A multicompartment model of carboxyhemoglobin and carboxymyoglobin responses to inhalation of carbon monoxide

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Bruce, Eugene N., and Margaret C. Bruce. A multicompartment model of carboxyhemoglobin and carboxymyoglobin responses to inhalation of carbon monoxide. J Appl Physiol 95: 1235–1247, 2003.—We have developed a model that predicts the distribution of carbon monoxide (CO) in the body resulting from acute inhalation exposures to CO. The model includes a lung compartment, arterial and venous blood compartments, and muscle and nonmuscle soft tissues with both vascular and nonvascular subcompartments. In the model, CO is allowed to diffuse between the vascular and nonvascular subcompartments of the tissues and to combine with myoglobin in the nonvascular subcompartment of muscle tissue. The oxyhemoglobin dissociation curve is represented by a modified Hill equation whose parameters are functions of the carboxyhemoglobin (HbCO) level. Values for skeletal muscle mass and cardiac output are calculated from prediction formulas based on age, weight, and height of individual subjects. We demonstrate that the model fits data from CO rebreathing studies when diffusion of CO into the muscle compartment is considered. The model also fits responses of HbCO to single or multiple exposures to CO lasting for a few minutes each. In addition, the model reproduces reported differences between arterial and venous HbCO levels and replicates predictions from the Coburn-Forster-Kane equation for CO exposures of a 1- to 83-h duration. In contrast to approaches based on the Coburn-Forster-Kane equation for CO exposures of a 1- to 83-h duration, the present model predicts uptake duration. In contrast to approaches based on the Coburn-Forster-Kane equation for CO exposures of a 1- to 83-h duration, the present model predicts uptake duration. In contrast to approaches based on the Coburn-Forster-Kane equation for CO exposures of a 1- to 83-h duration, the present model predicts uptake duration.

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Although the original purpose of the Coburn-Forster-Kane (CFK) equation was to predict the rate of endogenous carbon monoxide (CO) production (7), this equation has since been used, with varying degrees of success, to predict the rate of carboxyhemoglobin (HbCO) formation during inhalation exposure to CO. In one of the first studies to use the CFK equation as a predictive model, Peterson and Stewart (26) reported that HbCO levels in sedentary men exposed to 25–1,000 parts/million (ppm) for 0.5–24 h were in reasonable agreement with predicted values. Other investigators have also demonstrated that rates of HbCO formation predicted by this model were in basic agreement with results obtained in CO inhalation exposure experiments (4, 14, 27, 36, 37). As a result of these studies, the CFK equation has often been used under circumstances quite different from the one for which the model was initially intended.

Despite the usefulness of the CFK model for predicting HbCO levels in response to long exposures to low CO concentrations as well as brief exposures to high concentrations, the model has several limitations. Because the CFK equation provides a first-order approximation to the slow dynamics of CO transport and storage, it is unlikely to accurately predict a rapid increase in HbCO level. In addition, this equation does not accurately predict either arterial or venous HbCO levels but a value between the two (4). Furthermore, ad hoc modifications of the CFK equations have often been necessary to improve the fit of the model to the data acquired. For example, in agreement with predictions based on the CFK equation, Tikuisis et al. (37) found that HbCO levels measured shortly after multiple exposures were a function of total CO dose rather than concentrations of inhaled CO. These observations suggested that the CFK equation could be used to predict percent HbCO even when CO levels varied considerably during the exposure period. To improve the fit of their data to the values predicted by the CFK equation, the authors applied values from repeated measures of each subject's alveolar ventilation to the model. Despite this modification of the CFK equation, the predicted values for percent HbCO were systematically greater than the data at most observation times. Furthermore, the responses to such large but brief stimuli have limited usefulness because they are not likely to reflect the full range of properties of the physiological system.

Another limitation of the CFK model is that it does not include extravascular storage sites for CO. Muscle myoglobin (Mb) contains one heme group per molecule and is, therefore, a potential binding site for CO. In humans, muscle accounts for ~41% of total body mass. Assuming a value of 4.7 mg Mb/g wet wt of muscle (23), a 70-kg man would be expected to have ~135 g of Mb, suggesting that muscle could be a significant storage site for CO. Peterson and Stewart's observation (26)
that the half-time for washout of CO was almost 30% greater than predicted by the CFK equation (320 vs. 252 min) is consistent with the concept that CO was being removed from two compartments rather than one during the excretion phase.

CO exposure continues to be a significant cause of morbidity and mortality. Although the CFK equation can be used to estimate the rate of formation of HbCO under a variety of exposure conditions, it is difficult to predict clinical outcome on the basis of the information provided by the CFK equation alone. A more comprehensive model of CO uptake, distribution, and elimination will be necessary to guide treatment strategies more effectively. The objective of the present study was to develop a predictive model of CO exposure that takes into account the possibility that a significant fraction of inspired CO can be bound to muscle Mb.

METHODS

Model Development

Structure of model. The model comprises five major compartments: lungs (alveolar), arterial blood, mixed venous blood, muscle tissue, and other soft tissues (Fig. 1). CO enters the lungs via the alveolar ventilation and diffuses into the pulmonary capillary blood according to the prevailing CO diffusion capacity of the lung (DLCO), establishing an end-capillary CO concentration (CecCO). Both hemoglobin (Hb)-bound and dissolved CO are taken into account. End-capillary PO2 (PecO2) is assumed to equal arterial PO2, which is specified as a parameter. After a time delay, end-capillary blood undergoes mixing in the arterial compartment with a time constant determined by the ratio of the volume of the compartment to the blood flow rate [i.e., cardiac output (Q)]. Thus arterial levels of oxyhemoglobin (HbO2) and HbCO are established. Arterial blood flows into two parallel compartments, both of which are divided into vascular and extravascular (tissue) subcompartments. Inflowing blood undergoes mixing in the vascular subcompartments, and CO can diffuse from the vascular to the extravascular tissue subcompartments. This diffusion is governed by two CO diffusion coefficients: DmCO for muscle tissue and DotCO for nonmuscle (other) tissue. In nonmuscle tissue, CO exists only in dissolved form. In muscle tissue, CO may also combine with Mb in competition with oxygen (O2). Muscle O2 tension (PmO2) is a parameter of the model. For both Mb and Hb, the corresponding Haldane equation is satisfied in each relevant compartment. Venous outflows from the two tissue compartments are combined at the entrance to the mixed venous compartment, where further mixing occurs. After another time delay, this blood returns to the lungs.

