C

CARBON MONOXIDE POISONING

Contents

Clinical Findings, Sequelae In Survivors

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Introduction

Intoxication from carbon monoxide (CO) is a phenomenon that occurs in a wide variety of settings worldwide. CO is a major environmental toxic agent whose effects were described over a century ago by Haldane. The effects cover a range of physical and neurological signs and symptoms ranging from none to death.

Exposure occurs in two main ways – (1) acute exposure for varying lengths of time, where the effects are generally immediately obvious, and (2) delayed or chronic exposure, where the effects may be unrecognized for days, months, or years. The diagnosis of CO exposure may be one of exclusion. The problems of recognizing low-grade exposure to CO may result in a considerable underestimation of the problem.

It has been estimated that there are up to 6000 deaths per annum in the USA from CO poisoning, with up to 40 000 emergency department attendances for nonfatal exposure.

Pathophysiology

Incomplete combustion of hydrocarbons results in the formation of colorless, odorless, and nonirritant CO. CO dissolves in plasma and binds to oxygen-transporting proteins – hemoglobin (in plasma), myoglobin, and the cytochrome system in tissues. The most significant affinity is for hemoglobin (Hb). CO is absorbed through the lungs and binds to Hb, forming carboxyhemoglobin (COHb). This a reversible reaction which can be described as follows:

$$HbO_2 + CO \rightarrow COHb + O_2$$

The affinity of Hb for CO is up to 250 times greater than that for oxygen, and the presence of CO results in a shift of the oxygen–hemoglobin dissociation curve to the left, causing decreased oxygen-carrying capacity and impaired delivery of oxygen to the tissues. Cellular hypoxia results in this setting from the presence of CO and impaired (hypoxic) cardiac function. The link between levels of CO and effects is not direct. The amount of uptake is governed by a number of variables, all of which interrelate and include relative concentrations of CO and oxygen, alveolar ventilation, duration, and intensity of exposure. However, high levels of CO and chronic exposure lead to CO binding to those proteins with less affinity than hemoglobin, myoglobin, and cytochromes a3 and P450, and these may also account for some of the variations in response to exposure. Hypoxic stress caused by CO exposure alone would not seem to account for some of the longer-term effects and it is believed that CO also affects via a cascade of events, resulting in oxidative stress.

Atmospheric CO concentrations are generally less than 0.001%, although levels in urban areas will be more than in rural areas. Normal individuals who are nonsmokers have a base COHb level of about 0.5%, although normal ranges of 1–3% are described in some studies. These levels originate from endogenous CO, which is produced within the body from the breakdown of heme-containing proteins and in addition the atmospheric levels of

Table 1 World Health Organization maximum levels of carbon monoxide in air (to prevent carboxyhemoglobin rising above 2.5%)

100 mg m^{-3} (87.1 ppm) for 15 min
60 mg m^{-3} (52.3 ppm) for 30 min
30 mg m^{-3} (26.1 ppm) for 60 min
10 mg m^{-3} (8.7 ppm) for 8 h

Table 2 Examples of sources of carbon monoxide exposure

Paint stripping/varnish removal/certain paints
Barbecues
Wood stoves
Coal, oil, or gas boiler
Gas refrigerator
Leaking chimneys
Fireplaces
Cars in garages (domestic and work)
Warehouses with forklifts
Smoking
Cars
Building fires

CO. Endogenous sources are believed to contribute approximately 75% of the overall levels. These levels increase in smokers and are secondary to environmental CO.

Blood COHb levels of 2.5–4% have been shown to be associated with decreased short-term maximal exercise duration in healthy volunteers; levels from 2.7 to 5.1% decreased exercise tolerance in patients with angina; levels between 2 and 20% have been described by an Expert Panel on Air Quality Standards (in the UK) as leading to "equivocal effects on [amongst others] visual perception, motor and sensorimotor performance, vigilance, etc."

The World Health Organization has issued guidelines for the level of CO in the air which will prevent blood COHb levels from rising above 2.5%. These are shown in Table 1. Some countries identify their own levels, which are generally of similar orders of magnitude.

The significance of these different values is that low levels of CO may not result in clinically obvious effects, and that those exposed to low levels for prolonged periods may suffer marked effects that are not readily diagnosed.

Methods of Exposure

Exposure to CO may be difficult to detect. Table 2 lists a number of situations that have resulted in CO exposure. Many locations are fine with adequate ventilation. However, with no air movement or stagnant air, risks of exposure and adverse effects increase. Work, domestic, and leisure settings may all account for exposure. If exposure is suspected it is appropriate to use a system such as the CH^2OPD^2 mnemonic to try to explore the source of environmental exposure – enquiring about community, home, hobbies, occupation, personal habits, diet, and drug issues. Systematic enquiry is the most efficient way of establishing a cause and a source.

Clinical Findings

A vast range of symptoms of CO exposure have been described, hence the description of CO poisoning as a "disease with a thousand faces." Classically, acute CO intoxication is said to cause the triad of cherry-red lips, cyanosis, and retinal hemorrhages, but this type of presentation is rare. In many cases a more insidious presentation develops, with the only indicator a general malaise or suspicion of a viral-type illness. The group of illnesses broadly described as chronic fatigue syndromes may have features that are attributable at least in part to CO exposure.

It appears that CO particularly damages those organs that have high oxygen utilization, including the cardiovascular system and central nervous system. Specific symptoms include headache, dizziness, nausea, shortness of breath, altered vision, altered hearing, chest pain, palpitations, poor concentration, muscle aches and cramps, and abdominal pain. Sometimes these may occur in clusters and sometimes in isolation. More serious effects may be noted predominantly as a result of tissue hypoxia and include loss of consciousness, myocardial ischemia, hypotension, congestive cardiac failure, arrhythmias, mental confusion, and lability of mood. These symptoms and signs may be present during acute exposure at higher levels in nonfatal cases, but also in the more chronic or prolonged case.

Acute poisoning can cause ventilatory disturbances in almost two-thirds of those exposed, even if they have not previously suffered from respiratory disease. Rhabdomyolysis can result in renal failure, and this may be due to direct toxic effects of CO. Diabetes insipidus is also a rare complication. Postpartum hemorrhage has also been documented and this has been attributed to CO, via activation of guanylate cyclase causing arterial vascular smooth-muscle relaxation with subsequent vasodilation. Additionally CO inhibits platelet aggregation.

In addition to the symptoms and signs discussed above there are a variety of neurological, psychiatric, and psychological sequelae that may develop days, months, or years after initial exposure. These delayed sequelae are grouped together as the "neuropsychiatric syndrome." It has been suggested that the syndrome occurs in up to 30% of CO poisonings,

Table 3 Examples of specific carbon monoxide exposure-related sequelae

Source	*Exposure/circumstances*	*Sequelae*	*Treatment*
Kim JS *et al*. (1987) Mycoclonus, delayed sequelae of CO poisoning, piracetam trial. *Yonsei Medical Journal* 28: 231–233	Found in a comatose state in a room with a heater	One month after: uneven gait, incontinence, memory loss, disorientation, emotional instability. Myoclonic jerks of neck and lower limbs occurred spontaneously 8 weeks after poisoning	Piracetam administered for 11 days – myoclonic jerks ceased
Gillespie ND *et al*. (1999) Severe parkinsonism secondary to CO poisoning. *Journal of the Royal Society of Medicine* 92: 5–6	Found collapsed in house with gas fire switched on but unlit; COHb 42%	Discharged after 10 days. Six days later: deterioration – bradykinetic, marked rigidity, poverty of facial expression. CT scan showed mild atrophy. MRI showed increased signal in periventricular white matter; basal ganglia unaffected	Levodopa/benserazide and pergolide – no effect. Some temporary improvement with hyperbaric oxygen
Benaissa ML *et al*. (1999) Delayed transient loss of consciousness in acute CO intoxication. *Human and Experimental Toxicology* 18: 642–643	Malfunction of heater in a church resulted in multiple CO poisonings	Arrived in hospital 3.5 h after the incident fully conscious, with headache, nausea, vertigo and weakness. Loss of consciousness observed 1 h after incident. COHb 5.8%	Given hyperbaric oxygen due to loss of consciousness. No known sequelae
Simmons IG, Good PA (1998) CO poisoning causes optic neuropathy. *Eye* 12: 809–814	Three cases of visual loss following CO poisoning: (1) car exhaust: attempted suicide; (2) car exhaust: attempted suicide; (3) exposed to exhaust fumes after road traffic accident	(1) presented 3 weeks after with loss of central vision; (2) presented 10 years after suicide attempt; (3) comatose for 6 weeks; awoke complaining of visual loss	Findings suggest CO poisoning can cause a toxic optic neuropathy. Treatment with hydroxycobalamine may be of some benefit
Kelafant GA (1996) Encephalopathy and peripheral neuropathy following CO poisoning from a propane-fueled vehicle. *American Journal of Industrial Medicine* 30: 765–768	Presented 6 years after exposure as driver of propane fueled vehicle	At time of presentation had numbness in hands, feet and lips, loss of balance, slurred speech, inability to express thoughts, forgetfulness. Physical examination showed diffuse hyporeflexia	None
Mascalchi M *et al*. (1996) MRI of cerebellar white matter damage due to CO poisoning. *Neuroradiology* 38: S73–S74	12-year-old referred for MRI because of a generalized tonic–clonic seizure. Six years previously, he had been admitted to hospital following 1 h exposure to CO from gas stove. COHb 18.5%. Discharged without sequelae	MRI 6 years after exposure showed bilateral loss of tissue in parietooccipital regions with small areas of abnormal signal in overlying cortex and almost symmetrical altered signal in posterior cerebellar white matter	None
Balzan M *et al*. (1993) Intestinal infarction following CO poisoning. *Postgraduate Medical Journal* 69: 302–303	65-year-old male found unconscious in bathroom. Butane heater found to have blocked flue. COHb 90 min after removal was 45%.	Given hyperbaric oxygen. Deteriorated over 36 h. At autopsy was found to have ischemic necrosis of all abdominal organs with no evidence of significant atheroma or thrombotic or embolic occlusion	None
Florkowski CM *et al*. (1992) Rhabdomyolysis and acute renal failure following CO poisoning. *Clinical Toxicology* 30: 443–454	Two cases of rhabdomyolysis with acute renal failure: (1) attempted suicide in bathroom with petrol-driven lawnmower: COHb 7.5% some hours after; (2) rescued unconscious from smoke-filled room: COHb 13.8%	Both patients showed enzymatic and muscle biopsy evidence of muscle necrosis. Rhabdomyolysis and acute renal failure subsequently developed	(1) survived after hemodialysis and hemofiltration; (2) developed anuric renal failure together with acute respiratory distress syndrome and died

