12 Carbon Monoxide and Other Tissue Poisons

K.K. Jain

Hyperbaric oxygenation is a recognized treatment for carbon monoxide (CO) poisoning and has a supplemental role in the treatment of some other tissue poisons. Important sections in this chapter are:

Classification of Tissue Poisons

This chapter deals mainly with the role of hyperbaric oxygenation 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 shown in Table 12.1.

Table 12.1
Classification of Tissue Poisons Where HBO Has Been Used Successfully

1. Action by combination with cytochrome α_3 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

Carbon Monoxide Poisoning

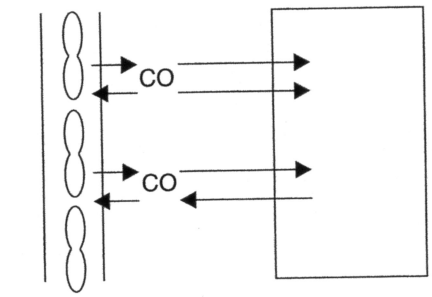
Historical Aspects of CO Poisoning

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 by Pineas (1924), and with parkinsonism by Grinker (1925).

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



$$pCO = \frac{[COHB]\ pO_2}{[O_2HB]}$$

Figure 12.1
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 (after Coburn 1970).

CO Body Stores

Most of the body deposits of CO are found in the blood chemically bound to Hb. However, 10 to 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 (Figure 12.1), 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:

$$\frac{COHb}{O_2Hb} = K \times \frac{pC=_2}{pO_2}$$

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.

Biochemical Effects of CO on Living Organisms

Carbon monoxide inhibits oxygen transport, availability, and utilization; its biochemical effects are summarized in Table 12.2. 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

Table 12.2
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 α_3 oxidase P-450

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 cellular energy metabolism (Figure 12.2). These basic mechanisms have been

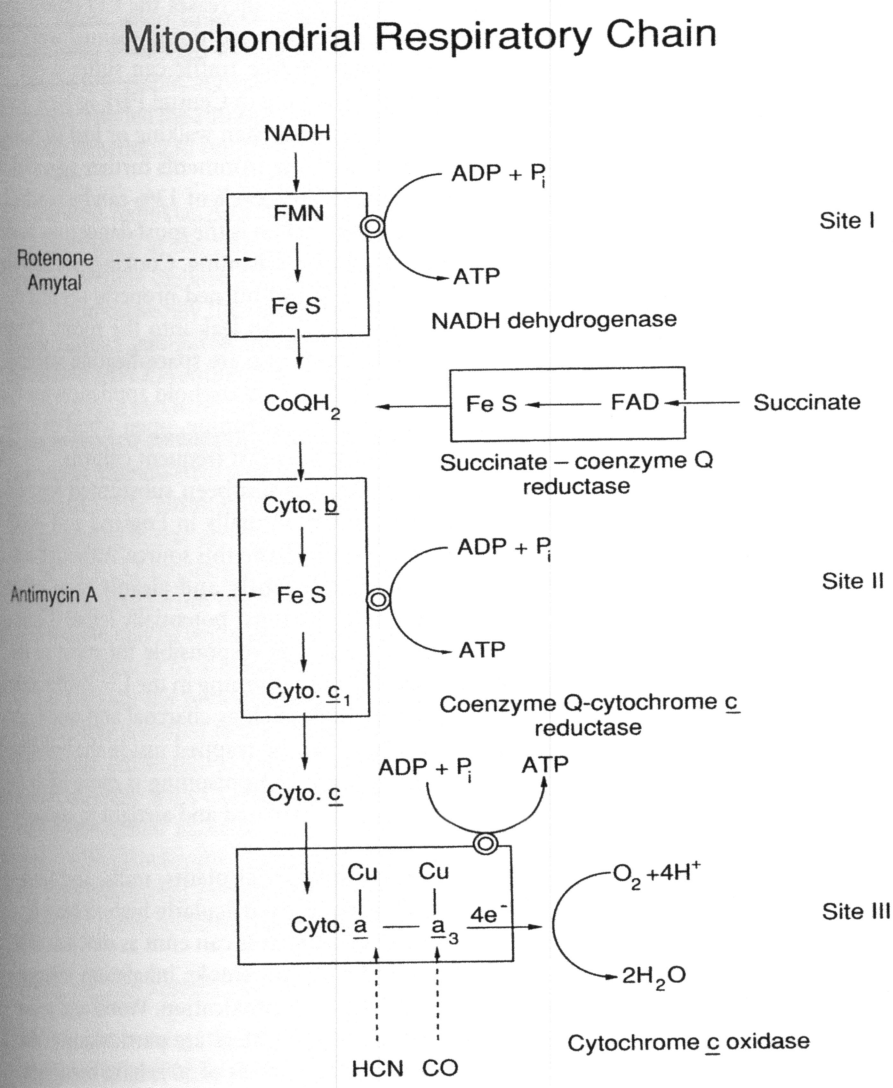


Figure 12.2
The mitochondrial respiratory chain indicating sequence of electron transport, three sites of energy coupling (oxidative phosphorylation), and location of action of CO (Piantadosi 1987).

