BRIEF COMMUNICATIONS

Influence of Capillary and Tissue $P_{O_2}$ on Carbon Monoxide Binding to Myoglobin: A Theoretical Evaluation

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In order to evaluate how much myoglobin is linked to CO at various HbCO concentrations and at different $P_{O_2}$, a three compartment model (arterial blood, venous capillary blood, and tissue myoglobin) has been considered. A steady-state condition has been assumed for $O_2$ consumption with no metabolization for CO. The curves obtained by computer simulation of the proposed model indicate that HbCO levels found in smokers entail values of MbCO which could be high enough to reduce intracellular oxygen transport significantly: especially where the $P_{O_2}$ is physiologically low (as in subendocardium) and/or hypoxemic–ischemic conditions are present.

INTRODUCTION

In recent years, strong interest has developed in oxygen delivery mechanisms in coronary patients, because of their impaired ability to increase coronary blood flow when myocardial oxygen demands are increased. An important factor affecting oxygen transport and oxygen diffusion mechanisms is represented by carbon monoxide: it has been claimed that the higher incidence of coronary events in cigarette smokers may be related to the absorption of CO which displaces oxygen from hemoglobin because of its higher affinity and causes tighter binding of hemoglobin, thereby inducing a leftward shift of the oxyhemoglobin dissociation curve (Aronow, 1976; Jain et al., 1977). Carbon monoxide also combines with myoglobin (Mb), and it has been suggested that this can impair the facilitated diffusion of oxygen to mitochondria (Wittenberg, 1970; Kreuzer and Hoofd, 1976). According to Coburn et al. (1973), the quantity of CO bound to Mb, constant over a wide range of arterial $P_{O_2}$, increases when arterial $P_{O_2}$ falls below a critical level of 30–35 mm Hg. The importance of the role played by Mb molecules in intracellular $O_2$ transport has been given support by the experiments of Wittenberg et al. (1975) showing an increase of $O_2$ consumption by hypoxic pigeon breast muscle fibers by functional Mb and of De Koning et al. (1976) indicating an increase on $O_2$ flux across the smooth muscle of chicken gizzard in the presence of functional Mb. However, Cole et al. (1978) were unable to show an augmentation of $O_2$ consump-

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tion by functional Mb in the isolated fluorocarbon-perfused dog heart and Gayeski and Honig (1978) believe that Mb does not facilitate O₂ diffusion in resting muscle. According to Schwarzmann and Grunewald (1978) Mb contributes to at most 40% of the total O₂ transport in chicken gizzard. Myoglobin also acts as a short period oxygen store to buffer fluctuations in the rate of flow of oxygen in the beating heart (Kagen, 1973). According to Wittenberg et al. (1975) "storage and transport are not necessarily separate functions but are extremes of a continuum, in which storage predominates during changing states of the muscle and transport is dominant in steady states." Therefore, we found it interesting to evaluate how much Mb will be linked to CO at different HbCO concentrations and at different P₀₂ levels. The results obtained by computer simulation are reported in the present paper.

MODEL BUILDING METHODOLOGY

Three compartments have been considered: (1) arterial blood, (2) venous capillary blood, and (3) tissue myoglobin. Oxygen partial pressure gradients do exist between these compartments because of oxygen consumption and have been settled as independent parameters in a range of reasonable values. The model is schematically illustrated in Fig. 1. Constant CO exposure and constant O₂ consumption have been assumed, giving a steady-state condition where saturations can be computed by the equilibrium equations. Kinetic effects have not been considered. Carbon monoxide has been entered as HbCO saturation at the arterial level and capillary P₇CO has been computed assuming that no HbCO saturation

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**Fig. 1.** Diagram of the model showing the three compartments. On the left the input parameters, within the boxes the functions which are further detailed in the text, and on the right the derived values.
changes occur at the capillary level, where only $P_{CO}$ variations with $P_{O_2}$ are allowed such as in closed systems. Actually, what is constant is the total CO, i.e., the CO linked to Hb plus the physically dissolved CO. Because of the very high CO affinity of Hb, almost all the CO is linked, and $P_{CO}$ variations take place with really very small HbCO saturation changes. Thus, the assumption of a constant HbCO saturation introduces a negligible error in the calculation of capillary $P_{CO}$.

The $P_{CO}$ of tissue Mb has been considered to be the same as in capillary blood, dealing with a steady-state system which does not metabolize CO.

The binding of $O_2$ and CO with Hb can be described by the following equations:

\[
(HbO_2)_{saturation} = \frac{x}{x+y} \cdot \frac{A_1(x+y) + 2A_2(x+y)^2 + 3A_3(x+y)^3 + 4A_4(x+y)^4}{4[1 + A_1(x+y) + A_2(x+y)^2 + A_3(x+y)^3 + A_4(x+y)^4]} 
\] (1)

\[
(HbCO)_{saturation} = \frac{y}{x+y} \cdot \frac{A_1(x+y) + 2A_2(x+y)^2 + 3A_3(x+y)^3 + 4A_4(x+y)^4}{4[1 + A_1(x+y) + A_2(x+y)^2 + A_3(x+y)^3 + A_4(x+y)^4]} 
\] (2)

where $A_1, A_2, A_3, A_4$ are the Adair’s constants, $x = P_{O_2}, y = M_{Hb} \cdot P_{CO}$ ($M$ being the coefficient of the Haldane’s formulation):

\[
\frac{HBCO_{sat}}{HbO_2_{sat}} = M \cdot P_{CO}/P_{O_2}. 
\]

The binding of $O_2$ and CO with Mb can be described by the following equations:

\[
(MbO_2)_{saturation} = \frac{P_{O_2}}{P_{O_2} + M_{Mb} \cdot P_{CO} + P_{50}} 
\] (3)

\[
(MbCO)_{saturation} = \frac{M_{Mb} \cdot P_{CO}}{P_{O_2} + M_{Mb} \cdot P_{CO} + P_{50}} 
\] (4)

where $P_{50}$ is the $P_{O_2}$ giving 50% MbO$_2$ saturation.