Continued

Table 3 Continued

Source	*Exposure/circumstances*	*Sequelae*	*Treatment*
Yanir Y *et al.* (2002) Cardiogenic shock complicating acute CO poisoning despite neurologic and metabolic recovery. *Annals of Emergency Medicine* 40: 420–424	Two cases, both from the same incident: (1) 29-year-old female: COHb 22.6%; disoriented after 1 h, comatose at 3 h; (2) 8-year-old female: unconscious: COHb 20.4%	(1) cardiogenic shock with recovery after 11 days; (2) cardiogenic shock: recovery after 24 days	Hyperbaric oxygen and full supportive intensive care
Chang M-Y, Lin J-L (2001) Central diabetes insipidus following CO poisoning. *American Journal of Nephrology* 21: 145–149	Two cases, both from the same incident: (1) 20-year-old female: exposure to CO in unventilated bathroom. Found unconscious. COHb 18.6% 90 min after exposure; (2) 9-month-old child: COHb 100 min after exposure: 4%	Both developed diabetes insipidus, with subsequent hypernatremia, subarachnoid hemorrhage, brain edema and permanent brain injury	ADH and desmopressin. Mother remained comatose in PVS. Child died of nosocomial pneumonia. Full supportive measures
Ramsey PS *et al.* (2001) Delayed post-partum hemorrhage: rare presentation of CO poisoning. *American Journal of Obstetrics and Gynecology* 184: 243–244	41-year-old female admitted to hospital. Later found to have faulty gas heater; COHb 17%	Presented with profuse vaginal bleeding 2 weeks after uncomplicated delivery. No problems until 2–3 h before presentation. Also reported light-headedness, nausea, blurred vision, headache, and chills	100% oxygen given and over 4 h bleeding resolved and mental status normalized

COHb, carboxyhemoglobin; CT, computed tomography; MRI, magnetic resonance imaging; CO, carbon monoxide.

although the true incidence may be more, but remains undiagnosed. A substantial minority of survivors will develop full neurological impairment such as dementia, psychosis, or Parkinsonism, whilst others will develop less florid subtle neurological and psychiatric disorders including cognitive deficit and personality change.

Cognitive deficits that have been observed include impaired memory, attention, visuospatial skills and executive function, with apraxia, and mood disturbances including psychosis. Aggressive behavior is not a common feature. Memory deficits appear to be due to damage to the hippocampus which is particularly vulnerable to anoxia and ischemia.

Table 3 lists specific cases of the less common complications of CO poisoning mentioned above but which were found to be directly related to exposure.

Diagnosis and Investigation

Diagnosis is made by measuring venous COHb levels; however, there is no absolute level which can confirm the presence or absence of poisoning, but a level above 10% is generally considered to confirm the diagnosis, unless the individual is a heavy smoker. COHb levels in arterial blood are not significantly different from venous levels and so an arterial sample is not required for diagnosis. Arterial blood-gas measurements can show a mixed picture of normal partial pressure of oxygen, variable partial pressure of carbon dioxide and decreased oxygen saturation in the presence of a metabolic acidosis. Problems arise particularly due to chronic, lower-dose exposure, because the COHb levels will revert to "normal" values once removed from the exposure, depending on the half-life of COHb in the particular setting. Normal COHb does not necessarily rule out CO poisoning.

Imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) scans show a number of specific lesions following CO exposure, including in both cerebral white and gray matter and the basal ganglia. Low-density white-matter lesions have been seen in the frontal lobes and globus pallidus on CT and bilateral symmetric hyperintensities of the periventricular white matter and centrum semiovale, with iron deposition in the thalamus and necrosis of the basal ganglia on MRI. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have shown evidence of cerebral hypoperfusion following CO poisoning, with some indication of reduced regional cerebral blood flow in frontal and temporal cortices.

Studies indicate significant links between neurobehavioral disorder and abnormalities seen using imaging techniques.

Management

Acute CO exposure should be treated immediately as a medical emergency with attention to the basics of airway, breathing, and circulation. Higher levels of exposure can result in reduced consciousness and cardiorespiratory compromise to a degree requiring intubation, ventilation, and circulatory support within an intensive care setting. The antidote to CO poisoning is the administration of oxygen. COHb half-life varies according to the amount of available oxygen. A mean $t_{1/2}$ of 320 min (range 128–409) has been reported in normal healthy volunteers in room air, down to 23 min in those breathing 100% oxygen at 3 atm. Thus, the administration of 100% oxygen via a tight-fitting face mask with a nonrebreather reservoir bag should be commenced and continued for several hours. Hyperbaric oxygen may have a role in the management of certain cases, particularly those with a history of unconsciousness, neurological signs, cardiovascular compromise, or a severe metabolic acidosis, but the evidence for improved outcome is not strong. It has also been recommended as treatment when CO exposure occurs during pregnancy if the conscious state is altered or if COHb reaches a level of 20%.

Summary

CO poisoning is a cause of great morbidity worldwide. It can give rise to a profuse number of complications – some that occur early and are reversible and some that occur very late and are irreversible. The vagueness of many of the signs and symptoms means that the diagnosis is often missed. A low threshold for consideration of the diagnosis should be held for any individual brought into hospital or found in a state of altered consciousness, and detailed histories should be taken from those whose symptoms might be accounted for by exposure to CO.

See Also

Carbon Monoxide Poisoning: Incidence and Findings at Postmortem

Further Reading

Abelsohn A, Sanborn MD, Jessiman BJ, Weir E (2002) Identifying and managing adverse environmental health effects: carbon monoxide poisoning. *Canadian Medical Association Journal* 166: 1685–1690.

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Incidence and Findings at Postmortem

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Introduction

Carbon monoxide (CO) is a ubiquitous gas, primarily encountered forensically as the product of incomplete combustion (oxidation) of reduced carbonaceous compounds. It constitutes one of the major pollutants in the lower atmosphere. Naturally occurring CO averages 1–2% in the blood of nonsmokers. Because it is odorless, colorless, and tasteless, CO may become an undetected "silent killer" even if only slightly elevated.

Recent studies of the frequency of CO intoxications extrapolate to some 40 000 cases annually in the USA. The actual number is likely significantly higher due to the lack of recognition of cases. In excess of 5000 deaths, over two-thirds of which are

suicides, are directly attributed to CO inhalation each year. Recent declines in accidental CO fatalities have coincided with an increased suicide rate. In addition, the vast majority of the estimated 3350 annual fire-related fatalities are due to CO inhalation in whole or in part. Most documented CO-related deaths occur at the scene of exposure, prior to receiving medical therapy. The most cited gross finding with significant CO exposure is bright-red or "cherry-red" coloration of the blood and tissues (Figures 1 and 2).

Ambient Concentrations

Relevant features in a CO exposure include a confined space, a CO source, and time. The major factors affecting carboxyhemoglobin (COHb) levels, and thus morbidity and mortality, are the dose and duration of exposure. Figure 3 provides a general range of concentrations and corresponding symptoms.

In addition to the primary source of vehicular exhaust, CO may be produced by any internal combustion engine, fires, malfunctioning furnaces/heating systems, dihalomethane (methylene chloride, dibromomethane, and bromochloromethane) metabolism, acetylene gas, carbonyl iron, coal gas, illuminating gas, and marsh gas. A small quantity of CO is produced endogenously at the rate of 0.4–0.7 ml h^{-1}, during the degradation of the heme protoporphyrin ring of hemoglobin (Hb). Cigarette smoking is a significant source of CO. Smokers can have up to 10% COHb compared to a nonsmoker's maximum of 5%. Pipes and cigars burn longer and at lower temperatures; thus may result in COHb concentrations of up to 20%. These levels are reached only rarely, as typically the user does not inhale pipe/cigar smoke as deeply. Figure 4 summarizes typical reference ranges for several "normal" populations. Individual baselines should be considered when interpreting deaths with low-level CO exposure.

