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REVIEW

Carbon Monoxide Poisoning: Systemic Manifestations and Complications

Carbon monoxide (CO) has the toxic effects of tissue hypoxia and produces various systemic and neurological complications. The main clinical manifestations of acute CO poisoning consist of symptoms caused by alterations of the cardiovascular system such as initial tachycardia and hypertension, and central nervous system symptoms such as headache, dizziness, paresis, convulsion and unconsciousness. CO poisoning also produces myocardial ischemia, atrial fibrillation, pneumonia, pulmonary edema, erythrocytosis, leucocytosis, hyperglycemia, muscle necrosis, acute renal failure, skin lesion, and changes in perception of the visual and auditory systems. Of considerable chinical interest, severe neurological manifestations may occur days or weekes after acute CO poisoning. Delayed sequelae of CO poisoning are not rare, usually occur in middle or older, and are clinically characterized by symptom triad of mental deterioration, urinary incontinence, and gait disturbance. Occasionally, movement disorders, particularly parkinsonism, are observed. In addition, peripheral neuropathy following CO poisoning usually occurs in young adults.

Key Words : *Carbon Monoxide Poisoning; Cardiovascular System; Encephalopathy; Peripheral Nervous System Disease; Movement Disorders*

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INTRODUCTION

Carbon monoxide (CO) poisoning is one of the important conditions causing organ damage as a result of cellular oxygen depletion. However, the incidence of CO poisoning has been decreasing in Korea (1).

In 1857, Bernard first described the toxic effects of tissue hypoxia (2, 3), and in 1895, Haldane (4) described the underlying mechanism of CO toxicity. Since then, there have been more than 3,000 bibliographic references on CO poisoning (5, 6).

CO affects nearly all the organs and tissues including the brain, heart, kidney, skeletal muscle, skin, peripheral nerve, etc. Clinical manifestations include a wide range of abnormalities, and various systemic complications and neurological sequelae develop after CO poisoning (5-11).

Of 2,759 patients with acute CO poisoning clinically examined at Severance Hospital, Yonsei University Medical Center, Seoul, Korea between 1979 and 1982, 654 were admitted. They consisted of 315 men and 339 women. In 243 patients (37.2% of those admitted and 8.8% of the total), 132 showed systemic complications and 154 developed neurological sequelae. Of the 132 patients with systemic complications, there were 42 with skin lesions, 35 pneumoniae, 20 local swellings, 10 pulmonary edemas, 8 atrial fibrillations, 7 acute renal failures, 3 fetal deaths, 2 gastrointestinal bleedings, 2 Volkman's contractures, and others, in order of frequency. Of the 154 with neurological sequelae, there were 75 with delayed neurological sequelae, 35 prolonged comae, 23 peripheral neuropathies, 5 hemiplegiae, 3 dysphasias, 3 amnesias, 3 cortical blindnesses, 2 hearing disturbances, 2 parkinsonisms, and others, in order of frequency (12).

The clinical symptomatology of CO poisoning may take either of two forms: the monophasic form, in which survival may range from hours to years but without remission of symptoms, and the biphasic form, in which a period of unconsciousness is followed by an interval of apparent normality (lucid interval) lasting 1 week to 1 month (13-15).

SYSTEMIC MANIFESTATIONS AND COMPLICATIONS

The systemic clinical features and complications after

Table 1. Systemic manifestations and complications in CO poisoning

System	Clinical findings
Cardiovascular	: ECG changes (T wave & ST segment), cardiomegaly, angina pectoris, myocardial infarct, tachycardia, bradycardia, A-V block, atrial fibrillation, premature ventricular contraction, ventricular fibrillation, shock
Respiratory	: Pneumonia, pulmonary edema, adult respiratory distress syndrome
Genitourinary	: Glycosuria, proteinuria, hematuria, myoglobinuria, acute renal failure, abortion, still-birth, menstrual disturbance, reduction in weight of testes and in number of spematozoa
Gastrointestinal	: G-I disturbance, G-I bleeding, gastric ulcer, hepatomegaly
Hematological	: Leucocytosis, erythrocytosis, anemia, pernicious anemia, thrombotic thrombocytopenic purpura
Metabolic and endocrinological	: Hyperglycemia, decreased T_3, acute hyperthyroidism
Dermatological	: Bulla, erythema, swelling, ulcer, gangrene, alopecia
Skeletomuscular	: Muscle necrosis, Volkman's contracture, osteomyelitis
Ophthalmological	: Retinal hemorrhage, papilledema, retinopathy, optic atrophy, amblyopia, scotoma, hemianopsia, blindness
Otologic	: Disturbances of cochlear and vestibular functions

