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Cardiovascular Manifestations of Moderate to Severe Carbon Monoxide Poisoning

Daniel Satran, MD,* Christopher R. Henry, BS,† Cheryl Adkinson, MD,‡ Caren I. Nicholson, RN,‡ Yiscah Bracha, MS,‡ Timothy D. Henry, MD†

Minneapolis, Minnesota

OBJECTIVES	We describe the cardiovascular manifestations of carbon monoxide (CO) poisoning.
BACKGROUND	Carbon monoxide poisoning is a common cause of toxicologic morbidity and mortality. Although the neurologic sequelae of CO poisoning have been well described, the cardiovascular consequences are limited to isolated case reports.
METHODS	We reviewed the cardiovascular manifestations of 230 consecutive patients treated for moderate to severe CO poisoning in the hyperbaric oxygen chamber at Hennepin County Medical Center (HCMC), a regional center for treatment of CO poisoning.
RESULTS	The mean age was 47.2 years with 72% men. Ischemic electrocardiogram (ECG) changes were present in 30% of patients, whereas only 16% had a normal ECG. Cardiac biomarkers (creatinine kinase-MB fraction or troponin I) were elevated in 35% of patients. In-hospital mortality was 5%.
CONCLUSIONS	Cardiovascular sequelae of CO poisoning are frequent, with myocardial injury assessed by biomarkers or ECG in 37% of patients. Patients admitted to the hospital with CO poisoning should have a baseline ECG and serial cardiac biomarkers. (J Am Coll Cardiol 2005;45: 1513-6) © 2005 by the American College of Cardiology Foundation

Carbon monoxide (CO) poisoning is a common cause of toxicologic morbidity and the most common cause of death from poisoning in the U.S. (1). Sources of CO poisoning include any source of combustion, such as faulty furnaces, automobile exhaust, charcoal, industrial solvents, and tobacco smoke. The neurologic consequences of CO poisoning have been well described, and symptoms include headache, dizziness, weakness, nausea, and confusion (2,3). However, the cardiovascular consequences of CO poisoning are limited to isolated case reports of ECG changes, myocardial dysfunction, and myocardial infarction (4-20). We describe the cardiovascular manifestations in 230 consecutive patients with moderate to severe CO poisoning treated with hyperbaric oxygen (HBO2) therapy.

METHODS

Hennepin County Medical Center (HCMC) is a Midwest regional center for the treatment of CO poisoning. We collected data on 230 consecutive adult patients treated for moderate to severe CO poisoning with HBO2 therapy at HCMC between January 1, 1994, and January 1, 2002. The study was approved by the institutional review committee and procedures were in accordance with institutional guidelines.

From the *Division of Cardiology, University of Minnesota, Minneapolis, Minnesota; †Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; and ‡Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota.

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Patient demographics, cardiovascular history, and cardiac risk factors from a comprehensive HBO2 database were verified with the medical record. Cardiac biomarker results (creatinine kinase [CK], CK-MB, and cardiac troponin I) were obtained independently from the clinical laboratory and the medical record. Carboxyhemoglobin (COHb) levels were obtained from pre-hospital sources or at HCMC if not available in the field. Glasgow Coma Scale (GCS) measurements were obtained at initial pre-hospital evaluation and upon arrival at HCMC.

Indications for HBO2, regardless of COHb level, included any history of altered consciousness, seizure, focal neurologic deficit, ischemic chest pain, ECG changes, new dysrhythmias or hypotension. In addition, a COHb level $\geq 40\%$ or a COHb level of $\geq 25\%$ plus a history of cardiovascular disease, cerebrovascular disease, age ≥ 60 , exposure ≥ 2 h, or a hemoglobin ≤ 10 mg/dl were indications. The HBO2 protocol was one treatment for 90 min on 100% oxygen at 2.4 absolute atm. Additional treatments were performed for continued lethargy or unresponsiveness (15 patients).

Electrocardiograms were reviewed independently from clinical data by a cardiologist (T.H.) and were classified by rhythm and ST-T wave changes. Ischemic changes were classified as new ST-segment elevation (≥ 1 mm), depression (≥ 0.5 mm), or T-wave inversion (≥ 2 mm) in two consecutive leads. Continuous ECG monitoring was performed on intubated patients and patients with chest pain, dyspnea, or ECG changes. Echocardiograms were performed after hyperbaric treatment and were classified by ejection fraction and wall motion abnormalities.

Abbreviations and Acronyms

- CAD = coronary artery disease
- CO = carbon monoxide
- COHb = carboxyhemoglobin
- ECG = electrocardiogram
- GCS = Glasgow Coma Scale
- HBO2 = hyperbaric oxygen
- HCMC = Hennepin County Medical Center
- MI = myocardial infarction
- WMA = wall motion abnormality

Statistical analysis. Univariate logistic regression models for predictors of myocardial injury (elevated cardiac biomarkers) were performed using chi-square tests of association for dichotomous predictive factors and *t* tests to compare means for continuous predictive factors using SAS software.