Location and environmental conditions significantly impact ambient CO levels. The established occupational threshold is 25 ppm. Ambient air may reach up to 50 ppm in a smoke-filled room or along a highway. Temperature inversions, especially with urban traffic, may escalate the level to 100 ppm. Further, tree-lined major thoroughfares may trap ambient CO, which may then affect drivers as well as pedestrians. Equilibrium COHb concentrations are 8% at 50 ppm and 16% at 100 ppm. Under such conditions, neuropsychiatric effects of poisoning could be contributory in motor vehicle collisions and even in pedestrian deaths.

Physiology

CO is a normal physiologic metabolite and may act directly as a neurotransmitter. The primary *in vivo* effect of exogenously introduced CO is to bind to the Hb molecule, which normally functions to transport

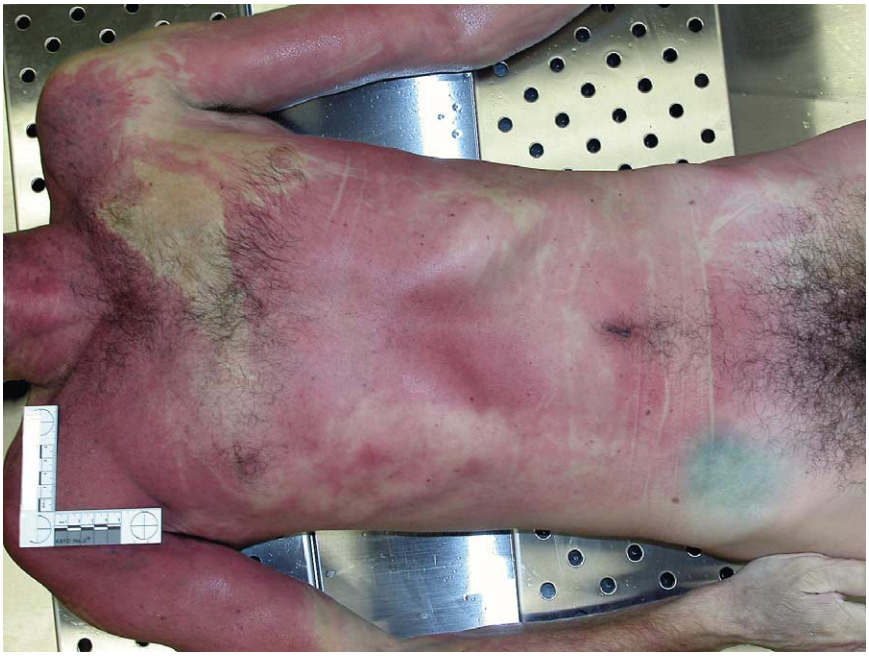

Figure 1 Cherry-red lividity. The most recognizable and cited gross correlate to elevated carboxyhemoglobin is a bright-red or ''cherry-red'' color to blood and other tissues. This is most likely to be recognized with carboxyhemoglobin ≥30%. In lightly pigmented individuals, the color may be easily appreciated in the livor mortis. Other sites that may be assessed, particularly in darkly pigmented bodies, are in the mucosae of the eyes and mouth.

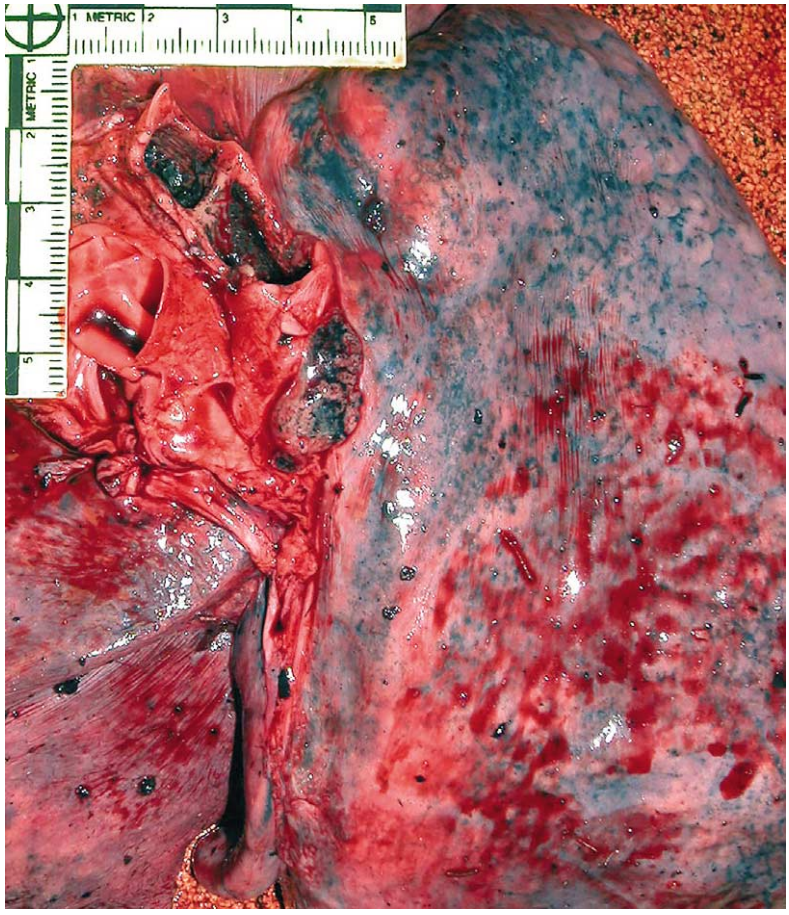

Figure 2 Cherry-red lung tissue and soot within airway. In addition to the classic ''cherry-red'' livor pattern, the soft tissues and organs exhibit the same hue. Here the lung tissue demonstrates the same bright-red color as is evident elsewhere. The carboxyhemoglobin in this fire fatality was 75%. Black foreign material is evident lining the bronchial tree, confirming smoke inhalation in a typical sooty blaze.

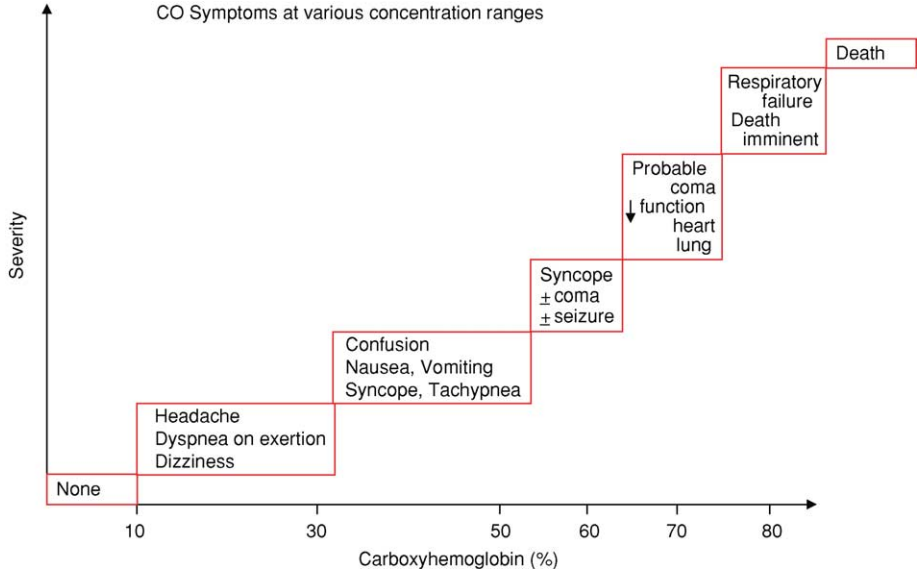

Figure 3 Carbon monoxide symptoms at various concentration ranges. The symptoms of carbon monoxide poisoning are myriad and overlap. In general, subjects are asymptomatic at carboxyhemoglobin of $\leq$10%. Symptoms are primarily dependent on ambient carbon monoxide concentration and duration of exposure. Gradually, blood carboxyhemoglobin levels climb, resulting in progressively worsening symptoms. Levels of $\geq$50% are generally considered lethal; however, with existing disease and/or other stressors impairing oxygen exchange, levels as low as 15–20% may be fatal.

