

# Chapter 4. Dosimetry and Pharmacokinetics of Carbon Monoxide

## 4.1. Introduction

Inhaled ambient CO elicits various health effects by binding with and altering the function of a number of heme-containing molecules, mainly Hb. Traditional concepts for CO pathophysiology have been based on the high affinity of CO for hemoglobin, resulting in COHb formation and consequent reduction in O<sub>2</sub>-carrying capacity of blood and impaired O<sub>2</sub> delivery to tissues. Research on CO pharmacokinetics dates back to the 1890s, but since the late 1970s has become limited. Current literature primarily focuses on endogenous CO produced by the metabolic degradation of heme by heme oxygenase (HO) and its role as a gaseous messenger. This chapter reviews the physiology and pharmacokinetics of CO. The chapter draws heavily from Chapter 5 of the previous AQCD (U.S. EPA, 2000, [000907](#)). Relevant new data are included when available. Recent models of Hb binding are characterized, as well as measurements of tissue CO concentrations using new methods of extraction.

CO binds with a number of heme-containing molecules including Mb and cytochromes, but none have been studied as extensively as Hb. The primary focus of this chapter is placed on the models and kinetics of such binding and the factors influencing this event. The chapter discusses effects at ambient or near ambient levels of CO leading to low COHb levels ( $\leq 5\%$ ); however few studies are available at ambient CO concentrations. Both human and animal studies using higher CO exposure concentrations, resulting in moderate to high COHb levels ( $<20\%$ ), are discussed where needed to understand CO kinetics, pathophysiologic processes, and mechanisms of cytotoxicity. Where human studies could not experimentally test certain hypotheses or were unavailable, animal experiments were used as surrogates. CO uptake and elimination has been shown to be inversely proportional to body mass over environmentally relevant exposure levels, meaning the smaller the animal, the faster the rate of absorption and elimination (Klimisch et al., 1975, [010762](#); Tyuma et al., 1981, [011226](#)). However, the basic mechanisms of CO toxicity between experimental animals and humans are similar and are thus extrapolated from animals to humans in this chapter, keeping in mind a number of interspecies differences.

## 4.2. Carboxyhemoglobin Modeling

### 4.2.1. The Coburn-Forster-Kane and Other Models

Investigators have modeled the effect of CO binding to Hb in a number of ways. Empirical and mechanistic models are two distinct approaches that have been taken to model in vivo COHb formation after CO exposure. First, empirical models were used to predict COHb by regressing concentration and duration of exogenous CO exposure with observed COHb, with or without the inclusion of physiological predictors such as initial COHb levels and alveolar ventilation ( $V_A$ ). These methods were reviewed in depth in the previous AQCD (U.S. EPA, 2000, [000907](#)). It is important to note that CO empirical regression models are limited to estimating COHb in the exact conditions on which the models were based. These simple models include those by Peterson and Stewart (1970,

---

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

[012416](#)) and Ott and Mage (1978, [011124](#)), as well as various others (Chung, 1988, [012749](#); Forbes et al., 1945, [012850](#); Selvakumar et al., 1992, [013750](#); Sharan et al., 1990, [003798](#); Singh et al., 1991, [013583](#)). Using a linear differential equation where ambient CO concentrations varied, it was shown that the presence of brief ambient CO concentration spikes averaged over hourly intervals may lead to underestimating the COHb concentration by as much as 21% of the true value. To avoid this problem, it was suggested that ambient CO measurements be monitored and averaged over 10- to 15-min periods (Ott and Mage, 1978, [011124](#)). Other empirical models predict COHb as a function of exposure time (Sharan et al., 1990, [003798](#); Singh et al., 1991, [013583](#)) or exposure time and altitude (Selvakumar et al., 1992, [013750](#)). A comparison of empirical model predictions showed a wide disparity in predicted COHb values, highlighting the inaccuracy of these models outside of the conditions on which they were presented (Tikuisis, 1996, [080960](#)).

Secondly, mechanistic models use physical and physiological processes and an understanding of biological processes to predict COHb production. The most commonly used mechanistic method for predicting levels of blood COHb after CO inhalation is the Coburn-Forster-Kane equation or CFK model developed in 1965 (Coburn et al., 1965, [011145](#)). This differential equation was developed to examine endogenous CO production, using the major physiological and physical variables influencing this value. Since then, it has been shown to provide a good approximation to the COHb level at a steady level of inhaled exogenous CO (Peterson and Stewart, 1975, [010696](#); Stewart et al., 1973, [012428](#)). The CFK model describes a four-element, physical system containing an exogenous CO source, a transfer interface, an endogenous CO source, and a storage compartment. The linear CFK model assumes O<sub>2</sub>Hb concentration is constant and is as follows in Equation 4-1:

$$V_b \frac{d[\text{COHb}]_t}{dt} = \dot{V}_{\text{CO}} - \frac{[\text{COHb}]_0 P_c \text{O}_2}{[\text{O}_2\text{Hb}]M} \left( \frac{1}{\frac{D_L \text{CO}}{1} + \frac{P_B - P_{\text{H}_2\text{O}}}{\dot{V}_A}} \right) + \left( \frac{P_i \text{CO}}{\frac{D_L \text{CO}}{1} + \frac{P_B - P_{\text{H}_2\text{O}}}{\dot{V}_A}} \right)$$