RESULTS

Clinical characteristics (Table 1). For 230 consecutive patients, 72% were men and the mean age was 47.2 years. Although 56% were active tobacco smokers, other cardiac risk factors were uncommon, including 23% with hypertension and only 7% with diabetes. Previous history of cardiovascular disease was also uncommon (7% previous myocardial infarction [MI] and 3% previous revascularization). The etiology of the CO poisoning was accidental in 59% of patients (fire exposure, furnace, space heater, stove, or industrial equipment malfunction), intentional (suicide attempt) in 40%, and unclear in 1%.

Markers of illness severity. Glasgow Coma Scale was abnormal (≤ 14) in 106 (46%) patients (range 3 to 15) upon arrival at HCMC. Loss of consciousness occurred in 187 patients (81%) and 116 required intubation (50%). Lidocaine or nitroglycerin was used in 27 patients (12%), and 14 (6%) required agents for blood pressure support. The median number of hospital days was 3 (interquartile range 2 to 6).

Electrocardiograms. A baseline ECG was available for 98% of patients, of which 16% were normal. Sinus tachycardia was present in 41% of patients. Diagnostic ischemic

changes were present in 30% of patients (26% with ST- or T-wave changes and 4% with ST-segment elevation), whereas 41% had nonspecific ST changes and 27% had no ischemic changes.

Cardiac biomarkers. Of the 183 patients with cardiac biomarkers available (80% of the total population), 81 patients (35% of the total population or 44% of patients with biomarkers drawn) had cardiac biomarkers diagnostic of myocardial injury (CK-MB mass ≥ 5.0 ng/ml or cardiac troponin I ≥ 0.7 ng/ml). An additional four patients had ECG changes diagnostic of myocardial injury, but serial cardiac biomarkers were not available.

Echocardiograms. Of the 53 patients with echocardiograms, 30 (57%) had abnormal LV function, including 14 with global LV dysfunction and 16 with regional wall motion abnormality (WMA). Right ventricular dysfunction was present in 18 patients. The average age of patients with regional WMA was 64 years, in contrast to 43 years in patients with global LV dysfunction.

Outcomes. In-hospital mortality was 5% (12 patients), the most common cause being a composite of anoxic brain injury and burn injury (8 patients). Four patients had cardiac arrest with anoxic brain injury and none survived. Only six patients underwent cardiac catheterization. Three patients were found to have coronary artery disease (CAD) ($>50\%$ lesions) and underwent coronary artery bypass grafting.

Predictors of myocardial injury. Predictors of myocardial injury included male gender, a GCS score of ≤ 14 , and hypertension (Table 2). No other patient characteristics, including age; COHb level; diabetes; family history of CAD; hyperlipidemia; cocaine use; or a history of MI, cerebrovascular disease, congestive heart failure, renal disease or revascularization, were predictive of myocardial injury. Active cigarette smoking lowered the relative risk of myocardial injury.

Of patients with positive biomarkers, 53% had ischemic ECG changes, and in patients with ischemic ECG changes, 64% had positive biomarkers. Of patients with echocardiographic abnormalities (regional or global), 97% had positive biomarkers.

Table 1. Patient Characteristics (n = 230)

Age (yrs)	47.2 (19-91)*
Men	166 (72%)
Diabetes	15 (7%)
Hypertension	52 (23%)
Active smoker	129 (56%)
Previous myocardial infarction	15 (7%)
Previous revascularization	6 (3%)
Accidental poisoning	135 (59%)
Intentional poisoning	91 (40%)
COHb level (%)	33.1 (2-65)*
Intubated	116 (50%)
Requiring pressor agents	14 (6%)

*Average with range.

COHb = carboxyhemoglobin.

Table 2. Predictors of Myocardial Injury

	No Injury	Injury	RR	95% CI
Men	64.8	84.7	3.01	1.52-5.94
GCS ≤ 14	41.7	61.5	2.23	1.27-3.94
Hypertension	18.3	31.3	2.04	1.09-3.82
Previous revascularization	0.7	1.2	1.74	0.11-28.16
Diabetes	5.6	8.4	1.55	0.54-4.45
Previous MI	6.3	7.2	1.16	0.40-3.38
Age (5 yrs)	44.8*	51.2*	1.12	1.03-1.22
COHb level (10%)	32.7†	33.9†	1.03	0.93-1.14
Current smoker	64	48.2	0.52	0.30-0.91

Columns 1 and 2 represent percent of patients with predictor, except *average and †measured percent. 95% confidence intervals are derived from univariate logistic regression models, where myocardial injury (yes/no) is the outcome of interest.

COHb = carboxyhemoglobin; CI = confidence interval; GCS = Glasgow Coma Scale; MI = myocardial infarction; RR = relative risk.

DISCUSSION

Our results demonstrate that myocardial injury from moderate to severe CO poisoning is common, with 37% of patients having myocardial injury assessed by ECG or biomarkers. Myocardial injury by CK-MB or cardiac troponin I elevation occurred in 35% of the total population (44% of patients with biomarkers drawn) despite a low incidence of significant cardiac risk factors or known CAD.

Mechanisms of myocardial injury with CO poisoning.

