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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 absorbtion 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 fluocarbon-perfused dog heart and Gayeski and Honig (1978) believe that Mb does not facilitate O_2 diffusion in resting muscle. According to Schwarzmann and Grunewald (1978) Mb contributes to at most 40% of the total O_2 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 P_{O_2} 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 O_2 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 P_{CO} has been computed assuming that no HbCO saturation

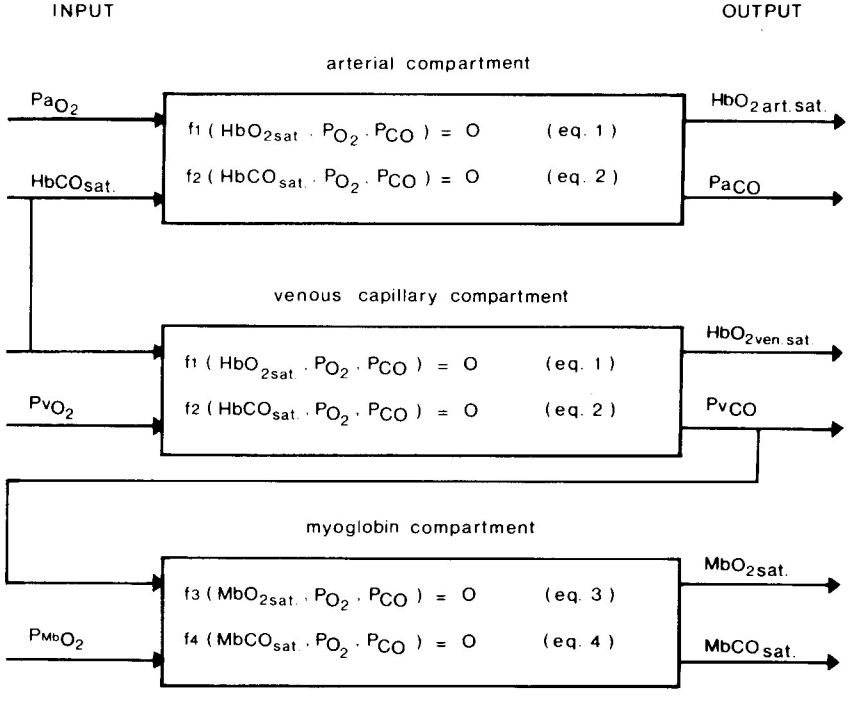

FIG. 1. Diagram of the model showing the three compartments. On the left the input parameters, within the boxes the functions which are further detailed in the text, and on the right the derived values.

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:

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

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

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:

$HBCO_{sat}/HbO_{2_{sat}} = M \cdot P_{CO}/P_{O_2}$).

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

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

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

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°. 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. Gayeski 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 Warme (1977) find values in reasonable agreement with the data of Antonini and Brunori if extrapolated at 37°, 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.

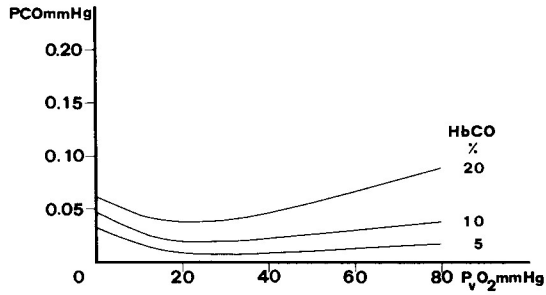

FIG. 2. P_{CO} in venous capillary compartment as a function of P_{VO_2} at HbCO levels of 5, 10, and 20%. The equations used and the values of the constants are detailed in the text.

