Myocardial and Systemic Vascular Responses to Low Concentrations of Carboxyhemoglobin

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ABSTRACT

Carboxyhemoglobin alters the oxyhemoglobin dissociation curve in such a manner that oxygen is released to the tissues with great difficulty and at a lower oxygen tension. The known effects on heart and brain of breathing low concentrations of carbon monoxide are primarily related to this leftward shift and perhaps also to its combination with myoglobin and certain iron-containing enzymes. Hemoglobin-oxygen equilibria in the presence of carboxyhemoglobin resemble the equilibria of more primitive forms of hemoglobin and give rise to the suggestion that this decrease in the access to oxygen is a form of counter-evolution.

The human toxicology of carbon monoxide was first studied in detail by Haldane in 1895.14 A series of courageous experiments performed on himself led to the conclusion that the symptoms of carbon monoxide intoxication closely resembled the effects produced by exposure to decreased concentrations of oxygen. Although he did not observe serious symptoms at rest until his hemoglobin was at least one third saturated with carbon monoxide, exertion produced mild dyspnea and palpitations when as little as 14 percent carboxyhemoglobin (COHb) was present. Recently presented data from our laboratory suggest that COHb concentrations as low as 5 percent may interfere with oxygen delivery to the diseased myocardium.5 More recent studies have confirmed this and demonstrated that low concentrations of carbon monoxide may provoke electrocardiographic abnormalities in patients with coronary artery disease.1

Theoretical Considerations

The respiratory characteristics of hemoglobin may be defined by (1) the oxygen capacity and (2) the shape of the dissociation curve. Since one gram of hemoglobin will reversibly bind 1.34 ml of oxygen, the oxygen capacity is closely related to hemoglobin concentration. Invertebrates have oxygen capacities ranging from one to two ml per 100 ml of blood; fish, amphibia and reptiles carry between 5 and 15 ml per 100 ml of blood while mammals carry between 15 and 20 ml per 100 ml of blood. The capacity may be as high as 40 ml per 100 ml of blood in certain diving vertebrates.

Equal in importance to the oxygen capacity of hemoglobin is the affinity of hemoglobin for oxygen. Many attempts to
describe mathematically the oxyhemoglobin dissociation curve have been made, but the concept of loading and unloading tensions, proposed by Krogh and Leitch in 1919, has survived as a simple and unique description of hemoglobin equilibria. The loading tension \( t_l \) is the oxygen tension permitting hemoglobin to become 95 percent saturated with blood; the unloading tension \( t_u \) is the tension associated with half saturation. The former is related to ease of uptake within the lung, the latter to ease of unloading within the peripheral tissues. Generally, the two values move in the same direction so that a conflict exists since a low \( t_l \) is needed to insure adequate saturation in the lung while a high \( t_u \) is needed to insure rapid diffusion of oxygen from blood to tissues.

Another characteristic of hemoglobin, important in an understanding of the pathophysiology of carboxyhemoglobin, is the Bohr shift. Decreasing pH shifts the curve to the right and raises the \( t_u \), enhancing tissue oxygenation; increasing pH shifts the curve to the left and increases \( t_l \), which benefits oxygen uptake in the lung but decreases tissue oxygen tension by decreasing \( t_u \). In general, a pH decrease of 0.2 units in human blood produces an increase in \( t_u \) from 27 to 34 mm Hg. One might predict a rightward shift in conditions associated with decreased tissue oxygen availability (low blood flow) and an increase with conditions associated with decreased atmospheric oxygen concentration (altitude).

**Respiratory Characteristics**

The respiratory characteristics of carboxyhemoglobin approach those of primitive hemoglobins. The oxygen capacity is diminished by the volume of carbon monoxide bound and the dissociation curve is shifted to the left decreasing the \( t_u \). In figure 1 is shown the oxyhemoglobin dissociation curve, plotting oxygen content against oxygen tension instead of the more conventional oxygen saturation to demonstrate both of these effects. Increasing carboxyhemoglobin concentration decreases oxygen capacity and the \( t_u \).