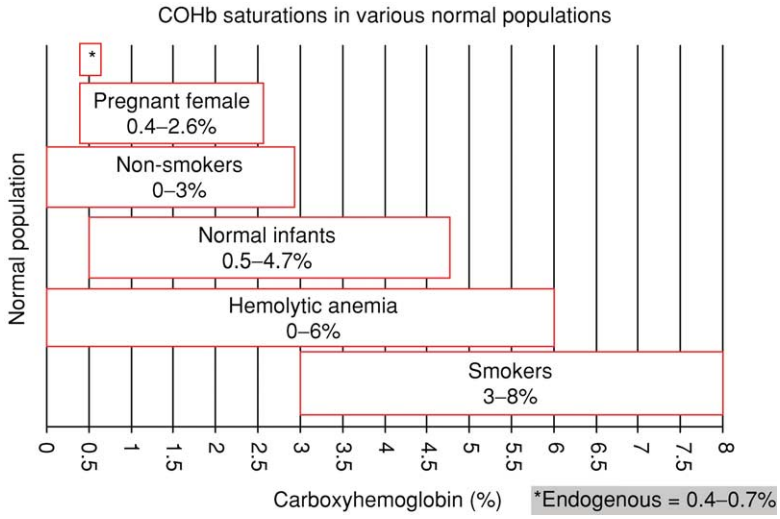

Figure 4 Carboxyhemoglobin (COHb) saturations in various normal populations. A trace of COHb is present (0.4–0.7%) due to endogenous metabolism from the degradation of the heme protoporphyrin ring; however, this is slightly higher in pregnant females (up to 2.6%). Nonsmokers usually have <3%, but may have up to 5% depending on environmental conditions and exposure. In conditions where the erythrocytes break down at an increased rate, the baseline COHb will be elevated. Smokers typically have twice the carbon monoxide content of nonsmokers, but may have even higher baseline concentrations, depending upon the type of tobacco used and the extent of inhalation. Second-hand smoke in a confined environment can also increase COHb in nonsmokers.

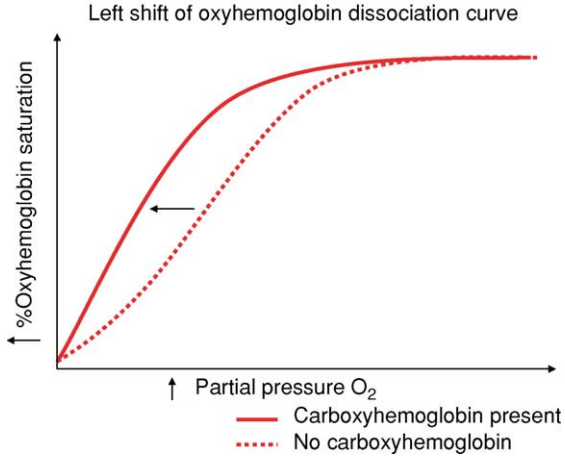

Figure 5 Left-shifted hemoglobin oxygen dissociation curve with carbon monoxide. At any given concentration of blood oxyhemoglobin (ordinate), if carboxyhemoglobin (COHb) is present (solid line) the hemoglobin molecule holds on to bound oxygen more tenaciously than if COHb is absent (dashed line). Thus, at any given partial pressure of oxygen (abscissa), the oxyhemoglobin level will be increased if COHb is present (solid line) in comparison to if COHb is absent. This occurs in skeletal muscle (myoglobin) where the partial pressure of O_2 is normally lower than in the blood; thus the oxyhemoglobin would normally tend to dissociate the O_2 in muscle. If COHb is present, more oxyhemoglobin remains bound, resulting in a net oxygen deficit in skeletal muscle.

oxygen in the blood. In addition to binding to Hb, forming COHb, CO can also bind to myoglobin (Mb) to form the muscle oxygen-storing protein carboxymyoglobin (COMb). CO binds to both Hb and Mb with an affinity ~250 times that of oxygen. Isolated in solution, a single heme molecule binds CO in a tight linear iron–carbon–oxygen array up to 25 000 times as tightly as it does pure oxygen (O_2). Biologically, this tenacious binding is tempered by an angled arrangement of the globin portion of the Hb molecule, such that the *in vivo* binding of CO is significantly decreased. The net result is that, under normal conditions, approximately 1% of all body Hb is bound to CO. Body Mb is a potential large reservoir for CO due to its high binding affinity and left-shifted dissociation curve (Figure 5).

The absolute amount of "bioavailable" O_2 is lessened, and this is directly proportional to the COHb level due to competitive binding. Hb transports oxygen from lungs to tissues where it then delivers (dissociates) the oxygen molecule from the Hb. This mass-action phenomenon follows a sigmoidal relationship (Figure 5, dashed line) with the percentage of oxygen saturation varying directly with the partial pressure of inspired O_2. When COHb is present, however, the dissociation curve shifts to the left (Figure 5, solid line). The net effect is that, for any given partial pressure of O_2, it is harder for the oxyHb to deoxygenate with COHb present, resulting in a higher percentage of circulating blood oxyHb than would normally be present while the tissues remain hypoxic.

In addition to blocking oxygen delivery to tissues, CO is a direct intracellular toxin, blocking cell respiration via the electron transport chain (P450 system

and cytochromes *a* and a_3 are blocked by CO binding to ferrous (2^+) iron).

With normal lung function, exchanging 6 l of air per minute, a 50% COHb can be reached in 8 min with a 1% ambient CO level. An estimated expected COHb concentration can be calculated by the formula:

$$[\%\text{COHb}] = (6\,\text{l}\,\text{min}^{-1})(\%\text{ambient air CO})(\text{min exposure})$$

There is no significant metabolism of inspired CO. Pulmonary elimination is the primary pathway, with only 1% of body CO metabolized to CO_2 *in vivo*. The half-life ($t_{1/2}$) of CO in the body is also affected by competitive binding of O_2 to Hb. The latter is exploited therapeutically to cause a CO-poisoned patient to "blow off" CO. The usual $t_{1/2}$ of COHb in ambient air (21% O_2) is 4.5–6 h. The $t_{1/2}$ can be reduced to 0.5–1.5 h with 100% ambient oxygen and to 23–30 min with 200% (2 atm – hyperbaric oxygen).

Normal pulmonary CO elimination may pose difficulty for the treating physician as well as the forensic pathologist. Once the patient is removed from the CO source (e.g., removed from the smoldering building, taken out of the car, intubated by the ambulance, etc.) the victim begins to eliminate Hb-bound CO. Any subsequent analysis will report a blood COHb concentration "at the point in time when the sample was drawn." This may not be at all reflective of the true CO level. To make matters worse, in subtle poisonings, the possibility of CO may not be suggested for hours or even days, depending on the clinical picture. By his time, the COHb could have fallen into a normal range, mandating a retrospective, circumstantial diagnosis.

Therapy with O_2, especially combined with CO_2, can allow CO levels to dissipate 10–20 times more rapidly. This is critical in preventing deaths, as hyperbaric oxygen (HBO) given at $\geq$6 h postexposure has an almost one-third fatality rate while early HBO can cut the rate to less than 15%.

Testing

The optimal sample for postmortem forensic COHb analysis is ethylenediaminetetraacetic acid (purple-top tube) or sodium fluoride (gray-top tube) preserved whole blood. The tube should be as completely filled as possible, to minimize the empty headspace over the sample in the tube. With exposure of blood to air, bound CO can equilibrate with the headspace, artificially lowering the test result on the sample. Samples are best held frozen, but may be refrigerated. Improperly stored toxicology blood samples can artifactually lose 60% of the bound CO.

Spleen and other high-Hb fluid-containing tissues are also acceptable specimens. Spleen COHb is interpreted broadly as a significant or insignificant concentration. In general, spleen levels <10% are seen with blood COHb <10%, while >30% spleen COHb corresponds to blood toxic and lethal concentrations. Cases with spleen COHb between 10% and 30% COHb are indeterminate.

There are a few caveats regarding nonblood tissue CO samples. Severely charred tissues are unsuitable, as they tend to desiccate and thus contain little blood (Hb). In decomposed bodies, low-Hb-content serosanguineous fluid collects in the chest cavity. Spectrophotometric and other analyses reliant on an intact Hb molecule are compromised; however, quantitation is possible by direct analysis for CO independent of Hb.

The characteristic red color associated with CO exposure is based on the light absorbance of the COHb molecule as compared to that of oxyHb and other Hb moieties. The quantitation of CO can be performed toxicologically using co-oximetry and/or spectrophotometry. Because CO is a frequently encountered toxin and because of the potential for additional loss of life if CO poisoning goes undetected, several screening tests are available to the pathologist if immediate testing capacity is otherwise unavailable. A suggestive pink color results from the combination of 1 part 0.01 mol l^{-1} ammonia with 20 parts CO-positive blood. An easier screening test involves the reexamination of tissue sections retained in formaldehyde from the autopsy (the so-called "stock" or "save" container). Normally, non-CO-containing viscera will take on a brown tone after several hours in formaldehyde, as the proteins denature. CO-containing tissues retain their characteristic bright-red hue for days to weeks following formalin denaturation (**Figure 6**).

CO is not formed within the body to a significant extent postmortem, unlike cyanide (CN) – an important consideration in handling toxicology samples for quantitation. The characteristic CO color may persist for weeks in an unembalmed body and for at least several days following embalming. The embalming process interferes with CO analysis and may result in unreliable quantitative results. With time, CO livor color progresses from bright-red to dark-green to brown.