Equation 4-1

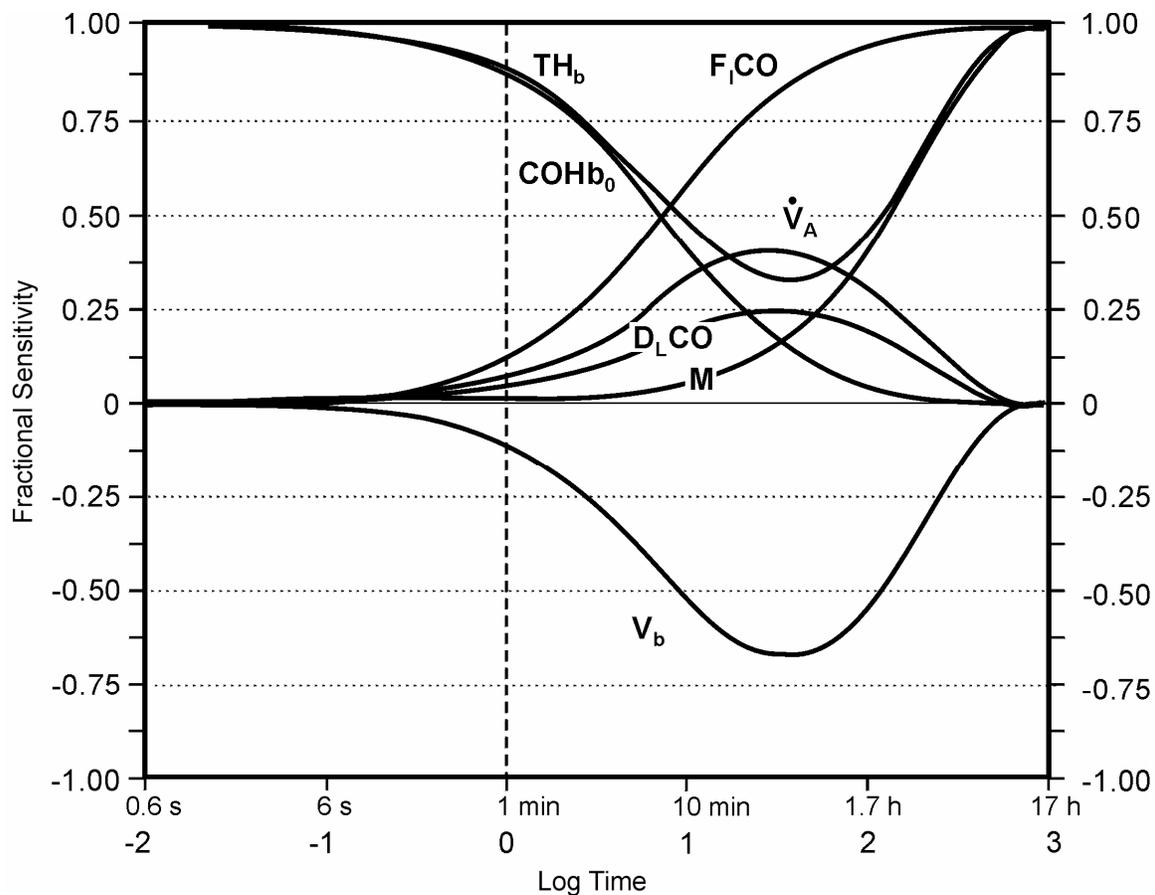
$V_b$	blood volume in milliliters (mL)
$[\text{COHb}]_t$	COHb concentration at time t in mL CO/mL blood, at standard temperature and pressure, dry (STPD)
$V_{\text{CO}}$	endogenous CO production rate in mL/min, STPD
$[\text{COHb}]_0$	COHb concentration at time zero in mL CO/mL blood, STPD
$[\text{O}_2\text{Hb}]$	O <sub>2</sub> Hb concentration in mL O <sub>2</sub> /mL blood, STPD
$P_c \text{O}_2$	average partial pressure of O <sub>2</sub> in lung capillaries in mmHg
M	Haldane coefficient representing the CO chemical affinity for Hb
$D_L \text{CO}$	lung diffusing capacity of CO in mL/min/mmHg, STPD
$P_B$	barometric pressure in mmHg
$P_{\text{H}_2\text{O}}$	saturation pressure of water vapor at body temperature in mmHg (47 mmHg)
$V_A$	alveolar ventilation in mL/min, STPD
$P_i \text{CO}$	CO partial pressure in inhaled air in mmHg

The linear CFK model assumes instant equilibration of COHb concentration between venous and arterial blood, gases in the lung, and COHb concentrations between blood and extravascular tissues, which is not physiologically representative. The nonlinear CFK equation extends the linear CFK equation to incorporate the interdependence of COHb and O<sub>2</sub>Hb levels since they are derived from the same pool of blood Hb. This interdependence can be modeled by substituting (1.38 Hb [COHb]) for O<sub>2</sub>Hb, where TH<sub>b</sub> refers to the number of grams of Hb per milliliter of blood (Peterson and Stewart, 1975, [010696](#)). The nonlinear CFK differential equation is as follows in Equation 4-2:

$$V_b \frac{d[\text{COHb}]_t}{dt} = \dot{V}_{\text{CO}} - \frac{[\text{COHb}]_0 P_{\text{CO}}}{(1.38[\text{TH}_b] - [\text{COHb}]_t)M} \left( \frac{1}{\frac{1}{D_L \text{CO}} + \frac{P_B - P_{\text{H}_2\text{O}}}{\dot{V}_A}} \right) + \left( \frac{1}{\frac{1}{D_L \text{CO}} + \frac{P_B - P_{\text{H}_2\text{O}}}{\dot{V}_A}} \right)$$