The \( t_u \) oxyhemoglobin in the presence of various concentrations of carboxyhemoglobin may be calculated by equations first published in 1912 by Douglas, Haldane and Haldane. By way of footnote, John S. Haldane and a young assistant, C. G. Douglas (of later altitude physiology fame), did the experimental work while Haldane's 20 year old son, John Burdon Sanderson Haldane, provided the mathematical treatment. Unloading tensions for a number of COHb mixtures together with those from a number of more primitive animals are shown in figure 2. One can envision hemoglobin evolution as an ascent up the \( t_u \) ladder. Note that a human with a COHb saturation of 30 percent has slipped well down the ladder and is somewhere between a newborn goat and an embryonic chick in the evolutionary ladder.
Changes in gas exchange, following exposure to carbon monoxide, are dictated by changes in the oxyhemoglobin dissociation curve in the presence of various concentrations of COHb. The curve is shifted to the left, so that oxygen tension must decrease if the same arteriovenous oxygen difference and venous saturation are to be maintained. The decrease in mixed venous oxygen tension is presumably the primary event; other hemodynamic changes are probably compensatory. The decrease in mixed venous and coronary sinus oxygen tension (and also in peripheral, tissue and myocardial oxygen tension) appears to initiate a series of stress responses which attempt to compensate for the decrease in oxygen tension. In general these responses resemble those seen with increased adrenergic activity.

**Myocardial and Systemic Oxygen Exchange**

Changes in coronary blood flow and myocardial oxygen extraction can best be appreciated by considering the differences between myocardial and systemic oxygen exchange. The coronary circulation differs markedly from the systemic circulation in its mode of adaptation to the increased oxygen requirements of stress. Peripheral tissues normally extract about 25 percent of the oxygen present in arterial blood and the remaining 75 percent serves as a reserve supply. Total oxygen uptake may be increased by increasing the amount of oxygen extracted from the perfusing blood and by increasing the rate of blood flow. In periods of stress, for example, mixed venous oxygen tension may drop from a normal of 40 mm Hg to below 20 mm Hg. In contrast, the exorbitant resting myocardial oxygen needs are met by extracting a much greater fraction of oxygen from the perfusing coronary blood than is extracted by the peripheral tissues from the systemic blood. Approximately 75 percent of oxygen is extracted from the coronary circulation at rest and coronary venous blood is about 25 percent saturated, corresponding to an oxygen tension of 20 mm Hg. If increased myocardial oxygen needs were met by increasing oxygen extraction, as in the peripheral circulation, coronary venous and myocardial cellular 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 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.

Myocardial oxygen consumption, the product of coronary blood flow and the
Responses to low concentrations of COHb

The difference between arterial and coronary sinus oxygen content, is a complex function of external ventricular work, myocardial wall tension and fiber length, rate of development of ventricular pressure and heartbeat rate. Increasing oxygen requirements must be met by increasing oxygen consumption, otherwise myocardial ischemia and necrosis will develop. If oxygen is plentiful, glucose and lactate are extracted from the coronary perfusate and metabolized to pyruvate in the glycolytic cycle. Pyruvate from this source, together with directly extracted pyruvate and acetate fragments from fatty acid degradation, are converted to acetyl coenzyme A and oxidized in the citric acid cycle liberating energy, carbon dioxide and water. In periods of insufficient oxygen supply, the citric acid oxidative cycle is inactivated and pyruvate accumulates in the cytoplasm. A small amount of energy is produced by glycolysis as the enzyme nicotinamide adenine dinucleotide (NAD, or DPN in the older classification) oxidizes one of the glycolytic intermediates and produces high energy bonds. The cytoplasmic supply of NAD would soon be exhausted if a mechanism for its regeneration did not exist. Accumulating pyruvate is reduced to lactate by the reduced form of NAD (NADH) and, in the process, NADH is oxidized to NAD, permitting continued operation of the glycolytic cycle. In summary, inadequate oxygen decreases the utilization of pyruvate by the citric acid cycle, pyruvate accumulates in the cytoplasm and lactate is produced from the accumulating pyruvate.

Metabolic Extractions

Increasing cellular concentrations of lactate and pyruvate decrease the diffusion gradient between coronary perfusate and cytoplasm and decrease the extraction of these metabolites. Normally, arterial lactate and pyruvate concentrations determine the diffusion gradient so that the arteriovenous difference (or extraction) is a function of arterial lactate or pyruvate concentration. The extraction ratio of either lactate or pyruvate (the arterio-coronary sinus difference divided by arterial concentration) is a useful index for expressing extraction, which is relatively independent of arterial concentration. Although increasing arterial concentrations may increase the extraction ratio slightly, the ratio does not decrease with decreasing arterial concentration so that a decrease in extraction ratio may be considered due to some intracellular alteration. The extraction ratio for both metabolites ranges from 15 to 30 percent when oxygen is plentiful. During periods of inadequate oxygenation, extraction decreases and lactate and pyruvate may actually be produced by the myocardium so that coronary sinus concentrations exceed arterial concentrations.