Table 2. Signs and symptoms at various concentrations of carboxyhemoglobin

CO in atmosphere	Duration of exposure	Saturation of blood	Signs and symptoms
Up to 0.01%	Indefinite	0-10%	None
0.01-0.02%	Indefinite	10-20%	Tightness across forehead, slight headache, dilatation of cutaneous vessels
0.02-0.03%	5-6 hr	20-30%	Headache, throbbing in temples
0.04-0.06%	4-5 hr	30-40%	Severe headache, weakness, nausea, vomiting, dimness of vision, dizziness, collapse, cherry-red color of lips and skin
0.07-0.10%	3-4 hr	40-50%	As above plus; syncope, increased pulse and respiratory rate
0.11-0.15%	1½-3 hr	50-60%	Tachycardia, tachypnea, Cheyne-Stokes respiration, coma, convulsion
0.16-0.30%	1-1½ hr	60-70%	Coma, convulsion, decreased heart action and respiration, possibly death
0.50-1.00%	1-2 min	70-80%	Weak pulse, depressed respiration, respiratory failure and death

CO poisoning are listed in Table 1.

General symptomatology

The maxinum allowable concentration of CO is 0.01% (100 ppm) for an 8-hr exposure and 0.04% (400 ppm) for a 1-hr exposure in an atmosphere (5). However, the correlation of subjective symptoms with the level of carboxyhemoglobin (COHb) is extremely difficult to evaluate. The degree of somatic consciousness, responsiveness to suggestion, preconceived ideas, and ulterior motives of the subject may all play an important part in determining the time of onset and the intensity of the symptoms. Furthermore, many authors (3-6, 16-24) have found that the symptoms which occur in subjects with the levels of COHb below 20% are vague and nondescript, and include such subjective complaints as mild frontal headache, vague generalized weakness, fatigue, lassitude, and drowsiness. The severities of these symptoms progress when the concentration of CO in the blood increases beyond 25%, and at this point, it is quite reasonable to attribute the symptoms to CO intoxication.

Table 2 illustrates signs and symptoms at various concentration of COHb.

Cardiovascular system

When bound to the intracellular myoglobin of cardiac muscle, CO impairs the transport of oxygen to mitochondria and subsequently their respiratory function, leading to myocardium dysfunction (25, 26).

In 1865, Klebs found diffuse punctiform hemorrhages and necrotic foci throughout the heart in CO poisoning, particularly in the septum and papillary muscles (27). Clinical evidence of specific myocardial involvement may be entirely lacking, may occur promptly, or occur several

days after acute CO poisoning (27-29). If symptoms develop, they suggest potentially lethal myocardial damage. At the present time, the electrocardiogram (ECG) is the most sensitive tool for evaluating or following myocardial damage. The most common findings of ECG in CO poisoning are flattening or biphasic changes in the T wave followed by a variable degree of T-wave inversion (27-32). In addition, atrial fibrillation, premature ventricular contraction and intraventricular block are sometimes observed. Cardiac arrhythmias such as ventricular fibrillations constitute the major threats to life during acute exposure (33-36).

Studies with intact anesthetized primate have shown that the mean arterial blood pressure in the group receiving 0.2% CO declined from 136/97 to 88/44 mmHg within 120 min following the onset of CO exposure, and the average heart rate rose by 20 to 25 beats per min during the first 30 min of intoxication (28). Arterial hypotension and metabolic acidosis evolved consistently, albeit to a variable extent (I, II, 28), but shock occurred only rarely (12).

Respiratory system

Haldane (37) first pointed out that even when one third or more of the circulating hemoglobin has been converted to COHb, there was no significant increase in pulmonary ventilation. Chiodi et al. measured the ventilatory responses in dogs and men during acute carboxyhemoglobinemia and showed that no detectable hyperpnea was evoked and the CO_2 capacity and pCO_2 of arterial blood were unaltered (38, 39). The gross pathologic changes of the lung in 351 fatal cases reported by Fink in 1966 were congestion and/or edema in 66% and hemorrhage in 7% of the cases (5).

