Elizabeth K. Balraj,[1] *M.D.*

Atherosclerotic Coronary Artery Disease and "Low" Levels of Carboxyhemoglobin; Report of Fatalities and Discussion of Pathophysiologic Mechanisms of Death

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ABSTRACT: Levels of carboxyhemoglobin that would ordinarily cause little or no noticeable symptoms or other effects proved fatal in individuals suffering from atherosclerotic coronary artery disease. All such deaths that occurred in the Cuyahoga County during a period of 23 years were studied. The pathophysiologic mechanisms that may be operative in these deaths are discussed. The importance of being aware of this fact, while one determines the cause and manner of such deaths, is stressed.

KEYWORDS: pathology and biology, cardiovascular system, carbon monoxide, death, atherosclerotic coronary artery disease, low levels of carboxyhemoglobin, pathophysiology, lactate pyruvate, cytochrome a_3, mitochondria, myoglobin

No single chemical agent causes more deaths than carbon monoxide, a product of civilization aptly termed the "silent killer." It is present in fumes of smoke, fire, in automobile exhaust fumes, in illuminating gases, and in tobacco smoke. Hence it is a constant hazard to man. Human perception of it comes only from its poisoning effect of oxygen starvation, and practical detection is only by instrumentation [*1*].

One encounters little difficulty in holding carbon monoxide solely responsible for causing death when the carboxyhemoglobin is in the range of 60% or more. But when the carboxyhemoglobin level is as low as 20 to 30% or less, the role then played by the carbon monoxide in bringing about the death is unclear. If one is not fully cognizant of the circumstances surrounding these deaths, levels as low as 20 to 30% of carboxyhemoglobin may go unrecognized at autopsy except by chemical examination, because at such low levels, the blood and body tissues do not possess the "cherry red" hue typical of carbon monoxide poisoning [*2*].

Although low levels of carboxyhemoglobin ordinarily have no harmful effects in a "healthy" individual, their impact on persons suffering from coronary vascular disease or pulmonary disease can be grave. If this fact is not taken into consideration, serious errors may be committed in determining the cause and manner of death. Although a level of carboxyhemoglobin of 20%

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[1]Deputy coroner and pathologist, Cuyahoga County, Cleveland, OH and assistant professor for forensic pathology, Case Western Reserve University, Cleveland, OH.

would produce barely noticeable symptoms such as frontal headache in a "normal" person, it could prove to be the "straw that broke the camel's back" in an individual with advanced coronary atherosclerotic heart disease [2].

The aim of this study is to present instances where individuals with atherosclerotic coronary artery disease died immediately or a few days following exposure to low (10 to 50%) nonlethal levels of carbon monoxide and to discuss the pathophysiologic mechanisms that may be operative in the deaths.

This study deals only with cases of acute exposure to carbon monoxide. Individuals subjected to chronic exposure to low levels of carbon monoxide, such as chain smokers or police officers directing traffic in heavily travelled thoroughfares are not the subjects of this study.

Materials and Methods

All deaths that were certified by the Cuyahoga County Coroner's Office from the years 1958 through 1980, wherein asphyxia by carbon monoxide was the *primary* cause of death and a natural disease was the "*other*" diagnosis or vice versa were reviewed. For the purposes of this study, the primary cause of death is defined as the disease or injury responsible for initiating the train of events brief or prolonged, which produced the fatal end result. The "other" condition is that condition or conditions contributing to death but not related to the primary cause of death. The carbon monoxide was given responsibility for causing death along with a natural condition because the amount of carboxyhemoglobin in the blood of these persons was not sufficient to cause death in and of itself. The Cuyahoga County Coroner's Office serves Cleveland, OH and its suburbs.

During this 23-year period the Cuyahoga County Coroner's Office certified 38 such deaths. These were divided into two groups.

Group 1 consisted of 28 cases where all diagnosis including the abnormal levels of carboxyhemoglobin were documented by complete postmortem examination. All major coronary arteries were studied in detail to determine the severity (mild, moderate, and severe) and extent (focal or diffuse) of the atherosclerotic process, by cross-sectioning these arteries at about 2- to 5-mm intervals. A gross examination estimate of percentage occlusion was thus made. The myocardium was sliced at about 1-cm intervals to look for areas of acute or chronic myocardial infarction. Microscopic sections of the coronary arteries and myocardium were examined in all of these cases. The left coronary artery with its anterior descending and circumflex branches and the right coronary artery with its posterior descending branch are considered major coronary arteries for the purposes of this study.