Carboxyhemoglobinemia Systemic Hemodynamics

Several investigators have studied the effects of carboxyhemoglobinemia systemic hemodynamics. Chiodi observed increases in pulse rate and cardiac output with COHb concentrations as low as 16 percent. Both Haldane and Haggard observed hyperventilation during carbon monoxide inhalation in man and in experimental animals although Chiodi et al were unable to measure significant increases in ventilation in their studies.

Chevalier et al evaluated the overall cardiorespiratory adaptation to exercise by measuring oxygen consumption before, during and after exercise in normal subjects prior to and after inhalation of sufficient carbon monoxide (0.5 percent) to raise COHb concentration to an average of 3.95 percent. Total oxygen consumption averaged 5,990 ml before CO inhalation and 5,794 ml after inhalation, the difference representing a slight training effect. The
Figure 3. Arterial oxygen tension (Pao2), mixed venous oxygen tension (Pvvo2), alveolar-arterial oxygen difference (AaD), minute ventilation (Ve), cardiac output (Qs) and oxygen consumption (Vo2) in a group of patients before and after breathing five percent carbon monoxide for 45 seconds. Brackets indicate standard error of difference between means.

Oxygen debt was 21 percent of total oxygen consumption prior to CO and rose to 24 percent (p < 0.05) afterwards, suggesting that oxygen supply during exercise was inadequate for metabolic requirements. The overriding importance of this study was that COHb concentrations as low as 3.95 percent could call forth adaptive responses on the part of the peripheral circulation. These investigators also observed small but significant decreases in inspiratory capacity and total lung capacity together with statistically borderline decreases in vital capacity following carbon monoxide inhalation.

In 1965 and again in 1970, we reported the systemic hemodynamic and respiratory response to acute elevation of COHb in man by means of measurements performed during diagnostic cardiac catheterization.3,4 Saturations of COHb between 6 and 12 percent were achieved by the breathing of either 5 percent CO for 30 to 45 seconds or 0.1 percent CO for 8 to 15 minutes.

In figure 3 are summarized our findings following administration of the higher concentration. Cardiac output increased from 5.01 to 5.56 l per min; minute ventilation increased from 6.86 to 8.64 l per min, while arterial carbon dioxide tension fell from 40 to 38 mm Hg. Systemic oxygen extraction ratios increased from 0.27 to 0.32, indicating more complete extraction of oxygen from perfusing arterial blood. Mixed venous oxygen tension fell from 39 to 31 mm Hg as a result of the leftward shift of the oxyhemoglobin dissociation curve.

Arterial oxygen tension unexpectedly fell from an average value of 81 to 76 mm Hg. This finding was recently discussed in detail4 and agreement reached with Brody and associates6 that it is related to enhancement of the venoarterial shunt effect and is more prominent in patients who initially have low oxygen tensions. Increased ventilation tends to minimize the decrease in arterial oxygen tension in conscious man, although the alveolar-arterial oxygen difference remains elevated. Dogs ventilated at constant tidal volumes show marked decreases in arterial oxygen tension with carbon monoxide breathing because of increased atelectasis and the inability to hyperventilate. Such observations suggest that carbon monoxide inhalation would have a significant effect on arterial oxygen tension in patients with pre-existing lung disease, individuals who are heavy smokers and patients in coma from severe carbon monoxide poisoning.

These studies were repeated using the lower concentration of carbon monoxide. Cardiac output did not change significantly, although arterial carbon dioxide tension decreased indicating hyperventilation. Changes in arterial and mixed venous oxygen tensions were similar to those observed with the higher concentrations.

Myocardial studies were performed before and after the administration of either 5 percent or 0.1 percent carbon monoxide for the time periods listed. Patients were divided into two groups, those with coronary artery disease and those with other cardiopulmonary disorders.
The myocardial arteriovenous oxygen difference is more than twice the systemic difference because of the high oxygen requirements of the contracting myocardium. Increased oxygen demands are met by increasing coronary blood flow since further increases in oxygen extraction would so lower coronary venous oxygen tension that myocardial cells would face certain hypoxia. In figure 4 it is shown that the lowest concentration of carbon monoxide decreased the myocardial arteriovenous oxygen difference an average of 6.6 and 7.9 percent (in the patients with other cardiopulmonary diseases and coronary disease respectively) while the higher concentration decreased the myocardial arteriovenous oxygen difference by 25 and 30.5 percent. The same figure also presents the effects of higher levels of carboxyhemoglobin in a series of canine experiments.