The lung damage seen in CO poisoning is probably related to impaired oxygen transport by the blood and is not a result of direct histotoxicity of the alveolar CO (40). The pulmonary changes in acute CO poisoning is attributed primarily to prolonged hypoxia. This factor may affect capillary permeability and cause pulmonary edema (41, 42). The second pathogenetic factor for the pulmonary lesion is myocardial damage in acute CO poisoning, which also may cause pulmonary edema (27, 35). The most common clinical feature of respiratory system is pneumonia, and the second is pulmonary edema (11, 12, 42-44). Rarely adult respiratory distress syndrome develops following CO poisoning (12).

Gastrointestinal system

Patterson et al. (45) found that food intake and gastrointestinal motility were compromised by repeated exposure to CO. Walther (46) reported that acute CO poisoning in rabbits produced no alteration in gastric secretion, but noted mucosal erosions, hemorrhages and edema on microscopic examination. In our clinical study, gastrointestinal disturbances such as indigestion and nausea were common, but bleeding and gastric ulcer were seen only rarely (1, 11, 12).

Serum aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) were increased in about half of the cases of acute CO poisoning, but hepatomegaly was seen only rarely (1, 11).

Genitourinary system

In animal experiment, Patterson et al. (47) reported reductions in weight of testes and in number of spermatozoa with increased elaboration of gonadotropic hormone, but the clinical evidences of specific genital organ involvement are lacking.

Fetal death frequently occurs in CO poisoning. Due to the presence of the placenta, fetal CO intoxication differs from that of the mother. The placenta delays fetal intoxication, but also delays fetal detoxification (48). Fetal hemoglobin has greater affinity for CO than adult hemoglobin. Thus CO dissociation is decreased in fetus and hypoxia is more profound than maternal tissue hypoxia. The estimated fetal mortality is 36 to 67% following significant exposures (49, 50). Fetuses that survive a significant CO poisoning may be left with limb malformation, hypotonia, areflexia, seizure, mental and motor disability, and microcephaly (51).

Genitourinary manifestations after CO poisoning are vesical irritability, nocturia, dysuria, polyakuria, incontinence, dysmenorrhea, menorrhagia, amenorrhea, and decreased libido in women (1, 11, 52). In addition, acute renal failure due to muscle necrosis is a potentially fatal complication of CO poisoning (53, 54). Glycosuria, proteinuria, hematuria, and myoglobinuria also can be seen (1, 11).

Blood

There is an extensive literature pertaining to the development of polycythemia and anemia in men exposed to CO (55-60). In our study of 17 patients with acute CO poisoning (60), the levels of hemoglobin and hematocrit rose initially, and these might be due to dehydration and hemoconcentration rather than hypoxia. Leukocytosis, mainly of neutrophils, observed during the first few days seemed to be a reactive phenomenon due to a physiological stress such as hypoxia. The number of platelets increased steadily following an initial decrease, but we failed to reveal any specific findings in bone marrow of

7 patients with acute CO poisoning (60).

There have been case reports of thrombotic thrombocytopenic purpura in CO poisoning (61) and of pernicious anemia in a woman with chronic CO poisoning (62).

Despite contradictory reports, CO appears to exert no significant effect on blood coagulation (63), activity of tissue thrombokinase (6) or the fragility of RBC (64).

Endocrine and metabolism

Several specific functional alterations in a number of endocrine organs have been attributed to CO (6). Raab (65) described acute hyperthyroidism following exposure to CO. Linnemann (66) found that repeated exposures to CO in guinea pigs produced increased activity of the thyroid and the hypophyseal depletion of thyrotropic hormone. On the contrary, there was an obvious decrease in T_3, even though blood thyroid stimulating hormone (TSH) level was variable in our study of 29 patients with acute CO poisoning (67). The CO-induced decrease in thyroid hormone secretion may not be mediated by depressed TSH secretion but by thyroid hormone dysfunction or extrathyroidal conversion defect (68-70). There also have been reports concerning various effects of acute and chronic CO poisoning on the adrenals and testes (6, 47, 71, 72).

Hyperglycemia and glycosuria during CO poisoning are commonly encountered (1, 6, 11, 67, 73-75). Smith and Penrod (76) found that albino rats developed a hyperglycemia with a linear relationship with the COHb saturation. There was no accompanying alteration in either insulin or glucose tolerance. Schulze (77) noted that in mice the hyperglycemia induced by CO was accompanied by a depletion of glycogen storage of the liver. He suggested that CO exposure stimulated a quick adrenal component along with a slower thyroid component as a so-called compensatory mechanism. In our study of 12 patients with acute CO poisoning (67), there was a rapid initial increase in blood sugar followed by an abrupt drop, and then progressive decrease to the normal level over a period of 5 days after exposure to CO.