Equation 4-2

The nonlinear equation is more physiologically accurate; however the linear CFK equation gives a good approximation to the nonlinear solution over a large range of values during CO uptake and during low levels of CO elimination (Smith, 1990, [013164](#)). The linear equation prediction of COHb concentration at or below 6% will deviate by no more than  $\pm 0.5\%$  COHb from the nonlinear equation prediction. Sensitivity analysis of the CFK equations has shown that alterations in each variable of the equation will affect the outcome variably at different times of exposure, so that the relative importance of the CFK variables will change with the experimental conditions (McCartney, 1990, [013162](#)). Figure 4-1 illustrates the temporal changes in fractional sensitivities of the principal physiological determinants of CO uptake for the linear form of the CFK equation, where  $\text{TH}_b$  is the total blood concentration of Hb in g Hb/mL blood and  $F_1\text{CO}$  is the fractional concentration of CO in ambient air in ppm. The fractional sensitivity of unity means that, for example, a 5% error in the selected variable induces a 5% error in the predicted COHb value by the nonlinear model. As Figure 4-1 demonstrates, a constant or given percent error in one variable of the model does not generally produce the same error in the calculated blood COHb, and the error is time dependent. Thus, each variable influencing CO uptake and elimination will exert its maximal influence at different times of exposure. This analysis found that only  $F_1\text{CO}$  (shown in Figure 4-1) and  $V_{\text{CO}}$  will not affect the rate at which equilibrium is reached (McCartney, 1990, [013162](#)).



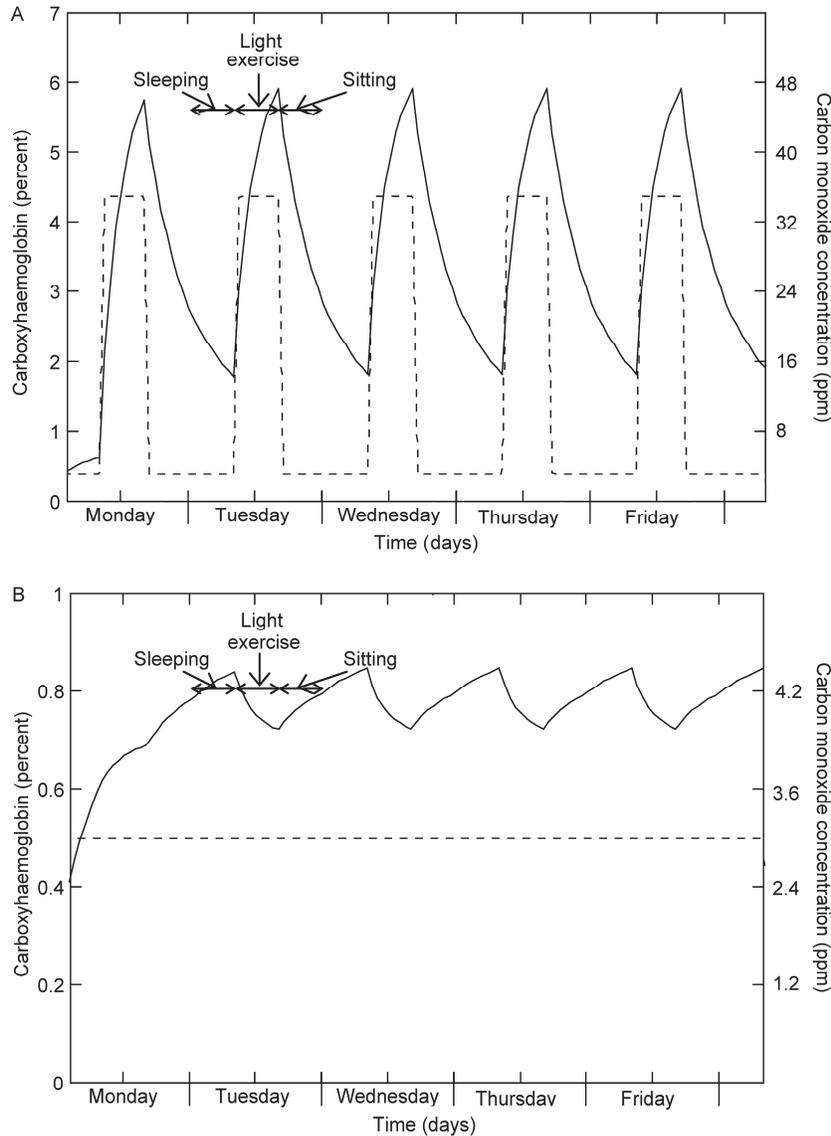
Source: Adapted with Permission of the American Industrial Hygiene Association from McCartney (1990, [013162](#))