Myocardial oxygen consumption could only be maintained in the face of a decreasing arteriovenous oxygen difference by the adaptive maneuver of increasing blood flow. In figure 5 it is demonstrated that coronary blood flow did increase in all but two of the studies, regardless of the dose delivered. These changes were statistically significant for three of the four groups. Neither the presence of coronary artery disease nor the concentration of carbon monoxide appeared to alter the response to increasing COHb. Myocardial tissue oxygen tension (coronary sinus measurements) decreased in all but one patient (figure 6).

Several recent studies have confirmed our findings that relatively low concentrations of carboxyhemoglobin can interfere with myocardial and systemic oxygen delivery in man. Dhinsda et al. administered carbon monoxide intermittently to three monkeys for 12 different 30 minute periods each day over an eight month period and achieved carboxyhemoglobin levels of 11 to 12 percent. Cardiac output was unchanged but the arteriovenous oxygen difference and oxygen consumption decreased while mixed venous oxygen difference was unchanged. DeBias et al. administered 100 ppm carbon monoxide continuously to a series of monkeys achieving carboxyhemoglobin saturations averaging 12.4 percent. These animals exhibited an increase in hematocrit from an average of 38 to 52 percent and also developed significant electrocardiographic abnormalities. T wave in-

**Figure 4.** Ratio of coronary arteriovenous oxygen difference during carbon monoxide breathing (Ca-Csco) to control arteriovenous oxygen difference (Ca-Cscontpoi) plotted on vertical axis against change in COHb saturation. Ann. N. Y. Acad. Sci., Oct. 5, 1970.

**Figure 5.** Coronary blood flow (CBF) following carbon monoxide breathing plotted against that obtained during control state. Line of identity is shown and points to left of line indicate increase in coronary blood flow with carbon monoxide. CAD refers to coronary artery disease; other indicates all other heart disease. Ann. N. Y. Acad. Sci., Oct. 5, 1970.
Adaptations to Carboxyhemoglobin Induced Hypoxia

The data reviewed suggest that the mammalian cardiopulmonary system exhibits one or more of the following responses, which minimize cellular hypoxia when exposed to carboxyhemoglobin-induced hypoxia: (1) decrease in oxygen requirements; (2) increase in blood flow; (3) polycythemia; (4) rightward shift of the oxyhemoglobin dissociation curve mediated through increases in 2,3 diphosphoglycerate and (5) increased oxygen extraction. The response chosen appears to depend upon species, status of the vascular bed and intensity and duration of the hypoxic stress.

Our studies in the resting human subject indicated that an increase in coronary blood flow was an almost universal response to either high or low concentrations of carbon monoxide. In contrast, systemic blood flow increased only when the subjects were exposed to the higher concentration. Vogel and Gleser exposed healthy volunteers to somewhat higher concentrations (225 ppm or 0.0225 percent) for a sufficient period of time to raise carboxyhemoglobin concentrations to 18 to 20 percent. Resting cardiac output and heart rate were not increased but were higher than control values at each of three levels of exercise. Maximal oxygen consumption was 23 percent less than control.

Dhinsda's resting monkeys, intermittently exposed to low concentrations, minimized hypoxia by decreasing oxygen requirements while Debias' monkeys, continuously exposed to somewhat lower concentrations, developed polycythemia. The inability of this polycythemic response to protect the monkeys against myocardial hypoxia is revealed by the uniformly observed electrocardiographic abnormalities. None of the studies demonstrated marked increase in oxygen extraction. This response would expose tissues to lowered oxygen tensions and is probably the least desirable of the physiologic responses suggested.

Most of these adaptive responses would probably serve admirably for normal man. The development of coronary atherosclerosis, however, might be predicted to render any of these adaptive responses ineffective and expose the myocardium to potentially lethal hypoxia. This prediction has been graphically confirmed by the recent observations of Aronow et al. These investi-
gators exposed 10 patients to heavy freeway automotive traffic by driving them in a station wagon for 90 minutes. Mean COHb concentration rose from 1.12 to 5.08 percent saturation and then decreased to 2.91 percent saturation two hours later. Four of the subjects exhibited electrocardiographic changes during the exposure period; they did not experience changes during a subsequent drive when provided with a source of uncontaminated air. Immediately following the exposure period, the subjects were exercised on a bicycle until they developed angina pectoris. The time necessary to develop angina was 249.4 seconds prior to exposure. The time fell to 174.3 seconds after exposure and rose to 210.8 seconds two hours later. In addition, angina developed at lower heart rates and systemic blood pressures following exposure to freeway air.

References

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