Mass balance equations. All compartments are represented by equations for conservation of mass for CO. In the alveolar compartment

\[
V_L \frac{dC_{ACO}(t)}{dt} = [P_{ACO}(t) - P_{ACO}(t)]V_A/P_B - CO_{fluxA}(t) \quad (1)
\]
where \( V_l \) is lung volume, \( C_{ACO} \) is the alveolar CO concentration, \( P_{ACO} \) is the alveolar partial pressure of CO (\( P_{CO} \)), \( P_{CO} \) is inhaled \( P_{CO} \), \( t \) is time, \( V_a \) is alveolar ventilation, \( P_B \) is barometric pressure, and \( CO_{flux_{LB}}(t) \) is the CO flux from lungs to blood, defined as

\[
CO_{flux_{LB}}(t) = (P_{ACO} - [(1 - K_v)P_{ECO}(t)]) \cdot DL_{CO} + K_vP_{ECO}(t - d_v) \cdot DL_{CO}
\]

where \( P_{ECO} \) is end-capillary \( P_{CO} \), \( d_v \) is the mean transport delay in mixed venous blood, \( P_{ECO} \) is mixed venous \( P_{CO} \), and \( K_v \) is used to apportion the effective pulmonary capillary \( P_{CO} \) between the mixed venous and end-capillary pressures. In all simulations here, \( K_v = 0.5 \) (see Tables 1 and 2 for definitions of variables and nominal values of parameters).

Vascular mixing in the pulmonary capillary compartment is ignored and \( C_{ECO} \) is determined by adding \( CO_{flux_{LB}} \) to the mixed venous blood, which enters the lungs after the mean transport delay, \( d_v \), from venous blood compartments. Thus

\[
C_{ECO}(t) = C_{MVCO}(t - d_v) + CO_{flux_{LB}}/Q
\]

The four blood volume compartments (arterial, mixed venous, and two vascular subcompartments of the tissues) are each described by an equation of the form

### Table 1. Glossary of variables

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Default Value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{ECO} )</td>
<td>Concentration of CO (ml/ml, BTPS) in end-capillary (ec), arterial (a), and mixed venous (v) blood, muscle venous (vm) and other tissue venous (vot) outflow, and lung alveolar (la) compartment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( HbCOj )</td>
<td>Carboxyhemoglobin concentration (ml CO/ml blood, BTPS) in arterial (a), muscle venous (vm), other tissue venous (vot), and mixed venous (v) compartments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( MbCO )</td>
<td>Carboxymoglobin (ml CO/ml tissue, BTPS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( d_j )</td>
<td>Time delay (min) between the end-capillary and arterial compartments (a), and between the mixed venous and pulmonary arterial compartments (v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{HbO}_2j )</td>
<td>Oxymyoglobin concentration (ml CO/ml blood, BTPS) in arterial (a), muscle venous (vm), other tissue venous (vot), and mixed venous (v) compartments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_{jO_2} )</td>
<td>Pressure (Torr) of ( O_2 ) in the arterial (a), alveolar (a), muscle (m) and other (ot) tissue, and mixed venous (v) compartments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_{jCO} )</td>
<td>Pressure (Torr) of CO in the arterial (a), alveolar muscle (m), and other (ot) tissue, and mixed venous (v) compartments</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Parameters and their default values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Default Value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( DL_{CO} )</td>
<td>Lung diffusion capacity for CO, normoxia</td>
<td>30 ml \cdot min^{-1} \cdot Torr^{-1}</td>
<td>26</td>
</tr>
<tr>
<td>( DL_{CO} )</td>
<td>Lung diffusion capacity for CO, hyperoxia</td>
<td>15 ml \cdot min^{-1} \cdot Torr^{-1}</td>
<td>21</td>
</tr>
<tr>
<td>( Dm_{CO} )</td>
<td>Muscle diffusion capacity for CO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( Hb )</td>
<td>Concentration of Hb in blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( Mv )</td>
<td>Myoglobin concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( M_h )</td>
<td>Haldane affinity ratio for Hb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( M_n )</td>
<td>Affinity ratio for Mb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( n )</td>
<td>Hill exponent for Hb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{HbO}_2 )</td>
<td>Oxygen capacity of Hb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_B )</td>
<td>Barometric pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_{O_2} )</td>
<td>Partial pressure of ( O_2 ) (arterial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_{MCO} )</td>
<td>Partial pressure of ( O_2 ) (muscle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_{O_250} )</td>
<td>Partial pressure of ( O_2 ) at 50% Hb sat.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_{O250} )</td>
<td>Partial pressure of ( O_2 ) at 50% Mb sat.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( S_{O_2} )</td>
<td>Solubility of ( O_2 ) in plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( Q )</td>
<td>Cardiac output</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( Q_m )</td>
<td>Blood flow to muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( Q_{ot} )</td>
<td>Blood flow to other tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( V_j ), ( j = a, v )</td>
<td>Volume (ml, BTPS) of the arterial (a) and mixed venous (v) blood, muscle venous (vm) and other (vot) tissue vascular compartments, and lung alveolar (la), lung (l), muscle (m), and other (ot) tissue nonvascular compartments</td>
<td>Estimated from data; see text</td>
<td></td>
</tr>
<tr>
<td>( V_{O_2} )</td>
<td>Metabolic rate</td>
<td>225 ml/min</td>
<td>10</td>
</tr>
<tr>
<td>( V_{CO} )</td>
<td>Endogenous CO production</td>
<td>7 ( \mu )mol/min</td>
<td>7</td>
</tr>
<tr>
<td>( V_{A} )</td>
<td>Alveolar ventilation</td>
<td>Measured for each subject (see text)</td>
<td></td>
</tr>
</tbody>
</table>
\[ V_i \frac{dC_{iCO}(t)}{dt} = [C_{iCO}^c(t) - C_{iCO}(t)] \cdot Q_i - Flux_i(t) \] (4)