**Figure 4-1. Plot of fractional sensitivities of selected variables versus time of exposure.**

The mechanistic CFK model contains a number of assumptions under which the model is solely applicable, including: (1) ventilation is a continuous process; (2) equilibrium between plasma CO concentration and COHb concentration is obtained in the pulmonary system; (3) percent COHb can exceed 100% saturation in the linear model; and (4) it does not account for the shape of the O<sub>2</sub> or CO saturation versus pO<sub>2</sub> or pCO relation (McCartney, 1990, [013162](#)). Estimations outside of these assumptions have been attempted but with less predictive agreement. For example, transient exposures such as those that would simulate everyday conditions would violate the assumption of a single, well-mixed vascular compartment. COHb levels during exposure of subjects exposed to frequent but brief high CO exposures (667-7,500 ppm for 75 s to 5 min) were not accurately predicted by CFK modeling (Benignus et al., 1994, [013908](#); Tikuisis et al., 1987, [012219](#); Tikuisis et al., 1987, [012138](#)). Consistently, the COHb value predicted by the nonlinear CFK overpredicted observed venous COHb (0.8-6%) and underpredicted arterial COHb (1.5-6.1%) and this disparity increased after exercise. Individual differences between arterial and venous COHb varied from 2.3-12.1% COHb (mean, 6.2 ± 2.7% COHb), where the observed steady state COHb averaged ~14% and the observed arterial peak COHb averaged ~17.5% (Smith et al., 1994, [076564](#))(Benignus et al., 1994, [013908](#)). These inaccuracies between measured and predicted COHb values disappeared after simulated mixing of arterial and venous blood and thus are likely due to delays in mixing of arterial and venous blood and differences in cardiac output and lung wash-in. This discrepancy in predicted and observed COHb suggests that over a short period (<10 min) the arterial COHb levels that are delivered to tissues could be higher than what is predicted by the CFK equation. A modified CFK was created to adjust for these issues and produce a more accurate COHb prediction (Smith et al., 1994, [076564](#)). This expanded CFK model used multiple compartments to model the lung, arm circulation, and the rest of the body (quickly and slowly perfused tissues). This model was more

accurate than the nonlinear CFK in predicting the individual peak or maximal values of arterial and venous COHb during CO uptake in the first 10 min after exposure. However, both the nonlinear CFK and this expansion produced accurate predictions several minutes after the 5-min exposure ended. The expanded model required the use of two parameters,  $V_A$  and  $V_b$ , that were not measured individually or derived from the literature, and instead were estimated by adjustments between the simulations and experimental subject data.

In addition to the limitations discussed above, the CFK model does not account for extravascular storage sites for CO, such as muscle Mb. CO will undergo reversible muscle Mb binding, similar to Hb, as well as uptake into other extravascular tissues (Vreman et al., 2006, [098272](#)). The most recent adaptation to the CFK equation incorporates alveoli-blood and blood-tissue CO exchanges and mass conservation of CO at all times (Gosselin et al., 2009, [190946](#)). This model has a single free parameter whose value is estimated from one data set; however, it better predicted COHb formation over a wide range of CO levels and several temporal scenarios (Stewart et al., 1970, [013972](#); Tikuisis et al., 1987, [012138](#); Tikuisis et al., 1987, [012219](#); Tikuisis et al., 1992, [013592](#)) compared to the linear CFK model. Like the linear CFK model, this modified model assumes a constant level of oxyhemoglobin. Sensitivity analysis of the model showed that the most important parameter influencing the level of COHb in this model is  $M$ , followed by  $P_{CO_2}$  and  $V_A$ . Ambient exposure scenarios were simulated with this model to determine the CO concentrations needed to reach certain COHb levels in humans from 3 months of age to 40-yr-old adults (Gosselin et al., 2009, [190946](#)). The CO concentrations needed to achieve 2% COHb vary from 24.4-48.1 ppm for a 1-h exposure, from 11.1-13.1 ppm for an 8-h exposure, and from 9.8-10.1 ppm for a daily exposure. Infants (1 yr old) were most sensitive to CO concentrations, whereas newborns (3 mo old) required the highest CO concentration to reach 2% COHb. Newborns required a higher CO exposure partially because the values used in the model for the newborn blood Hb concentration ( $170 \text{ g}_{\text{Hb}}/\text{L}_{\text{blood}}$ ) is higher than at infancy ( $115 \text{ g}_{\text{Hb}}/\text{L}_{\text{blood}}$ ) or adulthood ( $150 \text{ g}_{\text{Hb}}/\text{L}_{\text{blood}}$ ). The model was also used to simulate time profiles of COHb formation for two work week exposure scenarios in a healthy 40-yr-old man. Figure 4-2A represents a high exposure scenario where the work period is spent at 35 ppm and the rest of the time at 3 ppm. Figure 4-2B represents a lower exposure scenario where there is a constant 3 ppm exposure. Both figures consist of 5 days where 24 h are broken up into 3 consecutive 8-h periods: sleeping from 12 a.m. to 8 a.m.; working with light exercise from 8 a.m. to 4 p.m.; and sitting from 4 p.m. to 12 a.m..



Source: Reprinted with Permission of Informa Healthcare from Gosselin et al. (2009, [190946](#))

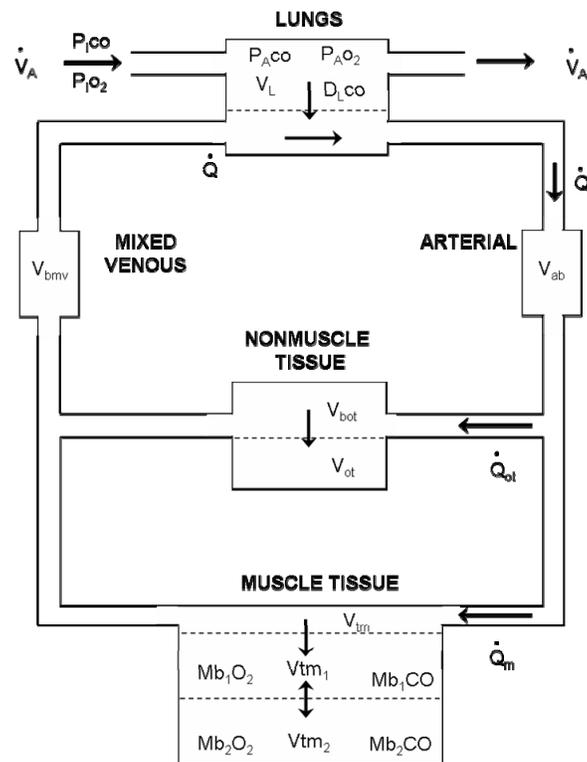
**Figure 4-2.** Simulated COHb formation for two 5-day workweeks. “The 24-h day consists of 3 consecutive 8-h periods: sleeping from 12 a.m. to 8 a.m.; working (light exercise) from 8 a.m. to 4 p.m.; and sitting from 4 p.m. to 12 a.m. (A) High exposure: work period at 35 ppm and the rest of the time at 3 ppm. (B) Low daily exposure at 3 ppm. The CO exposure periods are represented by dotted lines (----) and the COHb simulations by solid lines (—).”