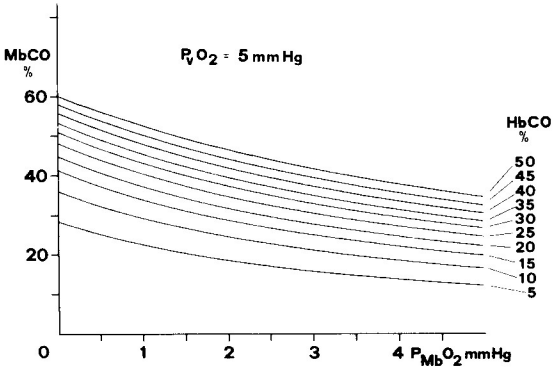

FIG. 3

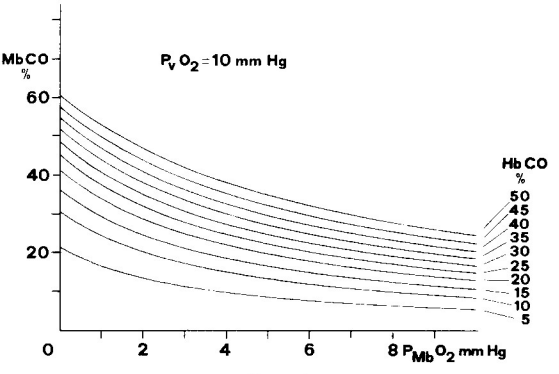

FIG. 4

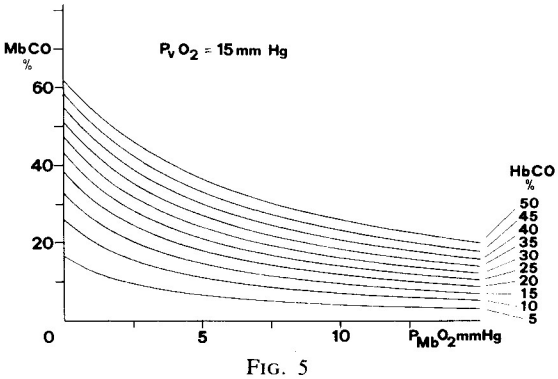

FIG. 5

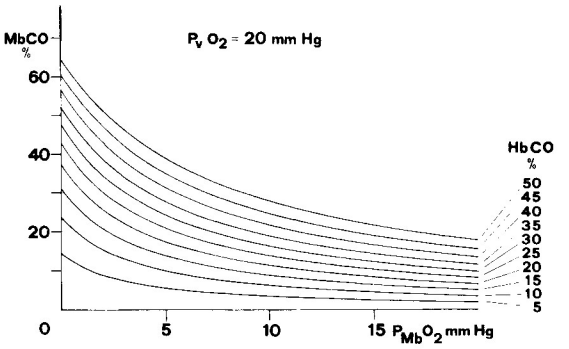

FIG. 6

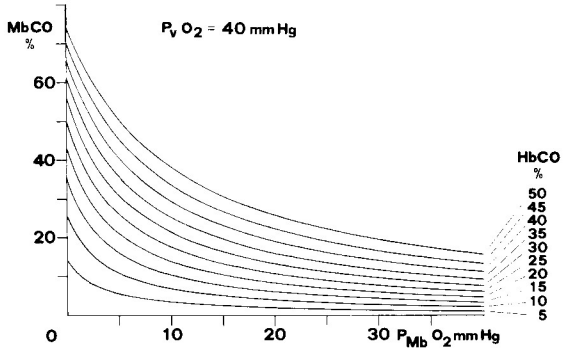

FIG. 7

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.

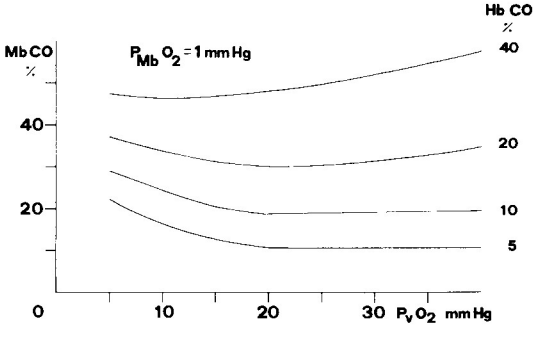

FIG. 8. MbCO levels at the most likely P_{O_2} at the neighborhood of mitochondria (1 mm Hg) as a function of P_{VO_2} at various HbCO levels. A ratio exceeding 4 between MbCO and HbCO can be found at low HbCO and P_{VO_2} levels.

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_{aO_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).

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