Scene Investigation

The physical performance of an autopsy is one test which must be integrated and interpreted in light of all other available data pertinent to a specific case. This includes medical records, symptoms expressed,

Figure 6 Persistence of cherry-red color in formaldehyde-fixed tissues with CO. A quick screen for the presence of COHb is a reexamination of tissue portions retained in formaldehyde. If examined within several days of autopsy, the COHb-positive tissues and fluid in the ''save'' container stay bright-red (left) while CO-negative tissues quickly turn brown (right).

signs observed, and investigative information. One of the most critical elements in the practice of forensic pathology is scene investigation. In many deaths, the definitive and even sole clues to the actual cause and manner of death are scene-derived. CO deaths, especially subtle ones, are prime examples. A (relatively) confined environment is one of the investigative clues to a potential CO fatality. Even something as apparently innocuous as smoking in the confined space of an automobile cabin or a submarine may produce potentially hazardous CO levels.

Location within a scene is also important, as CO has a density 97% that of ambient air and as a result, tends to accumulate at a height of 1.5–2 m (5–6 ft), which would enhance its potential action as a human intoxicant by concentrating the ambient CO at the level of the face.

Most often CO deaths affect one person; however, because the environment is actually poisoned, any and all living creatures in the area are potentially at risk. This includes pets and children who are at increased risk due to their higher basal metabolic rates. Thus, they may succumb at a lower %COHb than adults in the same environment.

An uncommon scenario would be a child sleeping in the back of an auto on a long trip. A defective exhaust may allow CO to build up in the rear of the cabin but not in the more adequately vented front. The net result is that the child, who had been thought to be sleeping, is discovered dead and those in the front are asymptomatic. In ambient asphyxiation cases, environmental testing may prove beneficial in determining the exact sequence of events and prevent additional deaths.

Based on the CO source as determined by scene investigation, most CO asphyxiations can be categorized by origin as fire, exhaust, or other.

Fire

The type of fire provides valuable information regarding how a case should be worked up. A fire that begins in bedding or clothing in a case with a history of alcohol and/or drug use in a cigarette smoker may suggest an accidental origin. Multiple or unusual points of origin or fires exhibiting features of accelerant use could indicate arson and an attempt to destroy evidence in order to evade detection. The data may also explain how a particular COHb level came to be.

In a typical fire the complete exothermic reaction is

$$C + O_2 \rightarrow CO_2 + \text{heat}$$

If the conditions of the fire are altered such that there is an overabundance of fuel (increased carbon) and/or a relative/absolute lack of oxygen, incomplete combustion results:

$$2C + O_2 \rightarrow 2CO + \text{heat}$$

The latter is the typical scenario in most fires; therefore, most fire-related deaths are directly attributed to smoke inhalation, primarily from the contained CO therein.

CO itself is a carbonaceous compound. Thus, it too may serve as a fuel. This is most often encountered when a superheated cloud of sooty smoke forms from smoldering fire, following exhaustion of the available oxygen in a relatively confined space. CO

may comprise one-sixth to three-quarters of atmospheric volume. As combustion continues, temperature increases to the flashpoint of CO, 1128 °F (608.9 °C). If a source of oxygen is made available, the result is explosive combustion of the smoke cloud, also known as a backdraft or flashover. In order to avoid such a massive advancement of an ongoing conflagration, firefighters are trained to verify manually the temperature of closed doors within a burning building. The same end result can occur during a controlled venting of smoke by allowing fresh air (oxygen) to displace the cloud.

Direct thermal body injuries are most often a secondary effect of fire, dependent on the intensity and duration of the blaze. High-temperature, rapid fires cause extensive skin charring with spared tissues, while cooler but longer ones cause extensive deep-tissue destruction. No direct correlation exists between the extent of damage and CO concentration. The CO level depends on the incomplete combustion of available materials. Most fuel-fed fires have low CO with high CO associated with the plastics and other materials in vehicular fires.

A body severely burned in a fire requires an autopsy to establish identity and determine if the subject was, in fact, alive during the course of the conflagration. There is no way to correlate the extent of thermal injury with the timing of burns as premortem or postmortem; however, blood associated with other injuries may be significant.

Ideally, a medical examiner is available to examine the fire scene with fire investigators with the body still present. A crude presumptive test for CO toxicity, and thus inhalation of smoke during the fire is possible at the scene, if indicated. The pathologist may incise into muscle in an area of preserved soft tissue and examine for the characteristic monoxide coloration. With an intact barrier, CO does not bind to Hb or Mb to any appreciable degree unless it has been inhaled; thus the presence of pink tissue is a predictor of CO inhalation. However, it is far from definitive. Final assessment is properly deferred to the autopsy.

Incisions into the area of the trachea should be avoided, as this may introduce carbonaceous artifact into the airway and could potentially cloud the issue of smoke inhalation in cases where the CO level is low (e.g., flash fire). Similarly, in cases where the burn is extensive in the area of the neck (**Figure 7**) sooty debris may fall onto the exposed airway surface. In such cases, more distal small airways may be assessed grossly (**Figure 2**) and/or microscopically for the presence or absence of carbon deposits.

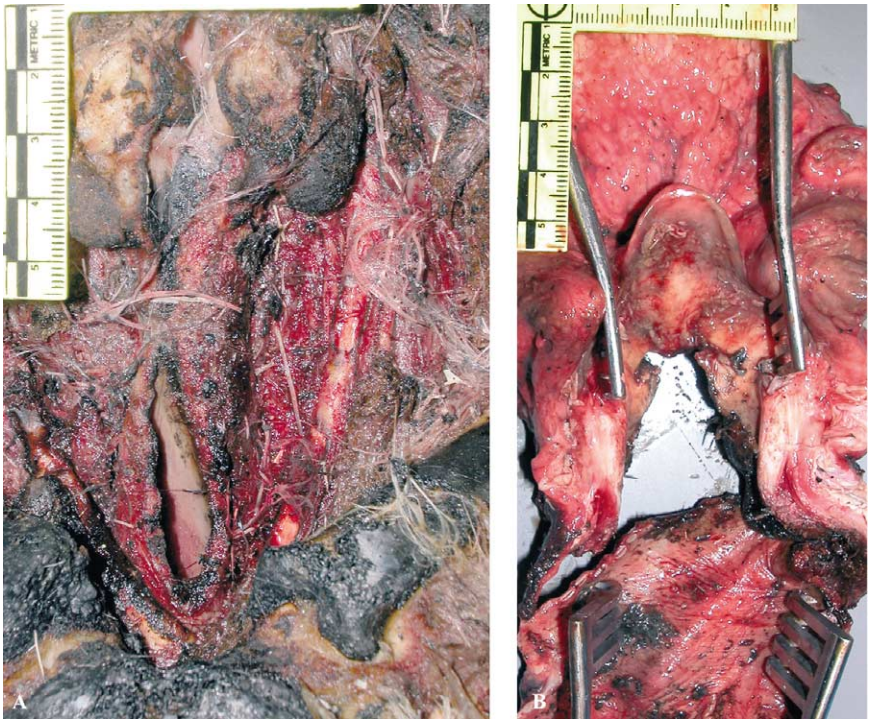

Figure 7 (A) Anterior neck with severe fourth-degree burn, exposing the trachea. In some cases of severe burn, the anterior neck structures are severely charred and may burn through the wall of the trachea. Although examination of the airway for soot is important at the scene, the airway should not be incised in order to prevent artifactual contamination by sooty debris falling into a created defect. (B) Opened trachea with anterior defect showing soot within lumen. This may pose problems as a defect allows sooty material to contaminate the tracheal mucosa.

Exhaust

Most auto exhaust fatalities are more straightforward. Normal incidental automotive exhaust inhalation may result in COHb concentrations between 0.5% and 10%. The typical example of a CO death is an inhalational suicide by means of automotive exhaust via a hose leading from the tail pipe into the cabin (Figure 8).

A common nonfire CO death scene involves an automobile in a garage, workshop, or other relatively enclosed space. The deceased succumbs to CO from the engine running and exhaust accumulating. This may be accidental, if the individual had no awareness of the potential danger, as might happen in cold climes when an auto is left running in the garage to "warm up" the heater. The victim(s) may be located elsewhere in the house, as CO is pernicious and easily permeates into the remainder of the dwelling undetected. Suicide is often accomplished in a like manner, with the decedent deliberately sealing the environment (by lowering the garage door or venting the exhaust into the car cabin).

Occasionally, the subject will attempt to conceal a suicide by staging such a scene. A typical scene is a vehicle with the hood up and automotive tools near the decedent's body, giving the appearance that the victim inadvertently succumbed to CO from the exhaust while working on the car. The most compelling argument against such an improbable occurrence is that the non-CO fraction of auto exhaust is highly irritating and would force out an unwilling subject from such an endangering situation within minutes, well in advance of loss of consciousness.

Figure 8 Typical carbon monoxide auto exhaust suicide with hose leading from exhaust pipe to cabin. Most suicides from carbon monoxide result from auto exhaust. These cases often involve running a hose from the vehicle exhaust into the vehicle cabin.