## 4.2.2. Multicompartment Models

A third approach applied more recently to model COHb formation is the use of multicompartment or physiologically-based pharmacokinetic (PBPK) models. Cronenberger et al. (2008, [194085](#)) described a two-compartment population-based model to describe and predict COHb pharmacokinetics from smoking. This model required a compartment for extravascular binding of

CO to accurately predict COHb formation during multiple short and rapid inhalations followed by a period of no exposure, as occurs in smoking.

A five-compartment PBPK model has been proposed to predict CO uptake and distribution from acute inhalation exposure and contains components for lung, arterial blood, venous blood, muscle tissue, and nonmuscle tissue (Bruce and Bruce, 2003, [193975](#); Bruce and Bruce, 2006, [193980](#); Bruce et al., 2008, [193977](#)). This model structure is illustrated in Figure 4-3 and includes the dynamics of CO storage in the lung and its dependence on ventilation and CO pressure of mixed venous blood, relaxes the assumption that Hb is saturated by including the role of CO in altering the  $O_2$  dissociation curve, includes a subcompartmentalized muscle tissue compartment, accounts for dissolved CO in blood and tissue, and predicts COHb based on age and body dimensions. This multicompartment model is limited by its exclusion of cellular metabolism or Mb diffusion, simplification of within tissue bed spatial variability, and assumption that ventilation and average partial pressure of alveolar  $O_2$  ( $P_{A}O_2$ ) are constant. Another limitation of this model is that some of the physiological parameters used in simulations are estimated through visual fits to the COHb profile and not from experimental or published data. This model better predicts COHb levels when inspired CO levels change rapidly or when incomplete blood mixing has occurred, and better predicts the CO washout time course compared to the CFK equation. Bruce and Bruce (2003, [193975](#)) compared the two models and found similar results for long-duration exposure settings (1,000 min); however, the multicompartment model predicted somewhat lower COHb levels compared to the CFK model during transient CO uptake conditions when using data taken from Peterson and Stewart (1970, [012416](#)).



Source: Adapted with Permission of Elsevier Science from Bruce and Bruce (2008, [193977](#))

**Figure 4-3.** Overall structure of the Bruce and Bruce (2008, [193977](#)) multicompartment model of storage and transport of CO. Includes compartments for lung, arterial blood, venous blood, muscle tissue, and nonmuscle tissue. The muscle compartment is divided into two subcompartments for diffusion of gases within the tissue.

A multicompartment model of the human respiratory system was developed using characteristics of the tissue representation of Bruce and Bruce (2003, [193975](#)), and the lung representation described in Selvakumar et al. (1992, [013750](#)) and Sharan (1999, [194673](#)), which considered the exchanges of CO, O<sub>2</sub>, and CO<sub>2</sub> (Neto et al., 2008, [194672](#)). The model contains six compartments including: alveolar, pulmonary capillaries, arterial, venous, tissue capillary, and tissues (muscular and non-muscular). The model was applied to four simulated physical activity levels, resting, sitting, standing, and walking, in a healthy subject exposed to the urban atmosphere of a metropolitan area of Brazil. The highest and lowest COHb levels were simulated in the walking individual, suggesting that greater variability in COHb occurs at higher physical activity levels.