Group 2 consisted of ten cases where the diagnosis of the "other" condition was based on review of medical records, including results of coronary angiogram, serum enzymes, and clinical history. Autopsy was not performed on these ten cases.

In all cases, hospital charts, office records of private physicians, and eyewitnesses accounts were reviewed.

In cases where death occurred immediately following exposure, chemical tests were performed to determine the level of carboxyhemoglobin. In instances where death occurred several days following exposure to carbon monoxide, such tests were not carried out. Tests to measure the level of carboxyhemoglobin in blood were conducted using spectrophotometric techniques [3]. Blood levels of ethyl alcohol were measured in all cases. Blood levels of drugs were measured in twelve cases belonging to Group 1 and in five cases belonging to Group 2.

For our control group all deaths that occurred at the Cuyahoga County Coroner's Office during the years 1958 through 1980 in individuals 35 to 86 years of age in whom the carboxyhemoglobin was 60% and more were reviewed. A complete autopsy had been performed in each of these cases. The coronary arteries and the hearts were examined adhering to the techniques that are outlined for the examination of cases in Group 1. There was a total of 100 cases in our control group.

Results

See Tables 1 and 2 for the results of the group studies.

The "Other" Condition

Of the 28 cases in Group 1, the primary cause of death was asphyxia by carbon monoxide in 21 cases. The "other" condition in 19 of these cases was atherosclerotic coronary artery disease. Of these, eight persons had hypertensive cardiovascular disease and two had pulmonary emphysema in addition to the atherosclerotic coronary artery disease. Acute and chronic alcoholism was the "other" condition in one individual and pulmonary emphysema alone was present in another person.

In the remaining seven cases belonging to this group the primary cause of death was atherosclerotic coronary artery disease. In these the "other" condition was asphyxia by carbon monoxide.

In Group 2 atherosclerotic coronary artery disease was the primary cause of death and asphyxia by carbon monoxide was the "other" condition in three cases. In the remaining seven cases asphyxia by carbon monoxide was the primary cause of death. The "other" condition in all but one of these cases was atherosclerotic coronary artery disease. Of these, two had hypertensive cardiovascular disease in addition to the atherosclerotic coronary artery disease. Bronchial asthma alone was the "other" condition in one case.

Atherosclerotic Coronary Artery Disease

Of the 28 cases in Group 1, 24 had severe atherosclerotic coronary disease, 2 had moderate, and 2 had mild coronary artery disease. Acute myocardial infarct was present in one and healed myocardial infarct was observed in four.

Size of the Heart

Of the 28 cases in Group 1, the hearts weighed 415 g or more in 20. Of these twelve had hearts weighing 500 to 700 g. The heart weights of the remaining eight persons were less than 415 g.

History of Exertion

Of the 28 cases in Group 1, history of exertion was present in 2. Those two were firemen who collapsed and died while fighting fire.

There was no history of exertion in any of the cases belonging to Group 2.

Carboxyhemoglobin

In 14 of the 28 cases in Group 1, the carboxyhemoglobin ranged between 10 to 30%. In four cases, the carboxyhemoglobin was 40 to 50%. The remaining cases were delayed deaths.

Of the ten cases in Group 2, the carboxyhemoglobin was 10 to 30% in five. It was 40 to 50% in three cases. The remaining were delayed deaths.

In instances where carboxyhemoglobin was 30% or less, the blood and viscera did not show the "cherry red" color. The circumstances surrounding these deaths were the reason for performing these tests.

Other Toxicologic Findings

Blood and urine (when available) were examined for ethyl alcohol on all cases in Group 1. Of these, five showed alcohol in the blood or urine or in both. Their levels in blood ranged from 0.11 to 0.27 mg/dL. Those in the urine ranged from 0.08 to 0.33 mg/dL.