where \( i = a, v, vm, \) or \( vot \) indicates one of the compartments, \( V \) is volume, \( C_{iCO}^c \) is the concentration of CO in blood entering the compartment, and \( Flux_i(t) \) is the rate of diffusion of CO out of the vascular volume. For the arterial and mixed venous compartments, this rate is zero. Otherwise

\[
\text{Flux}_{iCO}(t) = [\text{PotCO}(t) - \text{Pot}_{CO}(t)] \cdot \text{Dot}_{CO}
\]

with \( \text{Pot}_{CO}(t) \) and \( \text{Pot}_{CO}(t) \) representing the algebraic means of the partial pressures of CO in the arterial inflow and venous outflow for the muscle and other tissue compartments, respectively. Little information is available regarding \( \text{DM}_{CO} \) and \( \text{Dot}_{CO} \). Because \( O_2 \) diffusivity is similar in plasma and muscle tissue (20), the model assumes that these CO diffusion coefficients are equal. CO concentrations are approximated into dissolved and Hb-bound components so that

\[
C_{iCO}(t) = \text{HbCO}(t) + \text{SCO} \cdot P_{iCO}(t)
\]

where \( \text{SCO} \) is the solubility of CO in plasma.

CO concentration at the input to the mixed venous compartment is determined by a weighted summation of the concentrations of CO in the venous outflow from the two tissue compartments. Thus

\[
\text{HbCO}_{iCO}(t) = \text{HbCO}_{iCO}(t) \cdot \frac{Q_{it}/Q}{HbCO_{iCO}(t) \cdot \text{Qm}/\text{Q}}
\] (7)

This input concentration then passes through the mixed venous compartment and returns to the lungs after a delay \( (\delta) \). In this and all vascular compartments, the variables \( \text{P}_{O_2}, \text{P}_{CO}, \text{HbCO}, \) and \( \text{HbO}_2 \) are required to satisfy the Haldane relationship

\[
\frac{M_B \cdot \text{P}_{CO}}{\text{HbCO}} = \frac{\text{P}_{O_2}}{\text{HbO}_2}
\]

\[
(8)
\]

\( \text{P}_{CO} \) is determined by first solving for the other variables, assuming that \( \text{P}_{CO} \) is constant across an integration step, then updating its value via the Haldane equation. Although small relative to the exposures being considered, endogenous CO production has been included by assuming that all endogenous CO is delivered to the mixed venous compartment.

Similar compartmental mass balance equations are written for the \( \text{HbO}_2 \) concentration. It is assumed that \( O_2 \) diffuses from the vascular to the extravascular subcompartments of the tissues at rates just sufficient to meet metabolic demands. Total body metabolism is set at 225 ml \( O_2/min \) and is divided between the two tissue compartments in the same ratio as that of the blood flows to these compartments.

The various blood flows are assumed to be constant. \( \dot{Q} \) is estimated via a regression approach (see Eq. 12) and the fraction of \( \dot{Q} \) that flows to the muscle tissue is varied to obtain the best fit of the model to each data set.

Model of \( O_2 \) dissociation curves of Hb and Mb. The presence of HbCO not only reduces the maximum amount of \( O_2 \) that Hb can bind but also changes the shape of the \( O_2 \) dissociation curve (29). Except at low \( \text{P}_{O_2} \) values, a reasonable approximation to this curve for any given level of HbCO (15, 20) is the Hill equation

\[
C_{O_2} = C_{O_2\text{max}} \cdot \frac{(\text{P}_{O_2}/\text{P}_{O_2\text{so}})^n}{1 + (\text{P}_{O_2}/\text{P}_{O_2\text{so}})^n}
\]

(9)

where \( \text{P}_{O_2\text{so}} \) is the \( \text{P}_{O_2} \) necessary to half-saturate the Hb not bound to CO. Thus we derived a set of equations to represent the \( O_2 \) dissociation relationship in the presence of CO by determining the dependence of the Hill parameters on the HbCO level and then applying a correction to the Hill equation at low pressures. The \( O_2 \) dissociation curves for 0, 20, 40, and 60% HbCO (29) were digitized, and the Hill equation was fit to each curve individually by using the \( f_{min} \) function of MATLAB. \( C_{O_2\text{max}} \) was reduced in direct proportion to the percentage of HbCO. The values of \( \text{P}_{O2} \) and \( n \) were then fit to functions of the form

\[
\text{P}_{O2} = a_0[1 + \exp(a_2 \cdot \% \text{HbCO})]^{-1}
\]

(10)

\[
n = a_1 + a_2 \exp(-0.025 \cdot \% \text{HbCO})
\]

(11)

by using \( f_{min} \) to estimate the parameters \( a_0, a_2, a_1, \) and \( a_2 \). By trial and error, it was found that multiplying the Hill equation by the function

\[
f(\text{P}_{O2}) = 1 + [0.25 + (5\text{P}_{O2}/\text{P}_{O2\text{so}})^3]^{-1}
\]

produced a satisfactory fit at low pressures. Note that \( f(\text{P}_{O2}) \) is \( ~1 \) for \( \text{P}_{O2} > 20 \) Torr. Figure 2 shows graphs of \( \text{P}_{O2} \) and \( n \) as functions of percent HbCO and of actual dissociation curves, and the approximations at four levels of HbCO.