confirmed by 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

CO is the leading cause of death by poisoning in the United States. More than 4000 persons die annually from CO poisoning and 10,000 receive emergency treatment for exposure to CO fumes. In addition to this, CO accounts for more than half of the approximately 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% to 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 12.3
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 12.3. 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 to 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 approximately 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 to 40 mg/ml can raise COHb 1.5- to 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 to 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 work of Lim *et al* (1995) with spectroscopic techniques which provides 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 authors to conclude 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. These authors compared the effect in dogs of anoxia induced by 0.5% CO ventilation with that induced by breathing low oxygen mixtures. They 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 shown in Table 12.4.

Table 12.4
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 $V_{2\,max}$

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

Acute Effects on the Heart

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 to 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

Table 12.5
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

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 to 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 to 30%. These changes are reversible after withdrawal from exposure to CO. Various abnormalities in the ECG reported in CO poisoning are summarized in Table 12.5. 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 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.

Hemorrheological 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 intraalveolar 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 leads 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 a patient who died following CO poisoning (Balzan *et al* 1993).

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 2003c).

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:

- In immediate death after CO poisoning, there are petechial hemorrhages throughout the brain, but no cerebral edema
- In patients who die within hours or days after poisoning, cerebral edema is present. There is necrosis of the globus pallidus and substantia nigra.
- 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 carbon monoxide poisoning (Sohn *et al* 2000).

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. Putnam *et al* (1931) showed that CO damages the blood-brain barrier, particularly in the cerebral white matter, where the venous drainage pattern predisposes to focal edema. 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 rat brain cortex has been observed by reflectance spectroscopy, and this is a possible explanation of a non-hypoxic mechanism of CO toxicity (Brown & Piantadosi 1990). Zhang and Piantadosi (1992) have studied the generation of partially reduced oxygen species (PROS)in the brains of rats subjected to 1% CO for 30 min and then reoxygenated on air for 0 to 180 min. They propose that PROS generated in the brain after CO hypoxia originate primarily from mitochondria and contribute to CO-mediated neuronal damage during reoxygenation after severe CO intoxication. CO-mediated brain injury is a type of postischemic reperfusion phenomenon and xanthine-oxidase-derived reactive oxygen species

are responsible for lipid peroxidation (Thom 1992). These observations may provide an explanation for a number of poorly understood clinical observations regarding CO poisoning, particularly the neuropsychological effects at concentrations below 5%. Nabeshima *et al* (1991) have shown that delayed amnesia induced by CO exposure in mice may result from delayed neuronal death in the hippocampal CA1 subfield and dysfunction of the acetylcholinergic neurons in the frontal cortex, the striatum, and/or the hippocampus. In studies on mice 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. A recent finding that CO may act as a putative neural messenger by interacting with the enzyme guanylyl cyclase (Verma *et al* 1993), may provide an important clue to the pathomechanism of CO toxicity. Endogenously formed carbon monoxide arises from the enzymatic degradation of heme oxygenase to release a molecule of CO, which 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 (Johnson & Johnson 2000).

Relative cerebral hyperperfusion has been observed during CO-hypoxia and is considered to be due to a fall in the P_{50} (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 more than two-fold in anesthetized rabbits exposed to 1% CO, despite a 28% fall of mean arterial blood pressure (Meyer-Witting *et al* 1991). 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 (Sinha *et al* 1991).

Table 12.6
Degree of Severity of CO Poisoning, COHb Levels, and Clinical Features

Severity	COHb level	Clinical features
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
	30%–40%	Cardiac disturbances, muscle weakness Vomiting, reduced awareness
Severe	40%–50%	Fainting on exertion Mental confusion
	50%–60%	Collapse convulsions Paralysis
Very severe	60%–70%	Coma, frequently fatal within a few minutes
	Over 70%	Immediately fatal Respiratory and cardiac arrest

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 shown in Table 12.6. 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 12.7. 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 are late sequelae (listed in Table 12.8); 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.