### 4.2.3. Model Comparison

A number of models have been presented which predict COHb formation over numerous exposure scenarios. These models are often compared to the CFK equation to determine the most accurate predictive model under certain exposure conditions. As was mentioned in Section 4.2.1, Tikuisis (1996, [080960](#)) conducted a comparison of empirical model predictions that showed a wide disparity in predicted COHb values, highlighting the inaccuracy of these models outside of the conditions on which they were presented. Smith et al. (1990, [013164](#)) compared the linear and nonlinear CFK equations and concluded that the linear CFK equation gives a good approximation (within 1%) to the nonlinear solution over a large range of values during CO uptake and over a somewhat smaller range during CO elimination. The linear equation prediction of COHb concentration at or below 6% will only differ  $\pm 0.5\%$  COHb from the nonlinear equation prediction. Additionally, the most recently modified CFK model (Gosselin et al., 2009, [190946](#)) better predicted COHb formation over a wide range of CO levels (50-4,000 ppm) and several temporal scenarios (Stewart et al., 1970, [013972](#); Tikuisis et al., 1987, [012138](#); Tikuisis et al., 1987, [012219](#); Tikuisis et al., 1992, [013592](#)) compared to the linear CFK model. Linear regression slopes between the simulated COHb values from Gosselin et al. (2009, [190946](#)) and the observed experimental values were closer to 1 in all experimental scenarios, indicating a better fit to the observed data. When evaluating all validation studies the modified model had an estimated slope of 0.996 (95% CI: 0.986-1.001) compared to 0.917 (95% CI: 0.906-0.927) using the linear CFK model. Bruce and Bruce (2003, [193975](#)) compared their model to the CFK and found similar results for long-duration exposure settings (1,000 min [16.5 h]), however, their multicompartment model predicted somewhat lower COHb levels over transient CO uptake conditions when using data taken from Peterson and Stewart (1970, [012416](#)). The Bruce and Bruce model better predicts However, there has not been a quantitative comparison of the recent multicompartment models (Bruce and Bruce, 2003, [193975](#); Neto et al., 2008, [194672](#)) and the improved CFK equation models (Gosselin et al., 2009, [190946](#); Smith et al., 1994, [076564](#)) to determine which is most accurate in predicting COHb levels under exposure scenarios that include occasional peak concentrations. The nonlinear and linear CFK equations remain the most extensively validated and applied models for COHb prediction. COHb levels when inspired CO levels change rapidly or when incomplete blood mixing has occurred, and better predicts the CO washout time course compared to the CFK equation. However, there has not been a quantitative comparison of the recent multicompartment models (Bruce and Bruce, 2003, [193975](#))(Neto et al., 2008, [194672](#)) and the improved CFK equation models (Smith et al., 1994, [076564](#))(Gosselin et al., 2009, [190946](#)) to determine which is most accurate in predicting COHb levels under exposure scenarios that include occasional peak concentrations. The nonlinear and linear CFK equations remain the most extensively validated and applied models for COHb prediction.

### 4.2.4. Mathematical Model Usage

As no new data have become available on the distribution of COHb levels in the U.S. population since large-scale nationwide surveys – e.g., National Health and Nutrition Examination Survey II (NCHS; et al., 1982, [011442](#)) – and human exposure field studies – e.g., Denver, CO, and Washington, DC (Akland et al., 1985, [011618](#)) – were conducted in the 1970s and 1980s, mathematical models are used to predict the resulting COHb levels from various CO exposure scenarios. Table 4-1 illustrates the predictions of venous COHb after 1, 8, or 24 h of CO exposure at a range of concentrations in a healthy adult human at rest ( $V_A = 6$  L/min;  $D_LCO = 20$

[mL/min]/mmHg), during light exercise ( $V_A = 15$  L/min;  $D_LCO = 34$  [mL/min]/mmHg), and during moderate exercise ( $V_A = 22$  L/min;  $D_LCO = 43$  [mL/min]/mmHg). The Quantitative Circulatory Physiology (QCP) model, which integrates human physiology using over 4,000 variables and equations based on published biological interactions, was used to predict these values (Abram et al., 2007, [193859](#); Benignus et al., 2006, [151344](#)). This dynamic whole body model uses the nonlinear CFK equation with modifications presented in Smith et al. (1994, [076564](#)). The contribution of alveolar ventilation and lung diffusion to the changes in COHb levels is discussed in Section 4.3.1.2. Increased ventilation leads to an increased rate of CO uptake, causing COHb levels to reach equilibrium earlier. Also, increased ventilation leads to a decrease in steady state COHb levels due to increased CO expiration. For example, 35 ppm CO exposure at moderate exercise (22 L/min) results in a lower 24-h COHb saturation (4.73%), compared to COHb saturation from 35 ppm CO at rest (5.03%) (Table 4-1). Whereas, after 1 h, COHb levels are still increasing following exposure at all levels of exercise and have not reached steady state, thus the greater uptake from increased ventilation leads to initially elevated COHb in higher ventilation situations.