Model simulation has been conducted with a PDP8/e computer entering venous capillary $P_{O_2}$ ($P_{VO_2}$) values ranging from 5 to 40 mm Hg and HbCO saturations ranging from 5 to 50%, while tissue Mb $P_{O_2}$ has been assumed to be variable from $P_{VO_2}$ value to zero. For Adair’s constants the values recently proposed by Winslow et al. (1977) have been chosen. The temperature has been considered to be 37°C. Values of $M_{Hb} = 220$, $M_{Mb} = 39$, and $P_{50(Mb)} = 2.7$ mm Hg have been used according to Antonini and Brunori (1971).²

**RESULTS AND DISCUSSION**

The behavior of the proposed model, obtained by computer simulation in a wide range of variation of the parameters is visualized in Figs. 2–8. Figure 2 shows the changes of $P_{CO}$ in venous capillary compartment as a function of venous capillary $P_{O_2}$, in presence of various HbCO saturations. A notable increase of $P_{CO}$ occurs when $P_{VO_2}$ decreases below 20 mm Hg. This phenomenon, due to the competition

² The value of $P_{50(Mb)}$ has an important influence on the results. However, there is some uncertainty about this constant. Guyeski and Honig (1978) report a $P_{50}$ of 6.3 for dog muscle Mb. On the other hand, Tamura et al. (1973) and Ross and Warming (1977) find values in reasonable agreement with the data of Antonini and Brunori if extrapolated at 37°C. Wittenberg (1977) indicates a $P_{50}$ of 2.7 for human heart Mb, and Schwartzmann and Grunewald (1978) a value of 2.8 for chicken muscle Mb.
Fig. 2. $P_{CO}$ in venous capillary compartment as a function of $P_{VO_2}$ at HbCO levels of 5, 10, and 20%. The equations used and the values of the constants are detailed in the text.

Fig. 3

Fig. 4

Fig. 5
Figs. 3–7. MbCO saturation as a function of $P_{MbO_2}$ at various HbCO levels (from 5 to 50%) at $P_{VO_2}$ of 5, 10, 15, 20, and 40 mm Hg. The equations used and the values of the constants are detailed in the text.

Fig. 8. MbCO levels at the most likely $P_{O_2}$ at the neighborhood of mitochondria (1 mm Hg) as a function of $P_{VO_2}$ at various HbCO levels. A ratio exceeding 4 between MbCO and HbCO can be found at low HbCO and $P_{VO_2}$ levels.

between $O_2$ and CO in Hb ligation, is more evident at low HbCO saturations. Figures 3–7 completely characterize the tissue compartment in a range of HbCO from 5 to 50%, of $P_{VO_2}$ from 5 to 40 mm Hg, and of $P_{MbO_2}$ from 0 to 40 mm Hg.

If our assumptions and parametric values are correct, the model predicts that, for any given HbCO level, a marked increase of MbCO saturation does occur at low levels of $P_{MbO_2}$. Moreover, if one considers a $P_{MbO_2}$ of 1 mm Hg as it is
expected in the neighborhood of mitochondria (Coburn et al., 1973; Chance, 1976), the MbCO saturation depends on venous capillary $P_{O_2}$ and HbCO saturation. In fact, as illustrated in Fig. 8, relatively low levels of HbCO (5–10%) entail marked increases of MbCO at low $P_{VO_2}$, while with high levels of HbCO the MbCO saturation is less dependent on $P_{VO_2}$. This means that in smokers, who generally have values of 5–10% HbCO, the binding of Mb with CO will be higher where the venous capillary $P_{O_2}$ is physiologically low (as in subendocardium) and when conditions of hypoxemia, ischemia, and/or increased metabolic demand are present. Thus, in coronary patients (where the inability of coronary flow to rise could interfere with the compensatory response to CO and exacerbate a preexisting disparity between oxygen supply and oxygen demand) Mb saturation with CO will result much higher than HbCO.

These results could constitute a theoretical support of some experimental and clinical observations. In fact, there is evidence that as $P_{O_2}$ falls below 40 mm Hg, blood HbCO decreases indicating a shift of CO out of the vascular compartment into heart and skeletal muscle (Coburn and Clark, 1976). Moreover, it has been reported that cardiac arrhythmias constitute a major risk to life during CO exposure in monkeys (De Bias et al., 1973) and that the voltage required to induce ventricular fibrillation is lower for infarcted monkeys (De Bias et al., 1976) and dogs (Aronow et al., 1978) inhaling CO. In the clinical field, myocardial infarction and muscle necrosis can occur in CO poisoning, while moderate CO intoxication can precipitate myocardial infarction in coronary patients (Sharf et al., 1974; Stewart and Hake, 1976). Moreover, it has been demonstrated in double-blind randomized studies that exposure to moderate CO pollution (HbCO 2.7–2.9%) aggravates exercise-induced angina in coronary patients (Anderson et al., 1973; Aronow and Isbell, 1973) and intermittent claudication in patients with iliofemoral occlusive arterial disease (Aronow et al., 1974).

REFERENCES