The \( O_2 \) dissociation curve for Mb is also represented by a Hill equation (Fig. 5 of ref. 30), but it is assumed that its parameters are independent of the carboxymyoglobin (MbCO) level (except for the maximum \( O_2 \)-binding capacity). At each time step of the simulation, the dissociation curve for Mb and the Haldane equation for Mb are satisfied simultaneously via an implicit solution using an iterative procedure.

Calculation of subject-specific and other parameters. Nominal values for parameters are presented in Table 2. When available, subject-specific values of model parameters were obtained from the literature or directly from the investigators. Usually, the age, weight, and height of a subject were included as additional parameters, such as Hb concentration, total blood volume, \( \dot{Q} \), or ventilation, were supplied by investigators. In some cases, average values for a group of subjects were used. Predictive formulas were used to estimate \( Q \) (when it was not measured) and tissue volume of skeletal muscle (\( V_{tm} \)). As a function of body weight (BW), age (A), height (HT), and gender (G; G has a value of 1 for a male and 0 for a female subject)

\[
\dot{Q} = (54.1 + 7.9G) \cdot BW + 1400 - 200 \cdot G
\]

(12)

in ml/min (19), and

\[
V_{tm} = 1000(0.244 \cdot BW + 7.80 \cdot HT + 6.6 \cdot G - 0.098 \cdot A - 3.3)/1.04
\]

(13)

in ml (17). The volume of nonmuscle tissue is assumed to be proportional to \( V_{tm} \)

\[
\dot{V}_{ot} = (9.6/29.1) V_{tm}
\]

(14)

where 9.6 and 29.1 liters are the nominal normal values for nonmuscle and muscle tissue volumes for a 70-kg man (10). For obese subjects (body mass index \( >30 \)), \( V_{tm} \) is calculated by using the alternative parameter values for the preceding equation as given by Lee et al. (17).

The volumetric carrying capacity of Hb for \( O_2 \) or CO is calculated as the product of Hb concentration and the nominal maximum \( O_2 \) content, 1.38 ml \( O_2/g \) Hb. For Mb, the carrying capacity is proportional to that of Hb multiplied by the ratio of the molecular weights of Hb and Mb (i.e., 64,500 and 17,000, respectively) and divided by four. The concentration of Mb varies with the type of muscle, and an average value of 0.0047 g/g wet weight was used (23).
Arterial and muscle PO2 are parameters of the model. Arterial PO2 was set at 100 Torr during normoxia and 500 Torr in hyperoxia. In normoxic resting conditions, muscle PO2 has been estimated to be ~20 Torr (3). In hyperoxia, muscle PO2 increases much less than arterial PO2 (39), and a value of 30 Torr has been used.

*Estimation of other cardiovascular parameters.* The distribution of the total blood volume among the four vascular compartments and the distribution of Q between the two tissue compartments are unknown and were estimated for each subject. Initial values were determined by assuming that the muscle tissue corresponds to the slow vascular compartment of Smith et al. (33) and that the nonmuscle tissue corresponds to the fast compartment of that model. The values for blood flow used by Smith et al. (33) roughly correspond to those used by El-Hefnawy et al. (10) for muscle and nonmuscle tissue compartments, and the values for blood volumes roughly correspond to the relative sizes of the tissue volumes. Then, for each data set, the model was run repeatedly to determine the best visual fit to the data, attempting to utilize parameters that were within 30% of the initial values. Although this process did not optimize parameter estimates in a formal sense, it did demonstrate that comparable values for these parameters can be found that reasonably fit the data from several subjects representing three greatly different types of experimental situations.

Blood leaving the pulmonary vein returns to the pulmonary artery after an elapsed time that depends on the tissue that it perfuses. This time lapse is likely to be unimportant in determining HbCO levels after tens of minutes or hours of CO exposure, but one can expect it to have a significant role in responses to rebreathing of CO [e.g., Burge and Skinner (6)]. The average total time to traverse the circulation (Tc) equals the total blood volume divided by Q. Through washin/washout, each blood compartment imposes an effective time delay that is a function of its time constant, the compartmental blood volume divided by its blood flow. By considering the half-time of the step response as the effective delay, the delay times for the arterial, mixed venous, and parallel tissue compartments were calculated. The difference between Tc and the sum of these three delay times is assumed to represent an additional transport delay and is apportioned in a ratio of 1:2 between the arterial and mixed venous compartments (10, 22). When the total time delay is not matched to Tc, the predicted HbCO response to CO rebreathing is noticeably more sensitive to the relative distribution of blood volume among the compartments than it is in the final model.

*Implementation.* The model was implemented with the Advanced Continuous Simulation Language (ACSL) and the ACSLMath simulation environment. A fourth-order Runge-Kutta integration algorithm was used with a fixed step size of 0.02 min. Smaller step sizes were tested to ensure that accuracy was achieved with the one chosen.

*Testing the Model*

*Data sources.* Predictions from the model were compared with published observations on human subjects. CO rebreathing in hyperoxia was used by Burge and Skinner (6) to estimate total blood volume, and data from three of their subjects who rebreathed for 40 min were supplied to us by the authors. Benignus et al. (4) exposed human volunteers to 6,683 ppm CO for 4–6 min and compared HbCO levels obtained from simultaneous arterial and venous samples at several times during and after the exposure. These data also have been supplied to us by the authors. HbCO responses to long-term (e.g., 1–83 h) CO exposures can be described adequately by the CFK equation, and model predictions have been compared with solutions of this equation presented in Fig. 2 of Peterson and Stewart (27) by digitizing the curves from this figure. Finally, Tikuisis et al. (37) compared the responses to 5-min exposures of 1,500 ppm CO with those to

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**Fig. 2.** A: actual (solid line) and predicted (dashed line) oxygen (O2) dissociation curves of Hb at various levels (0, 20, 40, and 60%) of HbCO. See text for prediction equations. Nonlinear regression relationships (see text) for the parameters of Hill’s equation [PO2 necessary to reach 50% Hb saturation (P50; B) and n (C)] as a function of HbCO level.
1-min exposures of 7,500 ppm, and model predictions were compared with their findings.