Choi (1983) reported that 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. The lucid interval before appearance of neurological symptoms was 2 to 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

Table 12.7
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) 850 ppm – 90 min (50% COHb) 1200 ppm – 90 min (60% COHb)	Disruption of the rate at which the rats acquired a chain of response
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% – +0.5%)	Impairment in a two-dimensional compensatory tracking task combined with mental arithmetic. Symptoms of mild CO intoxication at COHb levels of 10%

Table 12.8
Delayed Neuropsychological Sequelae of CO Poisoning

- Akinetic mutism
- Apallic syndrome
- Apraxia, ideomotor as well as constructional
- Ataxia
- Convulsive disorders
- Cortical blindness
- Deafness (neural)
- Delerium
- 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

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.

Clinical Diagnosis of CO Poisoning

Few symptoms of CO poisoning occur at COHb concentrations of less than 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 CH2OPD2 mnemonic (Community, Home, Hobbies, Occupation, Personal habits, Diet and Drugs) is helpful in obtaining an environmental exposure history (Abelsohn *et al* 2002).

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 to 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
   Direct measurement of the COHb levels
   Measurement of CO released from the blood
   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
   Enzymes: creatine kinase, lactate dehydrogenase, SGOT, SGPT
   Serum glucose
5. Complete blood count
6. Electroencephalogram
7. Electrocardiogram
8. Brain imaging: CT scan, MRI, SPECT
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 tomethane. The values are given as parts per million (ppm) in the range of 0 to 500.

Clinical Significance of Monitoring Blood COHb. Fang *et al* (1986) monitored COHb in 192 Patients with acute CO poisoning:

1. Blood COHb greater than 10% has diagnostic significance and, COHb greater than 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 sliderule 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.

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 were evaluated as an objective, widely available and rapid test of brain dysfunction in a group of 11 patients in the acute phase (first 6 h) of mild-to-moderate CO poisoning (Emerson & Keilor 1998). N75 and P100 latency results were compared to nearly simultaneously obtained standard CO Neuropsychological Screening Battery (CONSB). Patients were sought in whom treatment decisions concerning HBO vs. normobaric oxygen (NBO) might be difficult, and were excluded from the study if confounding variables existed for CONSB or PSVEP. N75 and P100 latencies were also obtained after completion of NBO_2 or HBO_2 therapies. Only one patient, judged clinically to have the mildest poisoning in the series, had significantly abnormal initial PSVEP latencies. This patient's simultaneous CONSB was normal and the abnormal PSVEP latencies failed to normalize post treatment with NBO2. PSVEP latencies were not found to be a sensitive screening tool for treatment decision making in a group of acutely CO poisoned patients where treatment decisions might be difficult.

Neuropsychological Testing

It has long been known that CO poisoning has a spectrum of effects on cognitive functioning. Neuropsychological impairments in carbon monoxide-poisoned subjects include memory, intellectual, executive, and visuospatial defects (Rahmani *et al* 2006).Various psychological tests have been designed for patients with CO poisoning. One neuropsychological screening battery for use in assessment of such patients consists of 6 tests: general orientation, digit span, trail making, digit symbols, aphasia, and block design (Messier & Myers 1991). These tests can be administered in an emergency by a non-psychologist 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.

McNulty *et al* (1997) have investigated the effects of CO poisoning on short-term verbal memory, both rote and context aided. Impairment was measured before and after HBO treatment. Twenty-six patients who had been admitted for emergency treatment after exposure to significant CO poisoning were tested using a measure of short-term recall for word lists with no or varying degrees of internal context-aided structure. Impairment of context-aided memory (but not rote memory) has been previously reported to be associated with low relative frontal volume in psychiatric patients. Carbon monoxide poisoning was significantly associated with impairment of context-aided memory, with the degree of pretreatment impairment predicting the number 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, The are described in the following pages and a comparison of the value of various techniques is shown in Table 12.9

CT Scan. The CT scan is the most widely used neuroimaging method for patients with CO poisoning. Common CT findings 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. Post-contrast CT offers an advantage when non-contrast CT is normal in CO poisoning. Acute transient hydrocephalus has been observed in acute CO poisoning in one case and this resolved

Table 12.9
Comparative Value of Brain Imaging Studies in CO Poisoning

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

6 weeks later (Prabhu *et al* 1993). 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 three days after exposure to CO).

Magnetic Resonance Imaging (MRI). 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.

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. In one case with persistent impaired responsiveness for one year after CO poisoning, PET showed a 20% decrease of rCBF and rCMRG in the frontal cortex, whereas MRI and CT scans had shown only lesions of basal ganglia (Shimosegawa *et al* 1992). Diffusion tensor MRI is a promising technique to characterize and track delayed encephalopathy after acute carbon monoxide poisoning (Villa *et al* 2005).