TABLE 1—*Summary of results.*

	Number of Cases																				
	Age						Sex		Race		Carboxyhemoglobin, %				Ethyl Alcohol			Drugs			
	30 to 40	41 to 50	51 to 60	61 to 70	71 to 80	81 to 90	M	F	W	B	10 to 30	40 to 50	60 and More	Delayed Death	Present	Absent	Not Tested	Present	Absent	Not Tested	Total
Group 1	1	1	7	10	5	4	17	11	24	4	14	4	0	10	5	23	0	2	10	16	28
Group 2	0	0	2	4	2	2	9	1	7	3	5	3	0	2	2	8	0	0	5	5	10
Control	22	31	28	10	6	3	59	41	68	32	0	0	100	0	48	52	0	9	72	19	100

TABLE 2—*Summary of results (findings related to heart).*

	Number of Cases									
	Coronary Atherosclerosis			Myocardial Infarct		Heart Weight, g		History of Exertion		
	Mild	Moderate	Severe	Recent	Old	415 and More	415 and Less	Yes	No	Total
Group 1	2	2	24	1	4	20	8	2	26	28
Group 2	...	...	5	0	1	...	...	...	10	10
Control	89	5	6	0	2	13	87	0	100	100

Of the ten cases in Group 2, two had alcohol in the blood or urine or in both. Their level in the blood was 0.2 mg/dL and that in the urine was 0.25 mg/dL.

Of the 28 cases in Group 1, 3.3 mg/dL of salicylate was present in the blood of 1 individual and a trace amount of the same was found in the urine of another. Of the remaining cases, no tests were conducted for drugs in 16 persons. In ten the results were negative.

Out of the ten cases in Group 2, in five the results were negative. In the remaining five tests of this nature were not carried out.

Characteristics of the Deceased

The ages of the decedents in Group 1 ranged from 36 to 86 years. Two were under fifty, seven were between fifty-one to sixty and nineteen were more than sixty years old. Seventeen of the cases were men and eleven were women. Twenty-four were whites and four were blacks.

The ages of the decedents in Group 2 ranged from 55 to 85 years. Eight were older than sixty. Nine were men and one was a woman. Seven were whites and three were blacks.

Circumstances Surrounding Death

The circumstances during which these individuals were exposed to carbon monoxide included inhalation of smoke from fires at home, fire at institutions, fire in public transportation, inhalation of automobile exhaust fumes, and faulty heating systems. Two of the individuals in our study were firemen who collapsed and died while fighting fire. The details of the circumstances surrounding three of these deaths are cited below.

Case 1—The Cleveland Fire Department responded to an alarm of fire at a local residence. Upon arrival Mr. V. K.'s lifeless body was found in one of the rooms. Autopsy showed the presence of soot in his proximal respiratory passages. His carboxyhemoglobin was 23%. There was no alcohol or drugs in his blood. There were no burns. His heart weighed 680 g. There was severe atherosclerosis of all major coronary arteries. A healed infarct was present in the anterior wall of the left ventricular myocardium. His death was ruled accidental.

Case 2—Mr. D. C. was a Lieutenant in the Cleveland Fire Department. On the day of his death while fighting a house fire he suddenly collapsed and died. Autopsy showed that he had severe atherosclerosis of all major coronary arteries. His heart weighed 550 g. His carboxyhemoglobin was 15%. There was soot in his proximal respiratory passages. The blood and other body fluids were free of ethyl alcohol or drugs. The deceased was 55 years old. He was not in the habit of smoking cigarettes. His death was ruled accidental.

Case 3—A 36-year-old driver of an automobile collapsed behind the wheel of his car causing him to lose control of the vehicle and hit a parked automobile. He was the sole occupant of the car. Autopsy revealed slight external injury but no internal trauma. The examination of the cardiovascular system disclosed severe atherosclerosis of all major coronary arteries. The heart weighed 510 g. His carboxyhemoglobin was 20%. There was no alcohol or drugs in his blood and urine. Fumes from the rusted tail pipe found their way into the interior of the automobile through holes in its floor. The deceased was not a cigarette smoker. His death was ruled accidental.