Validation protocol. The model was tested first by using the CO rebreathing data (6). After available subject-specific parameters for each of the three subjects were assigned, a set of cardiovascular volumes was found that provided acceptable fits, which allowed for small intersubject variations in the fraction of Q assigned to the muscle compartment (Qmfrac). The value of the diffusion coefficient of CO from vascular to extravascular tissue subcompartments, DmCO, was also estimated. These parameters were then utilized to model the arterial and venous HbCO data from Benignus et al. (4). Because subjects in this latter study exhibited a range of temporal responses, it was necessary to adjust the cardiovascular volumes to fit the variety of responses. Blood volume and flow parameters determined from fitting the rebreathing data also were used to predict the venous HbCO responses to 25, 200, and 1,000 ppm CO for up to 5,000 min. These predictions were compared with the corresponding CFK solutions (27). Parameters not given by Peterson and Stewart (27) were assigned typical values (see Table 2). In all cases, we compared model predictions obtained when using the estimated value of DmCO with those that resulted when DmCO was set equal to zero.

RESULTS

Validation of Model

CO rebreathing. The subjects of Burge and Skinner (6) rebreathed from an external circuit containing 100% O2 into which a fixed bolus of CO was injected at time zero. For three of these subjects who rebreathed CO for 40 min, the following specific information was available: age, gender, height, weight, dose of CO administered, barometric pressure, Hb concentration, and total blood volume. DLCO is known to decrease considerably in hyperoxia (21), and a value of 15 was assumed. Q at rest also decreases in hyperoxia by ~15% (18). To simulate rebreathing, the lung volume of the model (1,500 ml) was augmented by the volume of the external circuit (3,500 ml) and alveolar ventilation was set to zero. The fraction of the total blood volume in each of the four vascular compartments and the Qmfrac are unknown parameters. Resting Qmfrac was set initially to 0.20 (2). The total blood volume was divided initially among the four compartments by associating the muscle compartment with the slow vascular compartment of Smith et al. (33) and the nonmuscle tissue compartment with their fast compartment. These initial fractional distributions of total vascular volume were adjusted until a set of satisfactory parameters, which were similar for the three subjects, was found. Qmfrac was allowed to change during these trials as long as the time constant of the muscle vascular compartment remained slower than that of the nonmuscle vascular compartment.

Attributing 40% of the blood volume to the muscle vascular compartment and 25% to the nonmuscle vascular compartment produced predictions that closely matched the data for all three subjects. Figure 3 demonstrates that the predicted HbCO level in the muscle venous blood (%HbCOvm) closely matched all data points for the two female subjects and all points except those at 2.5 and 5 min for the male subject. Qmfrac ranged from 0.25 to 0.30. The overshoot in the data from the male subject can be modeled by increasing Qmfrac to a level that causes the muscle vascular compartment to become the “fast” compartment, as shown by the dashed curve in Fig. 3A.

For each subject, the most appropriate value for DmCO was determined by comparing the predicted
responses for a range of values. An example from one subject is presented in Fig. 4. For both female subjects, a value of 0.8 ml · min⁻¹ · cmH₂O⁻¹ reasonably approximated the slope of %HbCOvm from 8 to 40 min. For the male subject, estimated DmCO = 1.75. The predicted responses of several variables for subject 2 are shown in Fig. 5. After 10 min of rebreathing, the predicted percentage of MbCO (%MbCO) is 2.61, from which one may calculate that 0.86 ml of CO has bound to Mb since the start of rebreathing.

Brief inhalation of a high level of CO. Benignus et al. (4) exposed subjects to 6,683 ppm of CO in room air for 4–6 min and acquired multiple simultaneous samples of arterial (radial artery) and venous (antecubital vein) blood during and after the exposure. The subjects exhibited a wide range of temporal responses of arterial and venous HbCO; however, in all subjects, the venous HbCO level lagged the arterial HbCO during CO exposure, and the two measurements converged at varied times after the CO exposure terminated. The following parameters were available for each subject: age, gender (all male), weight, height, Hb concentration, total blood volume, Q, V, and DLCO. The physiological parameters, however, had been measured 1 day before CO exposure. For validation of the model, predicted arterial and muscle venous %HbCO levels were compared with data from two subjects (subjects 114 and 120) representative of those having small or moderate differences between arterial and venous %HbCO responses (Fig. 6).

The distribution of blood volumes determined from the CO-rebreathing studies provided the starting values for these simulations, and the best visual fits to the data were obtained with similar final values. It was necessary to assume that Qm was larger than the corresponding value used for the three subjects of Burge and Skinner (6) (50% larger for subject 114; 100% larger for subject 120). Also, the observed decrease in %HbCO after termination of the CO exposure was faster than the model predicted using values of DmCO that were estimated from the CO-rebreathing studies. Because it is possible that these subjects may have hyperventilated during this period, no further estimation of DmCO was warranted. Finally, as was the case for the CO-rebreathing data, it was noted that the level of %HbCO after the CO exposure was terminated was very sensitive to the total amount of blood in the four vascular compartments. For subject 120, the vascular compartments comprised 92.5% of the measured total blood volume of the subject, whereas for subject 114 this value was 97.5%. [For the subjects of Burge and Skinner (6), the corresponding value was 85% for all 3 subjects.]