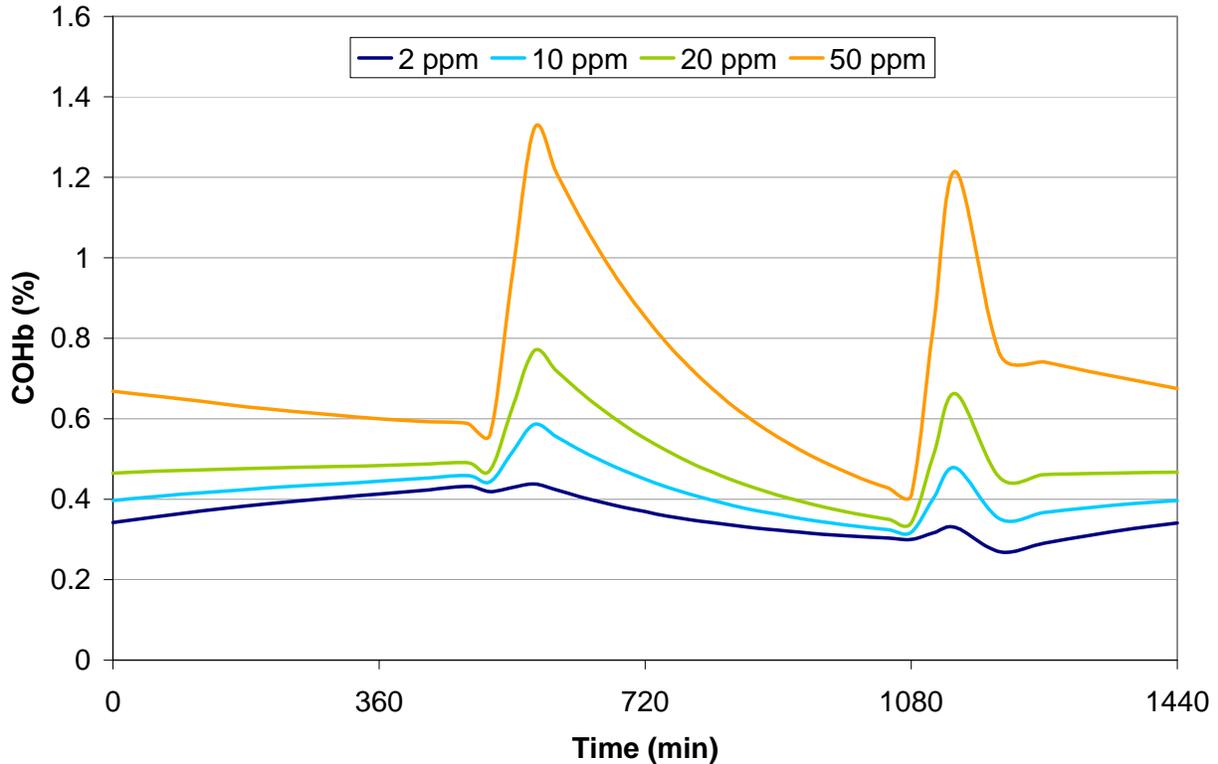
Endogenous CO production varies as described in Section 4.5 but generally results in <1% COHb, with a QCP modeled value of 0.27% at time zero. The rate of endogenous CO production was set at 0.007 mL/min for this simulation, whereas both higher and lower values have been reported (Coburn et al., 1966, [010984](#)) (Section 4.5). Table 4-1 illustrates that 35 ppm CO for 1-h results in between 0.9-1.9% COHb and 9 ppm CO for 8-h results in between 1.1-1.3% COHb, depending upon activity level. Also, this table shows that low concentration CO exposure over several hours can result in equivalent COHb levels compared to higher concentration, acute exposure. For example, in a resting condition without additional baseline COHb, COHb resulting from 35 ppm for 1 h (0.89%) is approximately equivalent to 6 ppm for 8 h (0.83%) or 4 ppm for 24 h (0.82%).

**Table 4-1. Predicted COHb levels resulting from 1, 8, and 24 h CO exposures in a modeled human at rest ( $V_A = 6$  L/min;  $D_LCO = 20$  (mL/min)/mmHg;  $V_{CO} = 0.007$  mL/min; initial COHb = 0.27%; Hb = 0.15 g/mL), during light exercise ( $V_A = 15$  L/min;  $D_LCO = 34$  (mL/min)/mmHg), and during moderate exercise ( $V_A = 22$  L/min;  $D_LCO = 43$  (mL/min)/mmHg). The QCP model used a dynamic nonlinear CFK with the Smith et al. (1994, [076564](#)) COHb algorithm and affinity constant  $M = 218$ .**

CO (ppm)	1 h			8 h			24 h		
	6 L/min	15 L/min	22 L/min	6 L/min	15 L/min	22 L/min	6 L/min	15 L/min	22 L/min
2	0.30	0.30	0.29	0.45	0.38	0.35	0.54	0.40	0.36
3	0.31	0.33	0.34	0.54	0.51	0.48	0.68	0.54	0.49
4	0.33	0.36	0.62	0.64	0.64	0.62	0.82	0.69	0.63
6	0.36	0.44	0.48	0.83	0.90	0.88	1.10	0.97	0.91
9	0.42	0.55	0.63	1.12	1.29	1.27	1.52	1.39	1.31
15	0.53	0.77	0.92	1.69	2.05	2.06	2.35	2.22	2.12
24	0.70	1.10	1.35	2.55	3.19	3.22	3.57	3.45	3.31
35	0.89	1.50	1.89	3.58	4.55	4.60	5.03	4.91	4.73

The QCP model incorporating the Smith et al. (1994, [076564](#)) COHb algorithm was also used to simulate population exposure scenarios including various commuting concentrations (Figure 4-4) and endogenous production rates (Figure 4-5). Commuting concentrations were modeled since the highest ambient CO exposure levels are generally observed during transit (Section 3.6.6.2). Figure 4-4 presents simulated COHb levels in a healthy adult throughout the second of 5 modeled days containing a 60-min commute at various CO concentrations. The U.S. Census Bureau estimates that 5% of the population commutes in automobiles for 60 or more minutes to work daily (U.S. Census Bureau, 2008, [194013](#)) and exposure studies have reported in-vehicle transit concentrations up to 50 ppm (Abi-Esber and El-Fadel, 2008, [190939](#); Duci et al., 2003, [044199](#)). However, U.S. studies have reported in-vehicle concentrations of <6 ppm, although peak

concentrations in congested urban areas have been reported to be higher than 50 ppm (Rodes et al., 1998, [010611](#))(Riediker et al., 2003, [043761](#)). CO concentrations during commuting lead to spikes in COHb in this model scenario with a 1% COHb increase over the initial COHb (0.3%) after 50 ppm exposure. Figure 4-4 also illustrates that the COHb saturation after CO exposure from commuting is not fully eliminated by the next commuting period. Modeling successive days results in the same pattern and degree of COHb formation, indicating no accumulation of COHb over time.