Control Group

All 100 cases in our control group had carboxyhemoglobin levels of 60% and more. Of these 89 had no significant coronary atherosclerosis; 5 had moderate coronary atherosclerosis and 6 had severe atherosclerotic coronary artery disease. Of these only one had organized myocardial infarct. Eighty-seven had hearts weighing 415 g or less. The heart weights of the remaining 13 exceeded 415 g. History of exertion was not present in any one of the individuals in the control group. Ethyl alcohol was present in the blood or urine or in both of 48 of these individuals. The

levels ranged from 0.04 to 0.5 mg/dL in the blood and 0.03 to 0.54 mg/dL in the urine. Traces of drugs such as phenothiazine, methadone, morphine, barbiturates (phenobarb, secobarb and pentobarb), valium, and salicylates were found in the blood of nine individuals. In none of these did the levels exceed the therapeutic values. Tests for drugs were not conducted in 19 persons. Forty-four of the decedents were less than fifty years old. Twenty-eight were between fifty and sixty and the remaining were more than sixty. Fifty-nine of these persons were men and forty-one were women. Sixty-eight were whites and thirty-two were blacks. The circumstances surrounding these deaths were similar to those in our study group.

Discussion

The pathophysiologic mechanisms operative in these deaths are discussed below.

The Mode of Adaptation of Coronary Circulation to Increased Demands of Oxygen

Coronary circulation differs markedly from systemic circulation in its mode of adaptation to the increased oxygen requirements created by stress. Peripheral tissues normally extract about 25% of oxygen present in arterial blood, and the remaining 75% serves as a reserve supply. Total oxygen uptake may be increased by (1) increasing the amount of oxygen extracted from the perfusing blood and (2) increasing rate of blood flow. In periods of stress for example, mixed venous oxygen tension may drop from a normal 40 mm of mercury to below 20 mm of mercury. In contrast, the exorbitant resting myocardial needs are met by extracting a much greater fraction of oxygen from the perfusing blood than the systemic tissues. Approximately 75% of oxygen is extracted from the coronary circulation at rest, and the coronary venous blood is about 25% saturated corresponding to an oxygen tension of 20 mm of mercury. If increased myocardial oxygen needs were met by increasing oxygen extraction as in the peripheral circulation, oxygen tension would fall to dangerously low levels. The coronary circulation avoids low oxygen tensions by increasing flow rate in response to increased oxygen demands rather than by increasing oxygen extraction. Near maximal resting extraction and the ability to increase oxygen consumption by increasing flow allow performance of continuous contractile work at rest and also provide the ability to increase cardiac work with exercise. Coronary vascular disease may prevent an increase in local coronary blood flow in response to need. In this situation, the myocardium is forced to extract more oxygen, but does this at the expense of a markedly reduced coronary venous and tissue oxygen tension [*4*].

Changes in gas exchange following exposure to carbon monoxide are dictated by changes in the oxyhemoglobin dissociation curve. By graphically plotting oxyhemoglobin saturation of hemoglobin not combined with carbon monoxide against oxygen tension, leftward shift of the curve is demonstrable. Thus if the same arterio-venous oxygen difference and therefore the same venous saturation is to be maintained, oxygen tension must decrease. The decrease in mixed venous oxygen tension is the major primary event. Other hemodynamic changes must be considered secondary.

The decrease in venous oxygen tension and presumably in tissue oxygen tension appears to initiate a series of stress responses which attempt to compensate for the decrease in oxygen tension [*5*].

Human and animal experiments conducted by Haldane [*6, 7*], Haggard [*8*], and Chevalier [*10*] showed that the coronary circulation responded to increasing amounts of carboxyhemoglobin with relatively greater increase in blood flow than was true in systemic circulation [*6, 9, 10*].

Oxygen extraction increased systemically so that increased oxygen consumption could be maintained with modest increases in cardiac output. The shift of the oxyhemoglobin dissociation curve and the maximal nature of the myocardial oxygen extraction presented the myocardium with a homeostatic dilemma. An unchanged coronary sinus oxygen saturation would lead to an extremely low coronary sinus and tissue oxygen tension and subject many myocar-

dial cells to near fatal conditions. Instead, myocardial oxygen extraction decreased allowing coronary sinus oxygen to remain almost normal. The critical response in this postulated chain of events is the coronary blood flow. A decrease in extraction must be balanced by an increase in coronary blood flow to maintain oxygen consumption. A normal coronary circulation could adequately increase coronary blood flow and keep tissue tensions within normal limits. A diseased vascular system might not be able to develop an adequate coronary blood flow response, explaining the sensitivity of patients with coronary artery disease to carbon monoxide [*5, 11*].