Comparison to CFK solutions. A graph presented by Peterson and Stewart (Ref. 27 and Fig. 2 therein) shows %HbCO predicted by the CFK equation vs. time for various levels of inspired CO for exposures lasting 5,000 min. We chose the two extremes (25 and 1,000 ppm) and an intermediate value (200 ppm) for comparison with our model. Some parameter values are given in Fig. 2 of the Stewart and Peterson paper (27); the remainder were taken from the simulations of CO rebreathing described above, except that values for DLCO, PmO₂, and Q in normoxia were used. The subject was assumed to be a 30-yr-old (middle of their age range) man, with a height of 1.8 m and blood volume of 74 ml/kg. The two models produce very similar results for these long exposure times, although the predictions of the present model are somewhat lower over much of the transient part of the response at all three inspired levels.
CO levels (Fig. 7). Not surprisingly, when DmCO = 0 (as the CFK equation assumes), the two predictions are essentially identical in the steady state. When DmCO = 1.75, there is a small decrease in the predicted steady-state level of %HbCO, but the difference between the two cases is probably too small to be detectable from actual data. Nonetheless, there is a significant effect of allowing for uptake of CO by muscle even at this slow rate. For the three CO exposure levels (25, 200, and 1,000 ppm), the predicted %MbCO levels after 5,000 min are 2.37, 14.5, and 42.1%, respectively.

Analysis of sensitivities to parameters. The sensitivity of the predicted transient response of %HbCOvm to variations in the circulatory volumes and other parameters was examined for the CO-rebreathing procedure. [The sensitivities observed for the Benignus et al. (4) protocol were qualitatively similar to those reported here for the rebreathing protocol.] Varying the Haldane coefficients over typical ranges reported in the literature (MH: 218–248, MM: 25–36) changed the slow rate of decay of %HbCO (Fig. 8A), but only slightly. On the other hand, changing Q˙m while other parameters were held constant had a substantial effect on the rise of %HbCO early during CO rebreathing. As muscle blood flow increases, the muscle venous HbCO level rises more quickly since turnover in the muscle vascular compartment is faster (Fig. 8B). Changing PmO2 has a noticeable but small effect on the slow decay of %HbCO (Fig. 8C) because CO competes more successfully for Mb at lower O2 tensions. Reducing PmO2 can offset the effect on the decay rate of a simultaneous reduction of DmCO, but the fit to the earlier data points becomes more problematic if DmCO and PmO2 are changed from the values used in the above simulations (not shown). Changing DLCO alters the initial rise of the response (Fig. 8D), as expected, but the “plateau” level and later decay are not affected. That is, after a pseudoequilibrium is reached, the rate of transfer of CO from the lungs to the pulmonary circulation is very small, and the dominant factor is a slow leak of CO out.

Fig. 6. Arterial (radial artery; ○) and venous (antebrachial vein; ●) %HbCO vs. time for 2 subjects from the study of Benignus et al. (4). Model predictions of arterial (dashed lines) and venous (solid lines) %HbCO. A: estimated fraction of blood volume in muscle = 40%; in nonmuscle = 32.5%; Qm = 0.20. B: estimated fraction of blood volume in muscle = 35%; in nonmuscle = 32.5%; Qm = 0.40.

Fig. 7. Calculated solutions of Coburn-Forster-Kane equation (●) for 3 levels of inspired CO, taken from Fig. 2 of Peterson and Stewart (26), and predictions of %HbCOvm from the model (dashed lines: DmCO = 0; solid lines: DmCO = 1.75) using parameters given in that figure.
of the circulatory system (which is modeled here as a flux into the muscle compartment).

The plateau level of the response during CO rebreathing is strongly affected by the distribution of blood volume among the circulatory compartments. As seen in Fig. 8F, the distribution of blood volume between the muscle and other tissue compartments has a significant effect on the plateau level. Consequently, the data provide a strong criterion for selecting these parameters. The ratio of mixed venous to arterial volumes also affects the plateau level, but less strongly (Fig. 8E). It should be noted that altering one volume without making a compensatory change elsewhere to keep total blood volume constant can have an indepen-

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**Fig. 8.** Sensitivity of the model solutions for subject 2 of Fig. 3 to changes in values of the following parameters: $M_H$ and $M_M$ (A); $Q_m$ (B); $P_m$ (C); $DLCO$ (D); ratio of mixed venous to arterial blood volume (E); and ratio of muscle to non-muscle tissue blood volume (F). Note the expanded vertical scales in A and C.
dent effect on the response. In addition, because changing these volumes also alters the compartmental time constants, the effective delays can change. In the present model, the total delay is kept constant by the addition of a pure time delay in the mixed venous circulation, as described previously. Without this additional compensation, the effects of changing the circulatory volumes are more profound.

Comparison of two different exposure protocols. Tikuisis et al. (37) compared the HbCO responses of human subjects to two different pulses of CO for which the areas of the pulses were equal. Thus one pulse had a CO level five times the other, but a duration of 1 min compared with 5 min for the latter. Each pulse of CO was administered five times at 8-min intervals. A simulation of this experiment, using nominal parameter values, is presented in Fig. 9. The simulation reproduces their experimental finding that both pulses produce the same %HbCO\textsubscript{vm} level by the end of each 8-min interval. The simulation also predicts that the %MbCO will differ in the two situations (%MbCO = 1.83 and 1.76 at 40 min for the larger and smaller CO pulses, respectively). It should be noted that it is also possible to devise two different exposures that would yield different %HbCO\textsubscript{levels} but the same %MbCO level. Thus %MbCO cannot be predicted on the basis of %HbCO alone.

DISCUSSION
Structure and Validation of Model

The transport and storage of CO in the body is dominated by the affinity of Hb for CO, and prior quantitative models, starting with the CFK equation, have emphasized this mechanism. Although the parameters of the CFK equation can be adjusted to fit measurements of venous %HbCO for CO exposures of tens of minutes or longer (14, 27), this equation does not accurately predict either venous or arterial %HbCO data for shorter exposures even when all or most of the needed parameters are determined experimentally (4). Neither is the CFK equation able to predict the difference between venous and arterial HbCO levels (4). Smith et al. (33) recognized the need to account for multiple compartments in the circulatory system to model arteriovenous differences. The present model adopts a similar framework but demonstrates that four circulatory compartments (instead of nine) are sufficient to reproduce available data on transient CO exposures. The reduced number of compartments simplifies the estimation of parameters at the loss of some physiological isomorphism.