Most of the knowledge of MRI findings in car monoxide poisoning is based on case studies of pati in the subacute or chronic phase following exposure. l studies in the acute phase of carbon monoxide poisor show that, although the globus pallidus is the commo site of abnormality in the brain, the effects are w spread. The white matter hyperintensities seen on MR not correlate with carbon monoxide poisoning sever In one study white matter hyperintensities occurrec both the periventricular and the centrum semiovale gions but only those in the centrum semiovale were s nificantly associated with cognitive impairments (Park son 2002).

Single Photon Emission Computed Tomograp (SPECT). This can provide imaging of cerebral perfusic Diffuse hypoperfusion has been shown in both the gray a the white matter of the cerebral cortex in CO poisonin SPECT is helpful in documenting the increase in cerebr perfusion along with clinical improvement as a result HBO treatment. Cerebral vascular changes may be the po sible cause of hypoperfusion in patients with CO poisonir and there is a good correlation between the clinical ou come and the findings of SPECT. SPECT can be used fc predicting and evaluating the outcome of delayed neurc logical sequelae after CO poisoning. SPECT performed o a patient 10 days after CO poisoning showed hypoperfu sion which preceded the onset of neurological sequelae b 20 days (Choi & Lee 1993). In comparison to traditiona brain imaging techniques, 99 mTc-HMPAO brain imagin with fanbeam SPECT in combination with surface 3-di mensional display is a better tool for early detection o 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 Chapter 19). The case history and SPECT scans of one of the patients are reproduced in Chapter 19.

Magnetic Resonance Spectroscopy (MRS). MRS is a non-invasive method that provides information about brain metabolites such as N-acetyl aspartate, choline and creatine. MRS can reflect the severity of delayed sequeale of CO poisoning precisely. Increase in choline in the frontal lobes indicates progressive demyelination. Appearance of lactate and decrease in N-acetylaspartate 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 (Terajima *et al* 2008).

Table 12.10
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 12.11
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

General Management of CO Poisoning

General guidelines for the management of CO poisoning are shown in Table 12.10. Once the patient is removed from CO environments, CO slowly dissociates from the Hb and is eliminated. The half-life of the COHb is shown in Table 12.11. 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 using 100% oxygen. 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 triage chart for handling patients with CO poisoning is shown in Figure 12.3. 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. Mg^{2+} can be used; the usual dose is 20 to 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,

Table 12.12
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 vs 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.