The Effect of Inadequate Oxygen on the Myocardial Cell Metabolism

Inadequate oxygen decreases the use of pyruvate by the citric acid cycle. Pyruvate accumulates in the cytoplasm and lactate is produced from the accumulating pyruvate. Increasing cellular concentrations of lactate and pyruvate decrease the diffusion gradient between coronary perfusate and cytoplasm and decrease extraction of these metabolites [*5*].

Ayres et al [*5*] conducted canine and human experiments to study the effect of low levels of carboxyhemoglobin (1 to 10%) on the heart. Their studies included seven patients with noncoronary heart disease and four with arteriographically proven coronary artery disease. Their work showed that raising the carboxyhemoglobin from a control level of 1 to 9% increased coronary blood flow significantly in patients with noncoronary heart disease but not in those with coronary heart disease. Lactate extraction changed to production in both groups, but the change was statistically significant only for the patients with coronary heart disease. Their studies also showed that raising the carboxyhemoglobin level produced about a 20% decrease in mixed venous and presumably cellular oxygen tension. Since certain cells and their mitochondria are located at a critical distance from a capillary source of oxygen, a 20% decrease in oxygen tension might well inactivate certain oxidative enzyme systems and either decrease the energy production of that cell or lead to its death.

Ayers et al [*5*] also presented correlated events in three patients before and after acute elevation of carboxyhemoglobin. In the patient with mitral stenosis, oxygen and pyruvate extraction decreased, lactate production developed, and a modest decrease in coronary sinus oxygen tension was observed. Similar changes were noted in patients with coronary artery disease although pyruvate extraction shifted to production. In each patient coronary blood flow response appeared inadequate.

The Effect of Carbon Monoxide on Other Heme Proteins such as Cytochromes and Myoglobins

Carbon monoxide competes with oxygen for cytochrome a_3, an important link of the enzyme system in cellular respiration. The cytochromes are located in the mitochondria. The mechanism of toxicity of carbon monoxide on the cytochrome system was suggested as early as 1926 by Warburg [*12*]. Ball [*13*] showed that carbon monoxide interfered with the activity of cytochrome oxidase. Chance et al [*14*] while reporting on the mitochondrial responses to carbon monoxide toxicity demonstrated the inhibitory effect of carbon monoxide on cytochrome a_3. Goldbaum performed a series of animal experiments to study the mechanism of carbon monoxide toxicity. In one such study, anemic dogs were transfused with carbon monoxide saturated red cells so that their carboxyhemoglobin concentration was greater than 50%. These dogs showed no toxic symptoms. Dogs inhaling carbon monoxide however experienced all the symptoms of carbon monoxide toxicity with death occurring at approximately the same carboxyhemoglobin concentration [*15*].

Goldbaum also studied the effect of intraperitoneal injection of 100% carbon monoxide in dogs. Although elevated concentrations of carboxyhemoglobin were obtained no carbon monoxide toxicity occurred. In as much as the combination of carbon monoxide and erythrocytes after intraperitoneal injection of carbon monoxide should be similar to that after inhaling of carbon monoxide, the lack of toxicity after intraperitoneal injection may be due to removal

of dissolved carbon monoxide from the blood by passage through the lungs. On the contrary, when carbon monoxide is inhaled there is significant dissolved carbon monoxide in the blood leaving the lungs and when it reaches the organs. Their explanation for the lack of toxicity in transfused dogs when their blood contained elevated carboxyhemoglobin concentrations was that there was little dissolved carbon monoxide in the plasma [*15*]. To cause toxicity, dissolved carbon monoxide must be present in the blood to cross into the tissues and interfere with the combination of oxygen and cytochrome a_3 [*16*]. The resulting concentration in the tissue cells was insufficient to interfere with the combination of oxygen with cytochrome a_3. As carbon monoxide is tightly bound to hemoglobin, even with high carboxyhemoglobin concentrations, the dissolved carbon monoxide in the plasma is insignificant [*15*]. When carbon monoxide is inhaled, however, a high concentration of dissolved carbon monoxide takes place in the blood of the lungs, because a high carbon monoxide tension is present in the alveolar air. Since the combining of carbon monoxide with hemoglobin is not rapid, the blood circulating to organs especially heart muscle and brain, will contain significant amounts of dissolved carbon monoxide. Dissolved carbon monoxide can cross into the tissue cells and combine with cytochrome a_3 and interfere with cellular respiration [*16*].