Skin and skeletal muscle

Severe CO poisoning can produce several types of lesions of the skin (11, 78-82). The lesions vary in degree from erythema and edema to marked vesicle and bulla formation. These lesions can easily be mistaken for burns or trauma. The bullous lesions heal by eschar formation. The scalp lesion of edema and erythema may evolve into areas of alopecia (78). In addition, there are ulceration and gangrene (81, 82). In our study of 6 patients with acute CO poisoning, the histopathological sites of the bullae were subepidermal in 4 patients and intraepidermal in 2 patients. There was a patient with intraepidermal bulla with ulceration (81).

Myoglobin has a CO affinity constant approximately eight times lower than that of hemoglobin (83). As with hemoglobin, the combination velocity constant between CO and myoglobin is only slightly lower than that between O_2 and myoglobin, but the dissociation velocity constant is much lower than in O_2. The combination of this greater affinity (myoglobin is 90% saturated at 20 mmHg of pO_2) and lower dissociation velocity constant for CO favors retention of CO in muscular tissue, and thus a considerable amount of CO can be potentially stored in the skeletal muscle. Any of the myoglobin functions may be affected by the presence of CO (83-85).

Hedinger (86) reviewed 30 patients of muscle necrosis following CO poisoning. The affected muscles were painful and swollen, and in 12 patients, histological confirmation was made. Skeletal muscle necrosis, particularly in lower extremity may lead to acute tubular necrosis of the kidney (54, 86-88). In addition, infrequently encountered are Volkmann's contracture and osteomyelitis due to secondary complication of muscle necrosis after CO poisoning (5, 12, 89).

Eye and ear

Ophthalmic features following CO poisoning are also noteworthy. Visual field defects attributable to cortical lesions are well documented. Paracentral scotomas, homonymous hemianopsia, and temporary or permanent blindness are also known sequelae of CO poisoning (7, 90-92). These field defects are usually discovered after arousal from coma, but blindness without antecedent coma has also been reported (93, 94). The specific retinal findings following CO poisoning include venous congestion, retinal hemorrhage, papilledema and optic atrophy (95).

It is also well known that CO has toxic effects on the vestibulo-cochlear nerves and brainstem (7, 96-98). Kowalska studied 78 men occupationally exposed to CO using audiometric and electronystagmographic approaches. Hearing impairment was found in 66.6% of cases, of which 79.5% showed vestibular changes (52). These effects were regarded as typical of CO exposure by investigators (52). In my study of 32 patients with acute CO poisoning, brainstem auditory evoked potential abnormalities were exhibited in 8 patients (99). Six patients had a peripheral pattern (cochlear nerve involvement) of prolongation of latency in wave 1 without prolongation of interpeak latency, and two had a central pattern (brainstem involvement) of prolongation to all waves and interpeak latencies. A conductive hearing deficit may also be brought

about by hyperbaric oxygen therapy in acute CO poisoning (100).

Nervous system

Lapresle and Fardeau (101) reviewed 22 patients with CO poisoning and classified them into four main pathological types: I. 16 had globus palldus lesions, consisting of varying degrees of necrosis depending on the duration of survival; II. 16 had white matter lesions containing many scattered or focal necrotic areas or confluent areas of demyelination; III. 12 had cerebral lesions, consisting of spongy changes, intense capillary proliferation, degeneration, and reduction of neurons; IV. 10 had hippocampal lesions, consisting of clearly delimited coagulation necrosis.

Of these four types, only the first two have been documented in the radiologic literature (102), but various neurological sequelae develop after acute CO poisoning (5-11, 103-112) (Table 3). Among them, delayed neurological sequelae are more characteristic of anoxic encephalopathy after CO poisoning than of other types of anoxia (14, 15, 113).

The cause of delayed neurological sequelae is unknown, but there are several hypotheses based on pathologic studies. Yant et al. (114) noted both extensive myelin and neuronal loss when dogs were exposed to CO for several hours. Ferraro (115) cited changes that more closely resemble findings in humans. Early workers, thinking the process following CO exposure a unique one, postulated that the gas was directly myelinotoxic (113), but this is unlikely, as demyelination readily follows many other types of anoxia. Courville (116) held that postanoxic demyelination was secondary to anoxically damaged small cerebral blood vessels, but in some patients with no serious vascular damage, demyelination is as extensive as ever. Cerebral edema has been thought to cause postanoxic demyelination (117), but there has been no evidence of delayed demyelination following experimentally induced cerebral edema. One well known delayed CNS response to injury is the allergic encephalomyelitis that, after an interval, follows exanthems or the use of certain vaccines (118), but the tissue elements, such as blood vessels, axons, and glia, that are severely impaired in allergic encephalomyelitis are different from those impaired in postanoxic demyelination.