A consideration in any motor vehicle crash is the potential of a mildly elevated CO leaking into the cabin, hindering performance and causing a subsequent vehicular crash. An example of the latter would be the crash of a passenger airliner, wherein the pilots (and passengers) were overcome by the CO produced by a fire in the plane's hold. As a result, the jet crashes shortly after takeoff, killing all aboard.

In a more likely scenario, toxic CO concentrations may accumulate in a driver in traffic. Internal combustion engines operate least efficiently while idling in heavy traffic, especially in an urban environment, and ambient CO levels may reach hazardous concentrations, dependent on the exposure time. Likewise, if a vehicle's exhaust is defective, CO may surreptitiously leak directly into the cabin. If the driver has an elevated COHb, adversely affecting motor skills (as may happen at COHb of 10–30%) with a resultant fatal crash, the CO was a significant factor in the death(s).

Relatively low COHb concentrations may not have any visible pathologic changes, thus the medical examiner can only detect such low-level poisonings with a high index of suspicion. Some advocate routine CO testing in all motor vehicle crash fatalities without clear accident causation, due to the possibility of exhaust leakage into the cabin. Should case circumstances suggest a need, the test may prove of benefit.

Catalytic converters have markedly decreased CO exhaust emissions, as they facilitate the complete oxidation of CO to CO_2. In some cases of auto exhaust asphyxia, the efficiency of the catalytic converter (increased with a warm engine) may be such that the ambient oxygen within the car cabin is consumed and replaced by the exhaust's CO_2. In such instances, CO concentration may be normal or minimally elevated. An ambient cabin air analysis could prove useful in explaining a low or negative COHb (Figure 9).

Other

Most other CO exposures are due to inadvertently becoming entrapped in an environment with an elevated CO. The earliest reported CO symptoms date from Aristotle when smoldering coals in a closed room were used for execution. Similar cases still occasionally occur with the use of charcoal grills on porches or in tents.

Electrical generators pose a hazard if used in improperly ventilated sites, such as indoors, in a motor home, or inside a motorboat. Rarely, air-compressor motors can serve as a CO contamination point for compressed air in scuba tanks. If possible, such equipment should be secured and analyzed in a

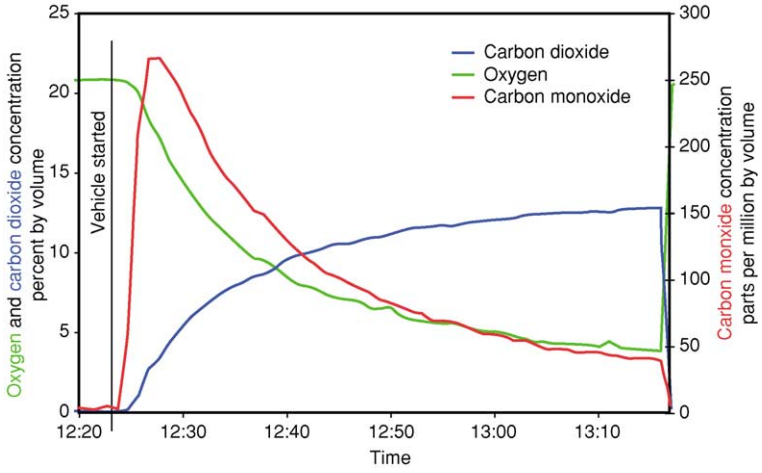

Figure 9 Assay of vehicle cabin with catalytic converter showing decrease in carbon monoxide and oxygen with concurrent increase in carbon dioxide with time. In cases where ambient air composition may be critical, analysis can quantitate the various gases present. In some cases, as in existing disease or with a late-model car, the carbon monoxide may be normal or mildly elevated. With a warm engine, the catalytic converter burns more efficiently and asphyxiation may result from accumulation of carbon dioxide and depletion of oxygen rather than by accumulation of carbon monoxide.

questioned death. The transom of a boat, an unvented deck of a boat, a motorboat ski platform, and the bed of a pickup truck may all be CO hazards, as exhaust may vent to the general passenger area and be retained by a negative-pressure suction phenomenon.

A recent trend of outdoor CO poisonings, specifically associated with boats, has been detected in the last decade. Over 100 such situations have occurred outdoors with almost one-third fatal and another 39% involving loss of consciousness, which potentially could result in drowning. Various identified sources include electric generators on-board, improperly vented engines, stationary position, passenger position at transom/rear, and boat density at or near shore. Over half of the pedestrians on shore have a >5–10% increase in COHb with concurrent symptoms.

Wells and tunnels likewise form contained environments, which can allow lethal collection of CO, especially affecting laborers within such environments. Tragically, these situations often have additional deaths as rescuers, unaware of the hazard, enter the lethal environment – often in an excited state. As with all common asphyxiant gases, detection equipment is available to avoid disasters.

Cause of Death

The general cause of death in most CO exposures is relatively straightforward – asphyxiation due to the inadequate O_2 delivery by Hb; however, fires can be more complicated. In fire fatalities, non-CO noxious gases (most often CN) may be produced. Various materials, including plastics and padding, can form CN during fires. As CN is another chemical asphyxiant resulting in bright-red livor and tissues, fatal exposure could easily be mistaken for CO poisoning. CO and CN act synergistically as cellular poisons, presumably at the intracellular cytochrome level. In over half of the fires, both CO and CN levels are elevated; thus, the combined action of these toxins (as well as several other potentially nonassayed agents) in concert causes death.

For the sake of accuracy, the medical examiner will often attribute the death to "smoke inhalation" to include such instances. Many pathologists will take this a step further, to include the circumstances of the fire proper and attribute the death to "smoke inhalation and thermal injury." Some contend that "thermal injury" is often euphemistically added to protect the sensibilities regarding how an individual suffered in a fire by basically suffocating to death from the smoke. Such a view ignores the physiology of heat with its impact on human performance and oxygen consumption. In addition, the thought of panic *in extremis* in a conflagration is far from comforting.

Mechanism of Injury

Even relatively low-level CO levels of short duration can be life-threatening. Because CO directly interferes with cellular energy and respiration, high-energy-demand organs such as the heart and brain are most at risk. This is demonstrated by some of the symptoms of acute CO poisoning: headache, seizures, and cardiac dysrhythmias (Figure 3).

The heart is especially susceptible to the effects of CO toxicity for myriad reasons. In energy terms, cardiac tissue is high-demand and low-supply, so a continuous ready supply of oxygen is crucial.

Direct CO histotoxicity also occurs at the level of cellular respiration and, if possible, other intracellular processes, as evidenced by the non-COHb level correlative pathology/sequelae: late-phase CO effects after return to a normal COHb, low COHb effects, and extent of CO neurotoxicity in sublethal poisonings. Possible means of delayed neurological effects include direct nerve damage, white-matter demyelination, peroxidation of brain lipids, and/or mitochondrial dysfunction.

Symptomatology

The net result of CO is hypoxic/anoxic anoxemia (the decrease/absence of blood O_2 due to the absence of O_2). In general, symptoms can be estimated based on the percentage of COHb (Figure 3). The toxicity and symptoms of CO exposure are highly variable and dependent upon: concentration, duration, O_2 consumption, physical exertion, other toxin(s) present, disease state, and altitude. Of these, the concentration and length exposure are the most critical (Figure 10). Although short-term exposure to high CO levels is more likely lethal, chronic or prolonged exposure to lower levels causes far more significant morbidity.

It is possible to predict time to incapacitation experimentally, primarily to compare adverse effects with those of other inhalational toxins. The relationship assumes no existing disease, light activity, and loss of consciousness at 30% COHb. The formula is:

$$\text{FED}_{\text{I}_{\text{CO}}} = (8.2925 \times 10^{-4})(\text{ppm CO})(\text{time}/30)$$

Adverse effects of CO are not due solely to its direct competition with oxygen binding. A net result of a 50% reduction in O_2 transport results from either a 50% COHb concentration or severe anemia (reducing a normal Hb level from 44% to 22%) and has vastly different potential consequences. In the former case, death is likely without treatment while the latter may have minimal symptoms. In part, this is due to the left shift in the oxygen dissociation curve (Figure 5). In addition, there is some direct cytotoxic effect of CO.

CO, as the prototypical suffocating asphyxiant gas, exemplifies the entire essence of forensic pathology. The myriad symptoms and signs lead to a broad differential. Its ubiquity and stealth may conceal its significance in any specific case. The primary target is oxygen (fuel) delivery derangement. This latter is accomplished through the three organs responsible for life in an immediate sense, thus the cause of most forensic pathology casework: the heart (fuel pump), the lungs (fuel source), and the brain (driving force).

The heart in particular is extremely sensitive to CO, with dysrhythmias, angina, and electrocardiographic abnormalities experimentally linked to CO exposure. Existing heart disease may be aggravated with a 5–10% increase of CO. The immediate mechanism of death in CO toxicity is believed to be acute myocardial hypoxia ("heart attack"). Existing disease affecting the oxygen delivery system as a whole, be it blood (e.g., anemia), lungs (e.g., asthma, emphysema, pneumonia), and/or heart (e.g., coronary artery disease) are at increased risk of morbidity and mortality from CO exposure (Figure 11). The clinical and pathologic alterations in brain tissue clearly demonstrate CO's toxicity. Any condition (be it increased humidity, temperature extremes, high altitude, or exertion) increasing respiratory rate will also increase CO absorption; cold is a particularly important stressor.