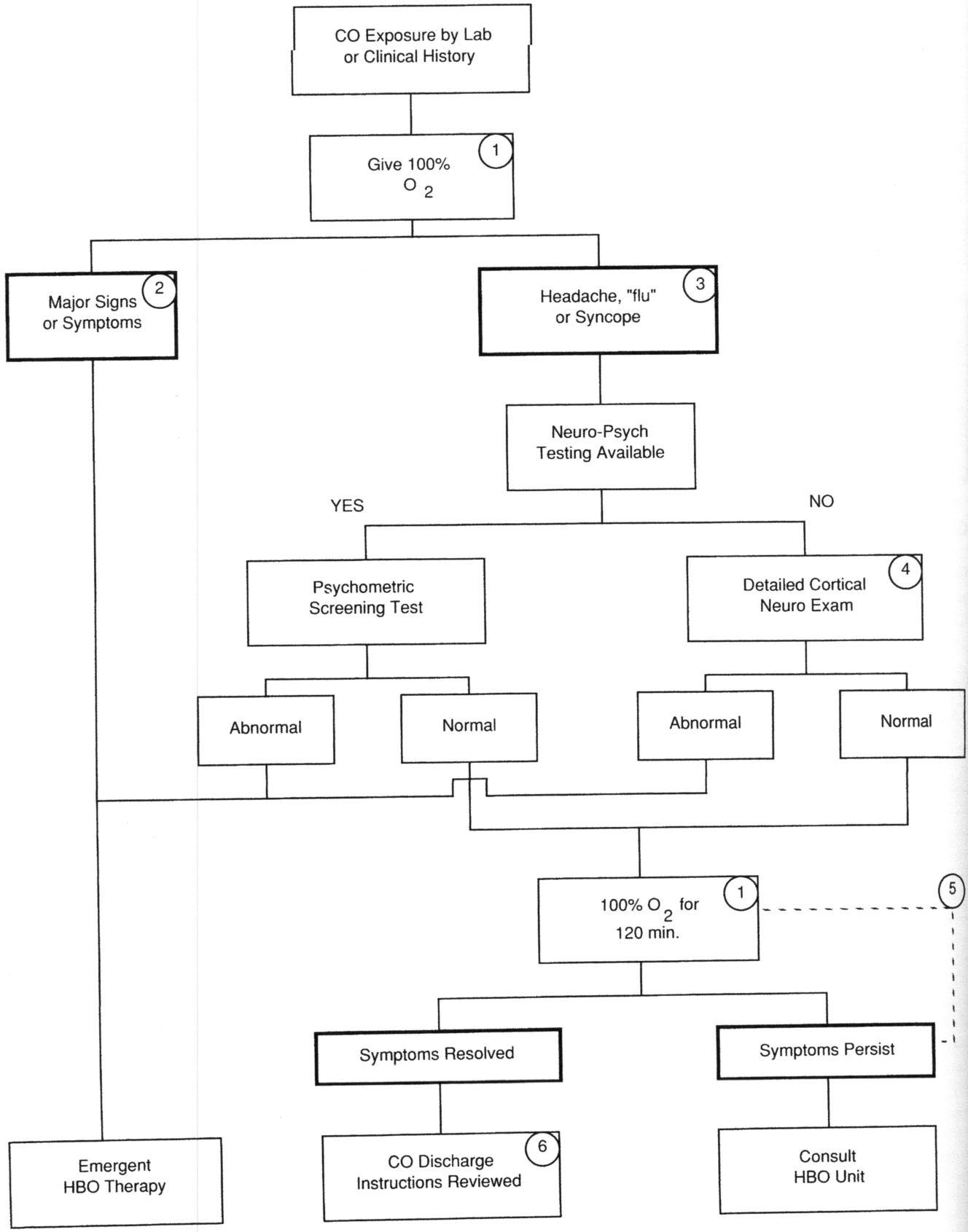


Figure 12.3
Carbon monoxide triage decision chart (Reproduced from Kindwall & Goldmann 1988, *Hyperbaric Medical Procedures*, Milwaukee, St. Luke's Hospital, by permission).

Notes for Figure 12.3 (see opposite)

1. O_2 should be delivered by tight-fitting system such as Scott mask, anesthesia mask, endotracheal tube, or CPAP mask.
2. Major signs and symptoms include: abnormal EKG, metabolic acidosis, lab or clinical findings of pregnancy, chest pain, confusion, disorientation, personality change, lethargy, or drug overdose with mental status change.
3. Headache may be severe and mimic intracranial hemorrhage in severity. Any suggestion of postsyncopal neurological dysfunction is a major sympton.
4. Detailed cortical neurological examination should include: general orientation, phone number, address, date of birth, serial 7s, digit span, forward and backward spelling of three and four-letter words, and short-term memory.
5. OPTION: One repeat 2 h O_2 cycle (4 h of surface O_2 total) is permissible. If symptoms persist beyond this point, con-sultation and possible referrals is indicated.
6. Follow-up of CO exposed patients is critical. Recurrent or indolent symptoms or family observation of abnormalities should be reevaluated as they appear.

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.

Rationale for Oxygen Therapy (Normobaric and Hyperbaric) 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. 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 $HbO_2 + CO = HbCO + O_2$, 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 (Thom *et al* 2006).

Experimental Evidence

The results of some experimental studies of the use of HBO in CO poisoning are shown in Table 12.12.

Clinical Use of HBO in CO Poisoning

Guidelines for the use of HBO versus normobaric oxygen are given in Table 12.13. Some open clinical studies of CO poisoning treated by HBO are shown in Table 12.14.

Hyperbaric oxygen, 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 possi-

Table 12.13
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%	Immediate referral to HBO center
	COHb < 40% no symptoms	NBO
	COHb < 40% with symptoms	Referral to HBO center

Table 12.14
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. 9 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 & 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 & Baykara (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 recovered consciousness during one treatment, 3 required a second treatment, and one who arrived in deep coma died.

ble, 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 normobaric oxygen 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.

Clinical Trials of HBO in CO Poisoning

Clinical trials of HBO in CO poisoning are listed in Table 12.15. These are discussed in more detail below.

Raphael *et al* (1989) carried out a trial of normobaric and hyperbaric oxygen for acute CO intoxication in 629 adults who had been poisoned at home in the 13 h preceding admission to hospital. 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 2 sessions of HBO 6 to 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 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.