Multifactorial influences balance myocardial oxygen supply with demand. Circulatory integrity and myocardial tissue needs are basic to this scheme. Carbon monoxide by competing with oxygen for cytochrome a_3 interferes with the oxygen transport between blood and tissues. In the race for tissue oxygenation those individuals with a decreased rate of oxygen release start with a handicap that may or may not be compensable. The existence of additional handicaps such as coronary artery disease within this system will greatly hamper their ability to compete. Coronary artery disease may preclude or limit delivery of adequately oxygenated blood to the myocardial tissue [*17*].

Wittenberg has reviewed the physical diffusion of oxygen in cells and proposed that myoglobin may facilitate the diffusion in skeletal and cardiac muscle by reversibly combining with oxygen molecules and taking a short "random walk" and passing on the oxygen molecule to another uncombined myoglobin molecule. He has experimentally demonstrated that oxygen diffusion is much more rapid in myoglobin solutions, as compared with solutions of similar viscosity that do not bind oxygen [*18*].

Wittenberg had postulated that it might account for 50 to 90% of oxygen reaching the mitochondria during heavy work. Carbon monoxide then might well be found to exert a deleterious role by combining with myoglobin and interfering with facilitated oxygen diffusion. The reaction between carbon monoxide, oxygen, and myoglobin has an M value (affinity constant) about one sixth that for the reaction between carbon, oxygen, and hemoglobin. However, cellular oxygen tension is less than one fourth that of arterial oxygen tension so that a blood carboxyhemoglobin of 10% saturation would be in equilibrium with 6 to 7% carboxyhemoglobin. It is interesting to speculate on the effect of 7% decrease in facilitated diffusion on mitochondrial tension in a normal subject during heavy exercise or in a patient with coronary artery disease at rest [*18*].

Conclusion

From 1958 to 1980, the Cuyahoga County (Cleveland, OH and suburbs) Coroner's Office certified the sudden deaths of 48 persons who were between the ages of 30 to 86 years, as caused by asphyxia by carbon monoxide, combined with an "other" natural disease as the condition that contributed to those deaths or vice versa. Of those 48 persons, 38 had levels of carboxyhemoglobin below that considered to be lethal in and of themselves. These 38 cases were studied in detail and an attempt was made to explain the reason for the vulnerability of these individuals to such low levels of carboxyhemoglobin. Atherosclerotic coronary artery disease was the "other" condition linked to the deaths of most of these individuals.

The difference between coronary circulation and the systemic circulation in their mode of

adaptation to the increased oxygen requirements of stress appears to be one of the factors in the basis for the vulnerability of persons suffering from coronary atherosclerotic heart disease to low levels of carboxyhemoglobin. The major effect of carboxyhemoglobin on myocardial oxygenation appears to be a decrease in oxygen delivery and the need for increase in coronary blood flow. Coronary vascular disease may prevent an increase in local coronary blood flow in response to this need. Under these circumstances, the myocardium is forced to extract more oxygen but does this in the face of a markedly reduced coronary venous and tissue oxygen tension.

Another action of carbon monoxide is at the cellular level where the hematin iron atoms of cytochrome a_3 are liganded by carbon monoxide, thereby losing their reactivity towards oxygen, thus resulting in impaired unloading of oxygen in the tissues.

Inadequate myocardial oxygenation is shown to interfere with cellular concentration of lactate and pyruvate and in the extraction of those metabolites.

The role played by carbon monoxide combining with myoglobin and interfering with facilitated oxygen exchange may also be a factor in bringing about these deaths.

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Address requests for reprints or additional information to
Elizabeth K. Balraj, M.D.
Cuyahoga County Coroner's Office
2121 Adelbert Rd.
Cleveland, OH 44106