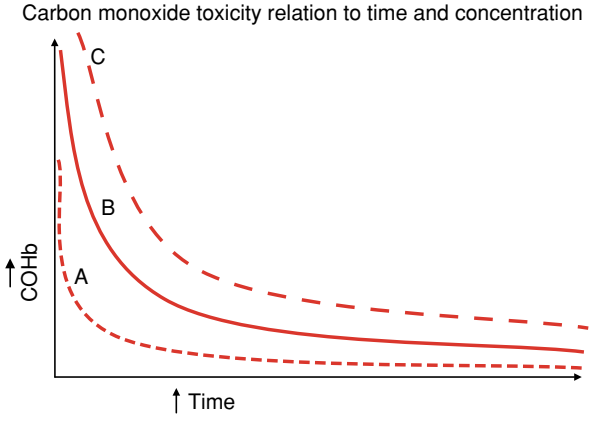

Figure 10 Equilibrium carboxyhemoglobin (COHb) concentrations as a function of ambient carbon monoxide concentration and duration of exposure. The concentration of COHb reaches an equilibrium based on the concentration of carbon monoxide in ambient air and duration of exposure. At lower ambient carbon monoxide concentrations (curve A), the equilibrium is reached more rapidly and the final COHb level is lower. Higher final equilibrium COHb concentrations are reached with higher ambient carbon monoxide concentrations (curves B and C).

Autopsy

Lethal CO Levels

Sudden death from blood loss (due to inability to transport O_2) may occur with a one-fourth decrease in total blood volume (hypovolemic shock). With CO, the functional equivalent holds true. A 25%

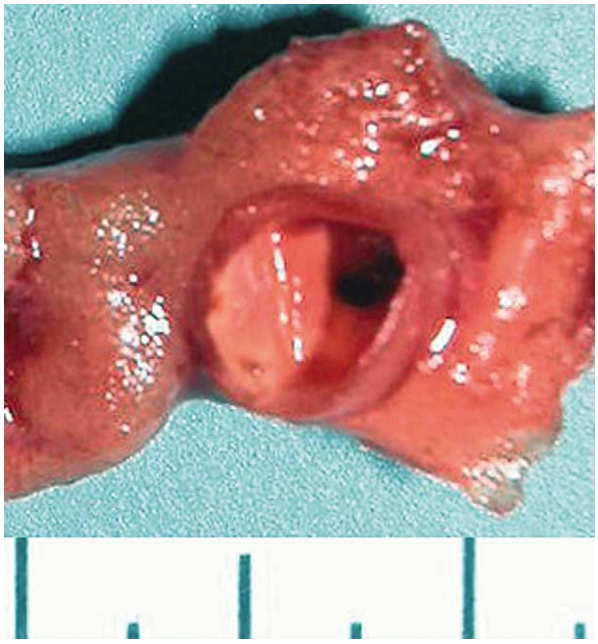

Figure 11 Severe coronary atherosclerosis in carbon monoxide death, 21% carboxyhemoglobin (COHb). In cases where natural disease and/or trauma may be significant prior to carbon monoxide exposure, the subject has an existing difficulty with delivery of oxygenated blood to target organs, most significantly the heart. In this case, the anterior descending coronary artery was 75% stenotic due to existing atherosclerosis. This helps explain why the decedent succumbed to carbon monoxide at 21% COHb.

COHb will most likely be symptomatic and may be fatal (Figure 3).

Typical forensic cases involve high CO concentrations. The two major fatal CO sources, fire and internal combustion engine exhaust, have significant differences in COHb levels: COHb in fire averages 59% (range 25–85%) and in exhaust cases 72% (range 48–93%). Other CO exposure sources are significantly less common and may be associated with variable CO levels.

Even low CO levels may be important in death causation. Some have erroneously held that COHb concentrations of less than 10% are not toxicologically significant; however, the recognition of chronic low-level CO toxicity and the phenomenon of "blowing off" (elimination) of CO point to the importance of considering more than just the isolated results of one COHb test. Most authorities believe that many nonlethal CO poisonings go undetected due to the myriad and confusing symptoms. No doubt less obvious death cases are also missed. Data need to be interpreted in light of all the case information and with a degree of suspicion.

An ambient air CO of 1% (1000 ppm) is typically lethal within about 30 min or as quickly as 10 min with exertion. CO concentrations above 50% are generally considered potentially lethal; however, half of fire fatalities have CO levels of <50%. With significant disease, especially to the heart or lungs, this may be as low as 15–20%. Lower COHb concentrations may be lethal when combined with other central nervous system depressants (e.g., ethanol, sedatives, etc.), toxins, and increased oxygen need (e.g., with exercise/activity).

In fire deaths, the CO may be helpful in assessing potential activity by the decedent during the course of the fire. Higher COHb levels (>50%) suggest survival for a longer period, with exceedingly high levels (>90%) favoring a subject resting, sleeping incapacitated, or otherwise inactive during the blaze. Levels of 20–50% COHb may indicate thermal burns, disease, activity, and/or traumatic factors in the death. A COHb >10% is presumptive evidence of life during the fire and calls for an investigative explanation. Normal CO levels may indicate that the subject was dead prior to the fire. In addition, during a flash fire (such as the explosive combustion of a fireball (e.g., the ignition of an accelerant vapor cloud)), all of the available oxygen in the immediate area is consumed, leaving none to inhale or to react in the fire, forming CO. The only finding at autopsy is a burned body with negligible smoke inhalation discernible (as soot in the airway: Figure 12). Extreme caution is urged to consider disease states and other toxins in avoiding conclusions based exclusively on the COHb result.

Both oxyHb and COHb are relatively stable after death. Thus, CO does not bind to blood in the absence of respiration. This can be useful in assessing injuries in a burned body. Areas of premortem trauma, and absent CO inhalation, will be negative for significant COHb. Areas of injury with contusion formed during the course of smoke inhalation will be positive for COHb at varying levels, depending on the temporal relation to ambient CO.

Of special note, CO crosses the placental barrier, where the fetus is more at risk than the mother. Due to delayed maternal COHb dissociation, the gradual build-up in fetal COHb is delayed; however, the final fetal concentration is 10–15% higher. A fetus is much more susceptible to hypoxic damage. Intrauterine fetal death could result in only mild or no maternal symptoms related to CO. Children often succumb at lower percentages of COHb than adults due to increased basal metabolic rate in the former. In infants a 20–25% COHb may prove fatal.

Physical Findings

All the physical findings in CO fatalities are nonspecific. While some features are more common or

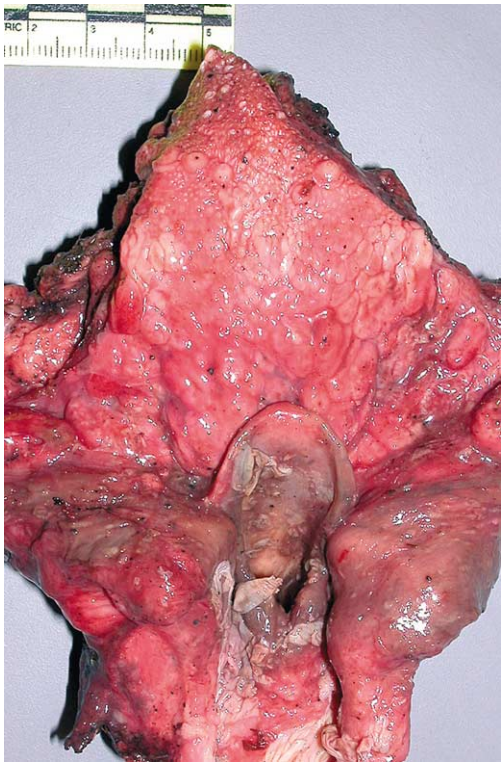

Figure 12 Trachea in flash fire with minimal soot. In a flash fire, all the oxygen in the local area may be consumed in the fireball, leaving no ambient air oxygen for respiration. In such cases, the upper airway may have focal thermal injuries while the remaining airway lacks significant surface soot.

characteristic than others, none is certain or specific. The only definitive observation is an elevated COHb.

Nonspecific Findings

Several features seen in CO-associated deaths are those common to many asphyxial deaths, including: unclotted blood; cerebral edema; acute visceral congestion; and petechial hemorrhages of the skin, serosa, brain, and heart. Also, CO poisoning with concurrent shock or cold temperature delays the onset of rigor mortis.

"Cherry-Red" Livor Mortis and Tissues

The most distinctive and oft-observed finding is neither specific nor uniform. The typical bright-red or "cherry-red" livor mortis (Figure 1) may also be seen in numerous other situations. Another electron transport toxin, CN, also produces a similar color but is distinguished by an odor of bitter almonds, detectable by a subset of the population. The red color associated with CN exposure is due to the continued presence of oxyHb after death. In addition, with deaths due to environmental hypoxia and submersion (especially in cold water), the presence of a moist or damp postmortem environment, early decomposition, and/or fluoroacetate exposure, the livor may appear pink.