Myocardial injury from CO poisoning results from tissue hypoxia as well as damage at the cellular level. The affinity of hemoglobin for CO is 200 to 250 times greater than its affinity for oxygen. This results in competitive inhibition of oxygen release due to a shift in the oxygen-hemoglobin dissociation curve, reduced oxygen delivery, and subsequent tissue hypoxia (3). In vitro, CO binds to cytochrome-c oxidase of the electron transport chain resulting in asphyxiation at the cellular level (21). Oxygen radical formation and subsequent lipid peroxidation has also been implicated as a mechanism for cell death (21). High concentrations of CO have been shown to induce cellular apoptosis mediated by nitric oxide (22). In preclinical models, CO poisoning in dogs results in global as well as relative subendocardial hypoperfusion (23).

Recently there has been interest in the potential beneficial effects of CO mediated by its activation of soluble guanylate cyclase similar to nitric oxidase (24). This results in vasodilation, inhibition of platelet adhesion, and inhibition of plasminogen activator inhibitor-1. It is interesting to note that current smoking (leading to elevated CO levels) lowered the risk of myocardial injury in our study. However, the deleterious effects of CO poisoning in our study population overwhelm any potential beneficial effects of low level CO.

Previous case reports. Descriptions of the cardiovascular manifestations of CO poisoning in humans have been limited to case reports (4-20). Colvin reported a patient with ECG abnormalities that ultimately normalized in 1928 (5). A case series by Stearnes 10 years later documented ECG findings in 22 patients (20). Anderson described ECG findings in seven cases (including ST-segment elevation and ST-segment depression) and pathology (apical mural thrombus and LAD thromboembolus) in one patient (4). Corya et al. (6) reported echocardiography findings in five patients, with variable resolution of abnormalities. ST-segment elevation MI with transmural myocardial necrosis in a 28-year-old patient (8) and myocardial injury with normal coronary arteries have been reported as well (13,14).

Hyperbaric oxygen (HBO2) therapy. Hyperbaric oxygen therapy is generally accepted as therapy for moderate to severe CO poisoning. Indications include coma, any period of unconsciousness, a COHb concentration of >40%, signs of cardiac ischemia, arrhythmias, or a history of CAD and COHb level >20%, all based on limited data (3). Hyperbaric oxygen therapy may reduce the risk of cognitive

sequelae after acute CO poisoning even for patients who do not meet these criteria (25).

Limited data exist regarding HBO2 therapy for prevention of myocardial injury. In a series of 18 patients with cardiac arrest who were resuscitated, outcomes were uniformly fatal despite HBO2 (26). Whether HBO2 may limit myocardial injury or infarct size without initial cardiac arrest is unknown. In dogs, HBO2 with and without thrombolytics has been shown to limit infarct size following coronary artery occlusion (27). Hyperbaric oxygen therapy has also been shown to limit infarct size in ischemic rabbit hearts, and the effect appears to be time dependent: the earlier the initiation of treatment, the better the outcome (27,28). Other investigators have shown no beneficial effect for HBO2 on infarct size in dogs (29). A small randomized trial (n = 122) of thrombolytics alone versus thrombolytics plus HBO2 demonstrated a nonsignificant improvement in peak CK levels and ejection fraction with the addition of HBO2 (30).

Patterns of myocardial injury. Two clinical patterns of myocardial injury were apparent in our study. One group of patients was younger (average age 43 years) with few cardiac risk factors but severe CO poisoning, demonstrated by abnormal GCS score. These patients were more likely to have global left ventricular dysfunction by echocardiogram, which improved or resolved consistent with stunned myocardium as a result of CO poisoning. A second group of patients with regional WMA was older (average age 64 years) with a higher frequency of cardiac risk factors, and 50% had a normal GCS. In these patients, CO poisoning appears to unmask underlying CAD by creating supply/demand mismatch.

In all likelihood, our results underestimate the incidence of myocardial injury in patients with severe CO poisoning. Serial cardiac biomarkers were not available in 20% of patients, and echocardiograms were not uniformly performed on patients who had positive CK-MB or cardiac troponin I. On the other hand, the percent of patients with echocardiographic abnormalities may be higher than expected because they may have been obtained in patients with myocardial injury. Our study focused on moderate to severely poisoned patients referred for HBO2 and admitted to the hospital, a higher risk cohort including some with signs of myocardial ischemia. One study of "mild" CO poisoning (based on CO levels) suggested no adverse cardiac sequelae, but ECG data and cardiac biomarkers were not included (31).

In conclusion, myocardial injury is common in moderate to severe CO poisoning. A baseline ECG should be performed and serial biomarkers should be followed in all patients. Patients with abnormal cardiac biomarkers should have an echocardiogram. Patients with persistent LV dysfunction, underlying CAD, or risk factors for CAD may benefit from further evaluation including angiography and revascularization. Further study is needed to determine the long-term clinical significance of the myocardial injury as well as the efficacy of

HBO2 as adjunctive therapy for patients with myocardial injury resulting from CO poisoning.

Reprint requests and correspondence: Dr. Timothy D. Henry, Minneapolis Heart Institute Foundation, 920 East 28th Street, Suite 40, Minneapolis, Minnesota 55407. E-mail: henry003@umn.edu.

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