The present model augments that of Smith et al. (33) in several regards. First, we have explicitly modeled the dynamics of CO storage in the lung and its dependence on ventilation and on the PCO\textsubscript{2} of mixed venous blood. Second, equations for the O\textsubscript{2}-dissociation curve and its dependence on the level of CO have been developed in a form that permits us to relax the assumption that Hb is saturated; thus it applies to both arterial and venous blood and in hyperoxia as well as normoxia. The Haldane relationship is also taken into account. Consequently, the model calculates HbO\textsubscript{2} levels as well as HbCO levels. Third, the model includes a muscle tissue compartment containing Mb and allows for a small flux of CO into this compartment. The Haldane equation for Mb is included in the model. Fourth, the model accounts for dissolved CO in blood and tissues. Fifth, when necessary, prediction formulas are used to estimate parameters on the basis of age and body dimensions. Sixth, total mean transport delay in the circulation is assessed and maintained constant as circulatory volumes are adjusted.

We validated the model by using data from transient CO exposures, then demonstrated that the model could also predict HbCO levels in response to inhalation exposures of up to 5,000 min. Thus this model provides a more complete representation of the dynamics of CO transport and storage than previous models. Except for the early overshoot in the arterial HbCO data from the male subject in the Burge and Skinner study (6), the parameter sets that were found to provide visually good fits to the data from CO rebreathing were very similar, suggesting that the model structure captures the dynamics adequately. The overshoot reported for the male subject was predicted well by the %HbCO in the venous blood from the nonmuscle tissue, suggesting the possibility that these data represent arterialized venous blood. Alternatively, it would be possible to reproduce the overshoot by increasing Q\textsubscript{mfrac}, but it was decided to maintain the muscle compartment as the “slow” vascular compartment. Furthermore, the parameters determined for CO rebreathing were also similar to those that provided good fits to the data from inhalation of a brief, high-intensity pulse of CO and were adequate for predicting the CFK solutions under three levels of long-term CO inhalation.
Some of the differences between our model predictions and the experimental data may be related to the values for total blood volume used in the model. For all subjects, the sum of the volumes of the four circulatory compartments was <100% of the total blood volume reported for each subject. The experimental methods for determining total blood volume, however, may have been inconsistent with the CO exposure that was tested. For example, Benignus et al. (4) measured blood volume using a dilution method wherein the labeled red blood cells were allowed a much longer time to circulate than the duration of the CO exposure. Therefore, the measured blood volume might have been larger than the accessible blood volume during the CO exposure. The difference between the modeled and measured blood volumes was no more than 10% for the two subjects from this study who were examined in detail; this difference might well have been due to the presence of a very slowly perfused compartment that did not significantly affect the response to 4–6 min of CO inhalation.

An overestimate of total blood volume also could explain the deviation of the model predictions from the CFK equation during the initial part of the response (Fig. 7). Because the CFK equation does not allow for flux of CO to muscle, it is possible that the blood volume found to produce a good fit to data using that equation systematically overestimates a subject’s actual blood volume. If it did not, then the predicted %HbCO would be too high (just as it is higher than the predictions of the present model). The blood volumes of our model also were less than the reported blood volumes for the subjects from the rebreathing study (6). By not accounting for loss of CO to muscle, that study might have overestimated blood volume by a few percent. Also, the calculated volume in that study depends significantly on an assumption about the venous-to-body hematocrit correction factor. Thus the blood volumes used in our model are not unreasonable. In fact, a formal statistical estimation of the parameters of the model could be utilized as an alternative estimate of blood volume.

Our present model does not include the effect of Hb saturation on the Haldane coefficient (9, 13, 25). However, based on Fig. 4B of Di Cera et al. (9), the change in the Haldane coefficient is <20% over the range of conditions we considered. Furthermore, Mb is effectively saturated with O2 or CO for the muscle Po2 values actually used. Given the small sensitivity of model responses to the Haldane coefficient values (Fig. 8A), these effects can be ignored in the situations modeled in this study.

PCO2 and pH also affect both M (1, 16) and the exponent n of the Hill equation (24). We have assumed that pH and PCO2 are constant, but the small effects on M should be included in a future model that would be applied to other conditions where these variables might change significantly. The effect of changes in pH on n for Hb is not negligible, but the pH effect on n for Mb is quite small (30).

**Interpretation of DmCO**

In the model, DmCO represents all the mechanisms through which CO could “leak” out of the circulatory system. We assume that the primary mechanism of leakage is diffusion into tissues. Because of the presence of Mb, virtually all of this CO is found as MbCO. Two lines of evidence support the conclusion that DmCO is not zero (as the CFK equation assumes). First, there is a small but steady decline of HbCO in the 10- to 40-min time period during CO rebreathing despite endogenous CO production. The rate of decline was greater in the male subject whose calculated muscle mass was 29.15 kg than in the two female subjects whose muscle masses were 21.83 and 20.52 kg. The model could not reproduce this decline when DmCO was set equal to zero. Second, the ratios of MbCO to HbCO predicted by the model after long-term CO exposures are compatible with findings in muscle samples obtained from anesthetized dogs and rats similarly exposed to CO (8, 34). Although these nonhuman data are highly variable, MbCO levels were far from negligible, ranging from 38 to 153% of HbCO levels. In the model, similar levels of MbCO were realized with DmCO values that were much lower than typical DLCO values.

DmCO should depend on multiple physiological factors, among which are the following: diffusion of CO across the capillary wall, diffusion of CO within tissue, rate of combination of CO with Mb, and the total surface area for diffusion. Although the total surface area of capillaries in muscle is unknown, the fact that DmCO was estimated to be an order of magnitude smaller than DLCO suggests that diffusion rates of CO from capillaries into tissues are indeed small. Furthermore, because Hb binds CO so effectively, PaCO is typically much smaller than PACO, and therefore the driving pressure for diffusion is much smaller in tissue capillaries than in the lung. Nonetheless, as noted above, the model predicts that exposures lasting more than a few minutes will be associated with measurable increases in MbCO levels. For the CO-rebreathing studies, however, the predicted increase in %MbCO at 10 min was only 0.71, 0.61, and 0.57% for the male and two female subjects, respectively, which represented the binding of an additional 1.33, 0.86, and 0.76 ml, respectively, of CO to Mb. These amounts are small enough compared with the 60 or 70 ml of CO originally injected into the rebreathing circuit that the loss of CO from the circulation has only a slight effect on the estimation of total blood volume. Note, however, that after 40 min of CO rebreathing, the increase of %MbCO was approximately one-third of that of %HbCO.