With extensive perimortem resuscitative efforts, including extensive artificial respiration, followed very quickly by low-temperature refrigeration, the result may be the same. Focal areas of similar bright-red tissue coloration may be apparent in the vicinity of chest tubes and open chest wounds (from firearms, sharp force, or blunt force), due to a high localized O_2 concentration. Also, contact firearm wounds in any location may have similar tissue coloration due to localized CO resulting from the burning of gunpowder expelling CO gas into the wound.

The typical description of a decedent with CO poisoning is that he/she "looks healthy." That is, the body retains a normal *in vivo* hue due to the continued presence of unutilized oxyHb. As livor may be subtle or unapparent early and/or in darkly pigmented bodies, other easily visualized vascular tissues can be assessed. The typical bright-red color is most readily appreciated in the mucosa of the mouth (Figure 13) and the conjunctiva. Fingernails are an excellent site to assess, as the nail beds are usually prominently cyanotic after death. With sufficient COHb, the nail beds appear pink. With a CO of less than 30% and in living patients, the classic "cherry-red" color is absent or barely perceptible, even in lightly pigmented individuals. In clinical cases the bright-red color may be dismissed as mild sunburn or flushing.

Soot in the Airway

An important observation in fire deaths is inhalation of smoke, as confirmed by examination of the upper-airway trachea/bronchi for surface soot (Figure 14). If a subject survives in a smoky environment, then soot likely will be present; however, the most reliable indicator of life during a fire is an elevated COHb, not soot deposits within the airway. Soot in the airway is not a reliable predictor of a high or even of an elevated COHb.

Heart

In addition to the brain, petechial hemorrhages can occur in the heart muscle. Microscopic myofiber degeneration may be evident as focal necrosis and/or fatty vacuolation.

Skin Blisters

In some delayed CO-exposure deaths following extended coma, the victim forms distinctive serosanguineous epithelial blisters around the skin of the knees and elbows. This is another nonspecific finding, as

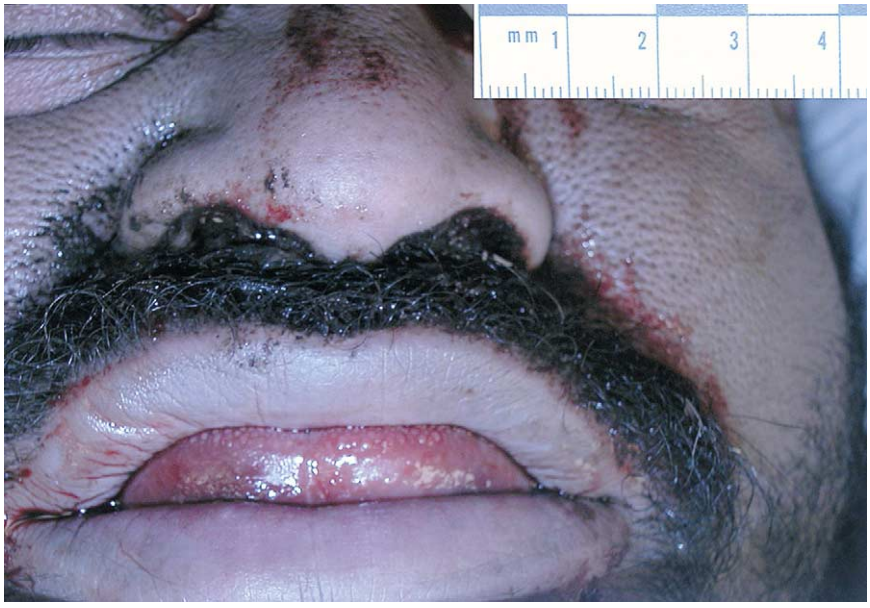

Figure 13 Bright-red tongue in a darkly pigmented individual. In darkly pigmented individuals and in those with low-level carboxyhemoglobin poisoning, the bright-red livor may not be apparent. In such cases, the mucosae of the mouth and eyes are more easily examined and may allow easier interpretation.

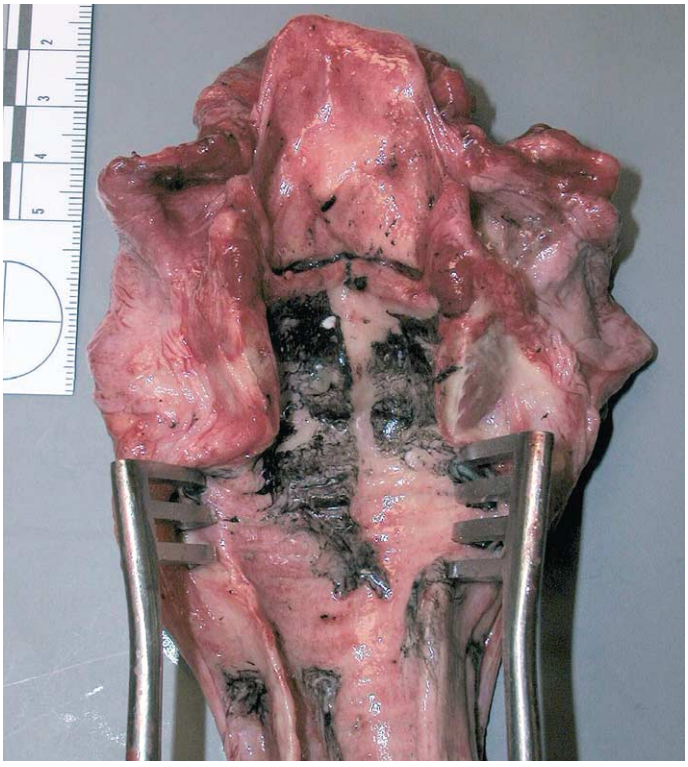

Figure 14 Soot within the trachea. In a typical sooty fire, a film of black smoke lining the tracheal mucosa confirms that the subject was alive during the blaze. In some cases, noncarbon monoxide asphyxiants such as cyanide are produced and kill with low or negative carboxyhemoglobin. In such cases, soot from the fire may be evident in the trachea.

similar damage may be seen following other prolonged comas. In cases where the subject is exposed to heat (e.g., an auto heater), the skin can show similar change.

Neurological

In the brain, CO exhibits pathoclisis, or targeted site-specific pathology. In particular, the extrapyramidal

brain and the basal ganglia are most vulnerable to CO. The single most characteristic lesion for significant CO exposure is the delayed development of symmetric necrosis of the bilateral globus pallidus (basal ganglia within brain). The necrotic areas may progress to 1-cm brown cysts.

Lesions of the corpus striatum vasculature and prolonged coma (especially from barbiturate overdose) can cause identical damage. Other brain changes, detectable with specialized radiology techniques, are summarized in Table 1. The histologic and gross changes in the brain are nonspecific. The earliest change observed might be gross surface petechial hemorrhages, which can form within 15 min. At 24 h, pallor is evident. A gradual progression of changes ensues (Table 2).

Table 1 Radiology imaging results in carbon monoxide poisoning

Imaging modality	*Findings*
Computed tomography	Symmetric low-density lesions in cerebral white matter
	Bilateral low-density lesions in globus pallidus
Magnetic resonance imaging	Symmetric hyperintensity in cerebral white matter
	Hypointensity of thalamus
	Bilateral hyperintensity in globus pallidus (T_2-weighted)

Table 2 Progression of microscopic changes in carbon monoxide poisoning with survival interval

Interval to death	*Microscopic*
34 h	Necrosis in cortex and white matter
	Eosinophilic cytoplasm of the fifth cortical layer and Purkinje cells
2 days	Focal white-matter ring hemorrhages
	Focal hemorrhages without ring
10 days	Globus pallidus axonal swelling
	Subendocardial necrosis papillary muscles
	Lipophages in myofibers
23 days	Transudate
	Neuronal necrosis
	Lipophagocytosis
	Reactive astrocytes
	Glial/capillary proliferation
	Axonal swelling
	Lymphocytic perivascular cuffs
	Decreased/necrotic Purkinje cells
30 days	Ferruginated nerve cells in second cell layer of cortex
40 days	Spongiform foci in globus pallidus
	White-matter lipophagocytosis
$9\frac{1}{2}$ months	Multiple necrotic areas with marked reactive gliosis
	Basal gangliar lipophagocytosis and perivascular lymphocytic cuffs

Summary

In CO deaths, the medical examiner serves in a public health role, protecting the decedent's family and the community from similar risks. The critical determinant in detection of hazards is the index of suspicion in the cryptic accidental death. The gross findings may be obvious, as in a significant fire, or unapparent with other CO inhalations. A red blood and tissue color is common with an elevated CO but is neither sensitive nor specific. In investigating the history, a prodrome of afebrile "gastrointestinal disease," especially one affecting multiple persons in the same environment, is a significant clue.

See Also

Asphyxia; **Carbon Monoxide Poisoning:** Clinical Findings, Sequelae In Survivors

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