Ducassé *et al* (1995) carried out a randomized study to compare the effects of normobaric oxygen versus HBO therapy in patients with moderate CO poisoning. 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%

Table 12.15
Clinical Trials of HBO in CO Poisoning

Authors and year	Study design	HBO pressure	Results
Weaver *et al* (2002)	Double-blind, randomized trial to study the effect of HBO on cognitive sequelae of acute CO poisoning. Control with normobaric oxygen + air.	HBO (2–3 ATA)	3 HBO treatments within a 24-hour period reduced the risk of cognitive sequelae 6 weeks and 12 months after acute carbon monoxide poisoning.
Scheinkestel *et al* (1999)	Randomized controlled double-blind trial and sham treatments in a multiplace hyperbaric chamber. Neuro-psychological 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 to 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.

(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 *et al* 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 life-saving.

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 minutes of 100% oxygen at 3 ATA followed by further treatment at 2 ATA for 2 hours 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 2,636 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.

HBO for CO Intoxication Secondary to Methylene Chloride Poisoning

Methylene chloride is converted to CO by cytochrome P-450 after it enters the human body. Rioux and Myers (1989) treated two cases of CO poisoning secondary to exposure to methylene chloride. Both recovered following treatment with HBO. Youn *et al* (1989) reported 12 cases of methylene

chloride poisoning from a single exposure. Nine of these required HBO treatment and made a good recovery. The authors observed that CO derived from methylene chloride has an effective half-life 2.5 times that of exogenously inhaled CO.

Rudge (1990c) reported a case of CO poisoning from exposure to methylene chloride that was successfully treated by use of HBO. He pointed out that 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 observed for 12 to 24 h after exposure and should be treated adequately with HBO.

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. Van Hoesen *et al* (1989) treated CO intoxication (COHb 47.2%) in a 17-year-old pregnant woman at 37 weeks of gestation using HBO at 2.4 ATA for a 90-min treatment. The patient recovered and produced a healthy baby at full-term normal delivery. If the mother had been left untreated, considerable morbidity would have been anticipated for the mother as well as for the fetus. These authors reviewed the literature on the subject and made the following recommendations:

- 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.

In a prospective uncontrolled study on 44 pregnant women, HBO treatment for acute CO poisoning was well tolerated without any hazards to the fetus or the mother (Elkharrat *et al* 1991). 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 in the maternal circulation, HBO may decrease fetal hypoxia and improve outcome. Careful documentation of the experience with this treatment is necessary to determine the long-term sequelae and effectiveness of treatment with HBO during pregnancy.

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 cover 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 (Thom *et al* 2001). 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 a_3 oxidase,

which is the determining factor for late sequelae, is not known. Further research is required to evaluate the CO bound to cytochrome a_3 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 (Gibson *et al* 1991;. Patients with severe CO poisoning who have abnormalities on CT scan, which persist after HBO treatment still develop neuropsychiatric sequelae (Fife *et al* 1989). Samuels *et al* (1992) reported a case of CO poisoning which was misdiagnosed as conversion disorder. Cognitive deficits demonstrated at time of assessment were successfully reversed by HBO, despite the delay of one week between the exposure and treatment.

Thom *et al* (1995) measured the incidence of delayed neurologic sequelae (DNS) in a group of patients acutely poisoned with CO and tested the null hypothesis that the incidence would not be affected by treatment with HBO. They conducted a prospective, randomized study in patients with mild to moderate CO poisoning who presented within 6 hours. Patients had no history of loss of consciousness or cardiac instability. The incidence of DNS was compared between groups treated with ambient pressure 100% oxygen or HBO (2.8 ATA for 30 min followed by 2 ATA oxygen for 90 minutes). DNS were defined as development of new symptoms after oxygen treatment plus deterioration on one or more subtests of a standardized neuropsychologic screening battery. In 7 of 30 patients (23%), DNS developed after treatment with ambient-pressure oxygen, whereas no sequelae developed in 30 patients after HBO treatment ($P < .05$). DNS occurred 6 ($\pm$ 1) days after poisoning and persisted 41 ($\pm$ 8) days. At follow-up 4 weeks after poisoning, patients who had been treated with ambient pressure oxygen and had not sustained DNS exhibited a worse mean score on one subtest, Trail Making, compared with the group treated with HBO and with a control group matched according to age and education level. The authors concluded that HBO treatment decreased the incidence of DNS after CO poisoning.

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.