Delayed CO encephalopathies are not rare. Shillito et al. (14) found only 13 patients of delayed encephalopathy among 21,000 patients of CO poisoning (0.06%), but Lee (119) described the incidence of delayed neurological sequelae after CO intoxication as 2.8%. The age of onset of delayed CO encephalopathy is usually middle ages or older, and young persons are rarely affected. None of my patients were younger than 30 yr (15). The reported lucid intervals (clear periods) have also varied; one to 21 days (14), two to ten days (105, 113), two to four weeks (120), and three to 47 days (119) after acute insults, but delayed CO encephalopathy usually develop within one week to one month after anoxic insult (15).

Delayed CO encephalopathy shows the characteristic symptom triad of mental deterioration, urinary and/or fecal incontinence, and gait disturbance. The mental signs include those of frontal lobe (grasp reflex, glabella sign, and retropulsion) and basal ganglia (short-step gait, masked face, and rigidity). Cerebellar signs (e.g., intentional tremor) are rarely found. Signs and symptoms fluctuate during the clinical course (15). The outcome of delayed encephalopathy is relatively good. About half of the cases of Shillito et al. (14) recovered completely within 2 yr, and 3/4 cases of mine (15) recovered within 1

Table 3. Neurological sequelae in CO poisoning

	Sequelae
Psychosis	: Dementia, mental retardation, hallucination, catatonia, manic depressive state, Korsakoff's syndrome, Kluver-Bucy syndrome
Psychoneurosis	: Depression, anxiety, neurasthenia, insomnia, melancholia, personality and judgment changes, amnesia, astasia-abasia
Striatal syndrome	: Parkinsonism, chorea, athetosis, ballism, myoclonus, tremor, dystonia, Gilles de la Tourett's syndrome
Motor deficit	: Hemiplegia, apraxia, hyperkinetic state
Sensory deficit	: Hemianopsia, cortical blindness, agnosia, anosmia, hearing disturbance
Speech deficit	: Motor or sensory aphasia, anomia, agraphia
Seizure disorder	: Convulsion, epilepsy
Spinal cord deficit	: Syringomyelia
Peripheral nerve deficit	: Polyneuropathy, mononeuropathy, facial palsy
Prolonged coma	: Vegetative state, akinetic mutism
Delayed deficit	: Delayed encephalopathy with / without basal ganglia signs

yr, although some of them had persistent sequelae including memory disturbance and parkinsonism. There is no specific therapy or prophylaxis for delayed encephalopathy after CO poisoning.

Peripheral neuropathy following CO poisoning is also not rare, and commonly occurs in young adults (12, 120-124). The lower extremities are especially vulnerable to peripheral neuropathy. It is usually associated with local swelling (due to muscle necrosis), which may be an important contributing factor to the development of neuropathy after CO poisoning. The pathologic finding is demyelination and the prognosis is excellent (12, 125).

Movement disorders can develop during or immediately after acute CO poisoning, but usually several weeks after the acute insult (15, 126). The movement disorders after CO poisoning reported in the literature include parkinsonism, chorea, athetosis, ballism, dystonia, tremor, myoclonus, and tic (126-137). In our study of 242 patients with CO poisoning, movement disorders were diagnosed in 32 (13.2%). Of these 32 patients, 23 (71.9%) had parkinsonism, 5 dystonia, 3 chorea, and 1 myoclonus. The median latency between CO poisoning and the onset of movement disorders was 4 to 8 weeks, except 51 weeks for dystonia. Movement disorders after CO poisoning usually appeared as a part of delayed encephalopathy. There was no correlation between the affected sites on neuroimaging and the symptomatology of movement disorders. The prognosis was good. Abnormal dyskinesias disappeared within 8 weeks, and the patients recovered from parkinsonism within 6 months (137).

In addition, there are case reports on syringomyelia (138), Korsakoff syndrome (139), Gilles de la Tourette's syndrome (131), and Kluver-Bucy syndrome (140) following CO poisoning.

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