DmCO in the male subject of Burge and Skinner (6) was found to be higher than DmCO for the two female subjects. Because of the surface area effect discussed above, one expects that DmCO will be larger in men because of their larger muscle mass. Also, the capillary density in muscle may be further increased in male subjects who exercise frequently (4).

The distribution of inhaled CO into muscle tissue as well as into multiple circulatory compartments compli-
icates the prediction of washout profiles after cessation of the exposure. If alveolar ventilation is constant, the washout profile will not be monoexponential. Furthermore, because of the slow transfer of CO between Mb and Hb, washout of the muscle tissue compartment will be much slower than washout of the circulation. Consequently, the washout profile is expected to exhibit a long tail, and the time required for full washout may be very much longer than twice the half-time of the washout (26, 32).

Comparison to Previous Models

The CFK equation is a first-order approximation to the dynamics of CO storage in blood under the assumptions that ventilation, \( P_{\text{ICO}} \), and \( \text{PaO}_2 \) are constant and that no CO leaks out of the blood. It provides a good approximation to the HbCO response to a steady level of inhaled CO (27). Furthermore, when measurements are made periodically and the equation is solved again for each time period, one often obtains a reasonable match to the data (5, 14, 27), although significant errors may accumulate as this procedure is repeated during successive time intervals. Although these approaches are useful approximations, they are limited because 1) the equation must be solved every time ventilation, inspired \( \text{PCO}_2 \), or \( \text{PaO}_2 \) changes; 2) the arteriovenous differences cannot be reproduced unless circulatory compartments are introduced; and 3) flux of CO into tissue is ignored. Thus these approaches are inefficient for situations involving frequent changes in \( P_{\text{ICO}} \) or ventilation and are inapplicable for CO rebreathing in which ventilation is effectively zero and \( P_{\text{ICO}} \) changes rapidly and continuously. Finally, these approaches would be unable to predict the levels of CO in compartments other than the blood, e.g., muscles and brain.

The present model utilizes a standard mass balance approach to describe CO storage dynamics. Although it assumes that ventilation and \( \text{Po}_2 \) are constant, extending the model to allow these variables to be time varying would be mathematically trivial. Thus, for example, the model could be enhanced by including \( \text{O}_2 \) transport and stores in the lung compartment and \( \text{O}_2 \) flux into the pulmonary capillary blood (22). It is possible to develop more detailed descriptions of lung-capillary exchange (31) and capillary-tissue exchange (20) than the simple structures used here; however, the parameters of these detailed descriptions would not be well specified by the type of data available from whole body CO exposures in humans.

The present results reinforce the need for precise measurement of the flux of CO from the circulation into muscle tissue; however, the predicted slow rate of flux will be difficult to measure. The amount of Mb in muscle is another important factor that influences whole body distribution of CO. Reported values for Mb concentrations differ both among species and among muscles in a given species. Model predictions would be improved by having more precise measurements of average Mb concentrations in human muscle tissues. In addition, although \( \text{PmO}_2 \) only has a small effect on HbCO levels in hyperoxia and normoxia, one can anticipate that it will be more important in hypoxia. Consequently, better measurements of this variable are necessary.

Our primary purpose was to establish the feasibility and potential importance of including MbCO formation in any model of CO uptake rather than to provide a subject-specific clinical or experimental tool. Nonetheless, one can offer some general guidelines. One expects that the accuracy of the model will be enhanced when more of its parameters are measured for each subject. The steady-state \%HbCO level is most dependent on inspired CO level, Hb concentration, ventilation, and total blood volume. The latter two variables may be unavailable in a clinical setting but should be measured in experimental studies. The time course of changes in \%HbCO depend also on the distribution of blood flows and blood volumes among the cardiovascular compartments. Aside from \( Q \), these flows and volumes represent "effective" or average values for muscle and nonmuscle tissue compartments and are not directly measurable; however, with the use of statistical estimation methods, average values for these parameters (and \( D_{\text{MbCO}} \)) could be determined in a representative population. The regression formulas used in this study to estimate muscle and nonmuscle tissue volumes (and \( Q \), if necessary) are reasonably accurate for clinical purposes. Finally, as shown in Fig. 8A, the specific values chosen for the Haldane coefficients for blood and muscle and the muscle \( \text{Po}_2 \) have small effects on the responses (in normoxia and hyperoxia), and therefore it is less critical that precise values for these coefficients be determined.

In conclusion, although changes in HbCO levels during CO inhalation can be approximated by the CFK equation, a more complete description of transport and storage mechanisms of CO is needed to account for HbCO levels when inspired CO levels change rapidly or when one needs to account for differences between arterial and venous HbCO levels. The model presented here reproduces whole body responses to both transient and long-term inhalations of CO and appears to be a minimal structure that can reproduce reported arteriovenous differences in \%HbCO during transient exposures. The present results further suggest that measurable amounts of CO diffuse out of the circulatory system and into tissue compartments in as little as 10 min. To ascertain the distribution of CO to tissue such as the brain (and its effects on \( \text{O}_2 \) delivery), it will be important to measure more precisely the flux of CO from the circulation into tissues. It is also likely that the CFK equation is inadequate to closely predict the washout of CO during treatment of CO poisoning, whereas the present model should provide improved predictions of the time course of CO washout from the body. Finally, in contrast to approaches based on the CFK equation, the present model predicts uptake and distribution of CO in both vascular and tissue compartments during inhalation of constant or variable levels of CO.
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REFERENCES