Among the clinical trials reviewed, Weaver *et al* (2002) report on the latest and most carefully controlled investigation of HBO for acute CO poisoning. Among the strengths of this trial are its large size, its use of a sham-treatment control group with blinding of both patients and investigators to the treatment-group assignment, its selection of seriously poisoned patients representative of those encountered in emergency departments, its employment of treatment regimens similar to those in common use, its very high rates of follow-up evaluation, and its explicit definitions of cognitive sequelae. This trial showed that HBO treatment significantly reduces the incidence of CO-induced delayed neurologic sequelae. The assessment of the primary end point (identification of patients in whom cognitive sequelae developed) took place 6 weeks after poisoning, but evaluations at 6 and 12 months also showed a large benefit of HBO. These findings lend further support to the use of HBO, particularly because neurologic manifestations may persist for variable intervals after CO poisoning. Randomized controlled trials have shown that HBO is the only effective therapy for acute CO poisoning if delayed neurologic sequelae are to be minimized (Stoller 2007). Normobaric oxygen should not be used between multiple hyperbaric oxygen 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 with the clinical severity of CO poisoning. The following approach is recommended for HBO treatment for CO poisoning (Prockop & Chichkova 2007):

- 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.

It would be helpful to have an objective biochemical serum marker that could help in the evaluation of CO poisoning and indication for HBO therapy. In two case reports, where the established criteria for the CO poisoning were not optimum for the decision regarding HBO therapy, S-100B

protein could be used as a biochemical marker of CO-induced brain injury (Brvar *et al* 2003).

There is some controversy regarding the pressure of HBO. Use of pressures between 2.5 and 3 ATA seems appropriate for CO poisoning (Thom 2002).

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 in fumigation. Propronitrile, 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-a_3-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.

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-a_3-oxidase. Possible mechanisms for the positive effect of HBO are:

- 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.

Table 12.16
Experimental Evidence for the Effectiveness of HBO in Cyanide Poisoning

Authors and year	Evidence
Ivanov (1959)	HBO restored normal activity of the brain in mice poisoned with cyanide
Skene *et al* (1966)	Drop in mortality from 96% to 20% in a group of mice treated with HBO at 2 ATA compared with those treated at 1 ATA
Takano *et al* (1980)	HBO at 2 ATA was shown to reduce the pyridine nuclide fluorescence (which represents the degree of blockage of respiratory chain) in the renal cortices of rabbits poisoned with cyanide
Isom *et al* (1982)	Showed that recovery of brain cytochrome oxidase was more rapid in rats poisoned with cyanide and treated by oxygen breathing, compared with those breathing air

The value of high tensions of oxygen in the management of cyanide poisoning in experimental animals was shown by Cope (1961). However, HBO at 4 ATA was not shown to be more effective than NBO as an adjunct to conventional antidotes in cyanide poisoning in mice (Way *et al* 1972). Other experimental studies showed HBO to be effective in cyanide poisoning; these are listed in Table 12.16.

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). 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. Litovitz *et al* (1983) reported the unsuccessful use of HBO in a case of cyanide poisoning. Later Trapp and Lepowski (1983) reported five cases of cyanide poisoning

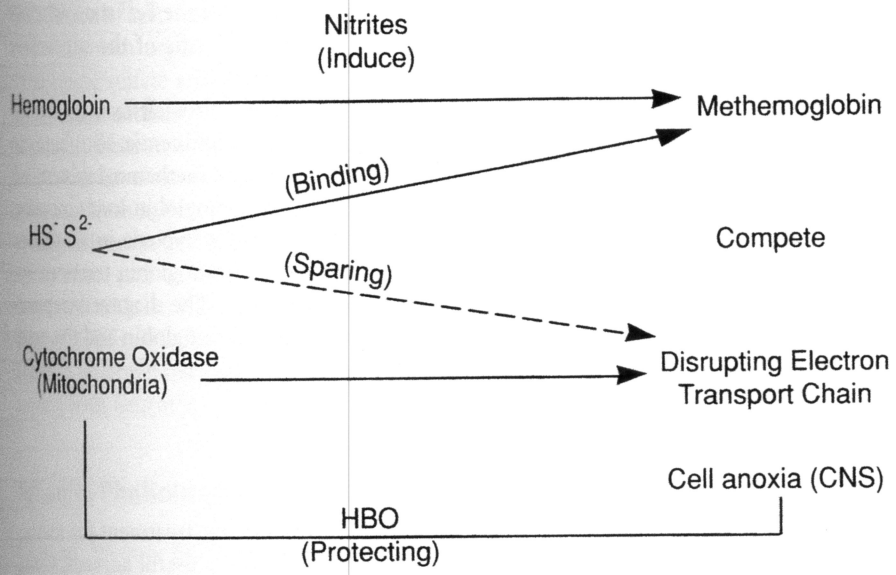


Figure 12.4
The role of hyperbaric oxygenation and nitrites in acute hydrogen sulfide poisoning (reproduced from Hsu *et al* 1987).

treated successfully by means of HBO. There are several anecdotal reports of cases of cyanide poisoning in which HBO was useful for treatment. Scolnick *et al* (1993) treated one patient with cyanide poisoning resulting from exposure to substituted nitrile using HBO for residual symptoms after initial treatment with sodium nitrite and sodium thiosulfate. A man who deliberately drank a potassium-gold cyanide solution survived after treatment with the Lilly Cyanide Antidote kit and hyperbaric oxygen (Goodhart 1994).

