, Alardo JP, Dimeglio G, et al. Traitement de l'intoxication oxycarbonée par l'oxygène hyperbare—propos de 370 observations. J Med Montpellier. 1974;9:237–43.

Klebs D. Ueber die Wirkung des Kohlenoxyds auf den tierischen Organismus. Arch Path Anat Physiol Klin Med. 1865;32:450–517.

Koren G, Sharav T, Pastuszak A, Garrettson LK, Hill K, Samson I, et al. A multicenter, prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy. Reprod Toxicol. 1991;5:397–403.

Koyama K. Acute experimental carbon monoxide poisoning and hyperbaric oxygenation (HBO). Tokyo Jikeikai Med J. 1976;91:195–215.

Lilienthal JL, Fugitt CH. The effect of low concentrations of carboxyhemoglobin on the "altitude tolerance" of man. Am J Physiol. 1946;145:359–64.

Lindenmann J, Fink-Neuboeck N, Schilcher G, Smolle-Juettner FM. Severe methaemoglobinaemia treated with adjunctive hyperbaric oxygenation. Diving Hyperb Med. 2015;45:132–4.

Mathieu D, Nolf M, Durocher A, Saulnier F, Frimat P, Furon D, et al. Acute carbon monoxide poisoning risk of late sequelae and treatment by hyperbaric oxygen. Clin Toxicol. 1985;23:315–24.

Messier LD, Myers RA. A neuropsychological screening battery for emergency assessment of carbon-monoxide-poisoned patients. J Clin Psychol. 1991;47:675–84.

Mikulka P, O'Donnell R, Heinig P, Theodore J. The effect of carbon monoxide on human performance. Ann NY Acad Sci. 1973;174:409–20.

Mutluoglu M, Metin S, Arziman I, Uzun G, Yildiz S. The use of hyperbaric oxygen therapy for carbon monoxide poisoning in Europe. Undersea Hyperb Med. 2016;43:49–56.

Norkool DM, Kirkpatrick JN. Treatment of acute carbon monoxide poisoning with hyperbaric oxygen: a review of 115 cases. Ann Emerg Med. 1985;14:1168–71.

Ogawa M, Katsurada K, Sugimoto T, Sone S. Pulmonary edema in acute carbon monoxide poisoning. Int Arch Arbeitsmed. 1974;33:131–8.

Pace N, Strajman E, Walker EL. Acceleration of carbon monoxide elimination in man by high pressure oxygen. Science. 1950;111:652–4.

Pineas H. Klinischer und anatomischer Befund eines Falles von CO-Vergiftung. Z Neurol. 1924;93:36–8.

Pontani BA, Warriner RA, Newman RK, et al. Delayed neurologic sequelae after hydrogen sulfide poisoning treated with hyperbaric oxygen therapy. Undersea Hyperb Med 1998;25:10 (abstract).

Putnam TJ, McKenna JB, Morrison LR. Studies in multiple sclerosis. I. The histogenesis of experimental sclerotic plaques and their relation to multiple sclerosis. JAMA. 1931;97:1591–6.

Raphael JC, Elkharrat D, Jars-Guincestre MC, Chastang C, Chasles V, Vercken JB, et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. Lancet 1989;ii:414–9.

Roderique JD, Josef CS, Newcomb AH, Reynolds PS, Somera LG, Spiess BD. Preclinical evaluation of injectable reduced hydroxocobalamin as an antidote to acute carbon monoxide poisoning. J Trauma Acute Care Surg. 2015;79(4 Suppl 2):S116–20.

Sasaki T. One-half clearance time of carbon monoxide hemoglobin in blood during hyperbaric oxygen therapy (OHP). Bull Tokyo Dent Univ. 1975;22:63–77.

Schaad G, Kleinhanss G, Piekarski C. Zum Einfluss von Kohlenmonoxid in der Atemluft auf die psychophysische Leistungsfähigkeit. Wehrmed Mschr. 1983;27:423–30.

Scheinkestel CD, Bailey M, Myles PS, Jones K, Cooper DJ, Millar IL, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. Med J Aust. 1999;170:203–10.

Schrot J, Thomas JR, Robertson RF. Temporal changes in repeated acquisition behavior after carbon monoxide exposure. Neurobehav Toxicol Teratol. 1984;6:23–8.

Schulte JH. Effects of mild carbon monoxide intoxication. Arch Environ Health. 1963;7:524–30.

Sloan EP, Murphy DG, Hart R, Cooper MA, Turnbull T, Barreca RS, et al. Complications and protocol considerations in carbon monoxide poisoned patients who require hyperbaric oxygen therapy. Ann Emerg Med. 1989;18:629–34.

Sluitjer ME. The treatment of carbon monoxide poisoning by the administration of oxygen at high pressure. Springfield: Thomas; 1963.

Smith G, Sharp GR. Treatment of carbon-monoxide poisoning with oxygen under pressure. Lancet. 1960;276:905–6.

Smith G, Ledingham IM, Sharp GR, Norman JN, Bates EH. Treatment of coal-gas poisoning with oxygen at 2 atmospheres pressure. Lancet 1962;i:816–8.

Thom SR. Dehydrogenase conversion to oxidase and lipid peroxidation in the brain after CO poisoning. J Appl Physiol. 1992;73:1584–9.

Thom SR, Taber RL, Mendiguren II, Clark JM, Hardy KR, Fisher AB. Delayed neuropsychologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen [see comments]. Ann Emerg Med. 1995;25:474–40.

Thompson JP, Marrs TC. Hydroxocobalamin in cyanide poisoning. Clin Toxicol (Phila). 2012;50:875–85.

Tirpitz D, Bakyara T. Hyperbare Oxygen bei CO-Intoxikationen. Der Inform Arzt. 1988;8:51–4.

Trouton D, Eysenck HJ. The effects of drugs on behavior. In: Eysenck HJ, editor. Handbook of abnormal psychology. New York: Basic Books; 1961. p. 634–96.

van Hoesen KB, Camporesi EM, Moon RE. Should hyperbaric oxygen be used to treat the pregnant patient for acute carbon monoxide poisoning? JAMA. 1989;261:1039–43.

Wattel F, Mathieu D, Neviere R, Mathieu-Nolf M, Lefèbvre-Lebleu N. L'intoxication au monoxyde de carbone. Presse Med. 1996;25:1425–9.

Wattel F, Mathieu D, Mathieu-Nolf M. A 25-year study (1983-2008) of children's health outcomes after hyperbaric oxygen therapy for carbon monoxide poisoning in utero. Bull Acad Natl Med. 2013;197:677–94; discussion 695–7.

Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med. 2002;347:1057–67.

Weaver LK. Hyperbaric oxygen therapy for carbon monoxide poisoning. Undersea Hyperb Med. 2014;41:339–54.

Yastrebov VE, Kustov VV, Razinkin SM. Effect of a short-term exposure to carbon monoxide high concentrations on man's psychophysiological functions. Kosm Biol Aviakosm Med. 1987;21:47–50.

Youn BA, Kozikowski RJ, Myers RA. The development of treatment algorithm in methylene chloride poisoning based on a multicase experience. Undersea Biomed Res 1989;12(Suppl):20 Abstract #16.

Yun DR, Cho SH. Hyperbaric oxygen treatment in acute CO poisoning. Korean J Prev Med. 1983;16:153–6.