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 shown in Figure 12.4. Nitrates aid the conversion of hemoglobin to methemoglobin. The latter, by binding free sulfide ions, spares intracellular cytochrome oxidase.

Bitterman *et al* (1986) studied the effect of oxygen at 3 ATA, both alone and in combination with intraperitoneal sodium nitrite in rats poisoned with LD_{75} hydrogen sulfide. They found that pure oxygen at 1 ATA was effective in preventing death, but oxygen at 3 ATA was more effective. The best therapy was the combination of oxygen at 3 ATA with sodium nitrite. The clinical usefulness of HBO in H_2S poisoning is based on the relief of cerebral edema and protection of the vital organs from hypoxia. Single case reports have shown that HBO treatment was successful in treating H_2S poisoning (Smilkstein *et al* 1985; Whitecraft *et al* 1985). Hsu *et al* (1987) reported five patients with severe H_2S poisoning who were treated successfully with HBO in combination with the use of nitrates. Pontani *et al* (1998) reported a patient in whom delayed neurologic toxicity from hydrogen sulfide was treated successfully with HBO. The pressure used was 3 ATA for 90 min during the initial treatment and this resulted in significant improvement. Daily treatments at 2.4 ATA were continued and neurological deficits resolved completely in three days. HBO therapy was used succeessfully in the management of two cases of hydrogen sulfide toxicity, who had not responded to normobaric oxygen (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, where-

as 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. Burk *et al* (1986) showed that oxygen at 2 ATA given 6 h after administration of CCl_4 to rats improved the survival rate from 36% to 50%. HBO inhibited the in vivo conversion of CCl_4 to its volatile metabolites $CHCl_3$ and CO_2 by 52%. The predominant effect was on CO_2, which is quantitatively the more significant metabolite.

Animal experimental studies of the effect of HBO on CCl_4 poisoning have been reviewed by Burkhardt *et al* (1991). Most of these studies show that the mortality of the HBO-treated animals is lowered and there is less impairment of the liver function tests (Bernacchi *et al* 1984). Troop *et al* (1986) conducted a carefully controlled study of the effects of HBO on rats poisoned with CCl_4 and concluded:

- HBO improves survival from CCl_4 poisoning.
- The response rate is time-related. There was 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 in patients with CCl_4 poisoning. Larcan *et al* (1973) described a case of CCl_4 poisoning treated by HBO. The treatment was begun 24 h after ingestion of 150 ml CCl_4, when severe hepatic necrosis was already present. The patient recovered, and a liver biopsy on the twelfth day showed only minimal hepatic centrilobular necrosis. Other cases of CCl_4 poisoning successfully treated by HBO have been reported (Montani & Perret 1967; Saltzman 1981; Truss & Killenberg 1982).

CCl_4 poisoning is rare these days as this toxic solvent is no longer used industrially. 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.

Many drugs and chemicals have toxic effects on the Hb molecule and produce methemoglobinemia. Nitrobenzene and nitrites provide examples. 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 methemoglobinemias 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. Timchuk *et al* (1981) treated three patients with drug-induced methemoglobinemia (methemoglobin levels 50–70%) who were admitted in a comatose state. HBO at 2.2 ATA was given. Methemoglobin decreased at a rate of 5to 8% per hour of exposure to HBO, and the patients recovered. In another 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 patient with severe life-threatening isobutyl nitrite-induced methemoglobinemia of 75% of total hemoglobin, toluidine-blue was administered as first-line antidotal therapy immediately, followed by HBO and the patient recovered uneventfully (Lindenmann *et al* 2006)

Miscellaneous Poisons

Quinine

Toxic effects of quinine and related antimalarial drugs includes cardiotoxicity with vascular collapse. Neurotoxicity and visual loss may also occur. Good recovery of visual activity and visual field defects resulting from quinine intoxication and treated with HBO at 2 ATA, has been reported.

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 to 4 h considerably prolongs the survival of the poisoned animals. The role of HBO in potential management of organophosphorus poisoning with neurotoxicity requires further investigation.

Amanita Phalloides

Cases of *Amanita phalloides* (mushroom) poisoning have been treated by using HBO with good results.

Ethacrynic Acid

Ototoxicity of ethacrynic acid on the inner ear can be reduced by HBO, with improvement of hearing.

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.