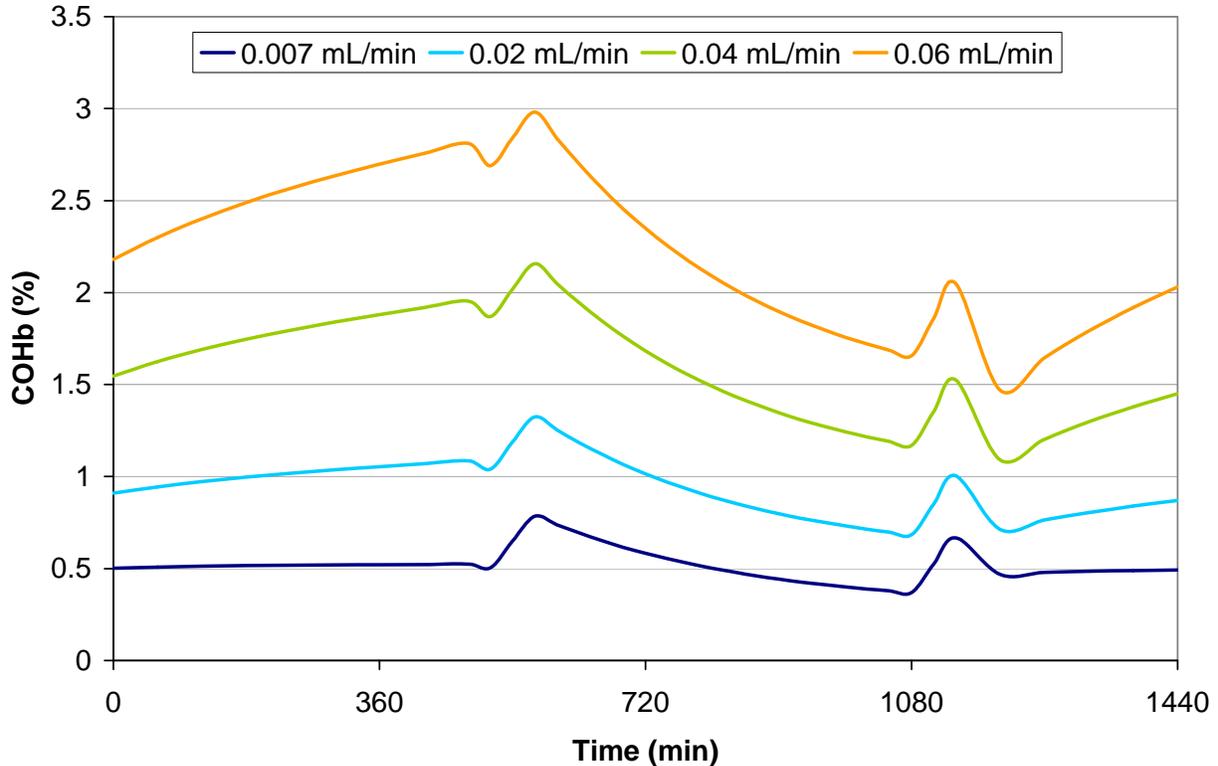


**Figure 4-4. Predicted COHb levels in healthy commuters exposed to various CO concentrations over a 60-min commute twice a day. Ambient CO concentration not during commuting time was 1 ppm. The activity pattern simulated: (1) sleeping for 8 h; (2) standing and light exercise for 30 min; (3) sitting during a 60-min commute; (4) light exercise for 8.5 h; (5) sitting during a second 60-min commute; (6) moderate exercise for 60 min; and (7) sitting for 4 h. The graph illustrates the second day simulated under these conditions.<sup>1</sup>**

Figure 4-5 presents simulated COHb levels in adults with various endogenous CO production rates throughout the second of 5 modeled days containing a 60-min commute at 20 ppm CO. The normal endogenous rate of CO production in young adult males with an average COHb of 0.88% averages 0.007 mL/min (18.7 ± 0.8 µmol/h) (Coburn et al., 1963, [013971](#)). However, a number of diseases and conditions described in Section 4.5 can affect this production rate. Patients with

<sup>1</sup> Sleeping/lying human parameters:  $V_A$ - 3.8 L/min,  $V_T$ - 467 mL,  $V_D$ - 147 mL,  $V_{CO}$ - 0.007 mL/min,  $D_LCO$ - 17.9 mL/min/mmHg, M- 218, initial COHb- 0.27%. Sitting human parameters:  $V_A$ - 5.2 L/min,  $V_T$ - 560 mL,  $V_D$ - 155 mL,  $V_{CO}$ - 0.007 mL/min,  $D_LCO$ - 18 mL/min/mmHg. Standing human parameters:  $V_A$ - 6.4 L/min,  $V_T$ - 636 mL,  $V_D$ - 161 mL,  $V_{CO}$ - 0.007 mL/min,  $D_LCO$ - 19.3 mL/min/mmHg. Light exercise (1 MPH, 32 W) human parameters:  $V_A$ - 13.4 L/min,  $V_T$ - 994 mL,  $V_D$ - 218 mL,  $V_{CO}$ - 0.007 mL/min,  $D_LCO$ - 30.4 mL/min/mmHg. Heavy exercise (3 MPH, 96 W) human parameters:  $V_A$ - 31.4 L/min,  $V_T$ - 1642 mL,  $V_D$ - 241 mL,  $V_{CO}$ - 0.007 mL/min,  $D_LCO$ - 49.6 mL/min/mmHg.

hemolytic anemia have endogenous CO production rates ranging from 0.012 to 0.053 mL/min (31-143  $\mu\text{mol/h}$ ) (Coburn et al., 1966, [010984](#)). The venous COHb levels in these same patients ranged from 0.77 to 2.62%.



**Figure 4-5.** Predicted COHb levels due to various endogenous CO production rates. The activity pattern presented in Figure 4-4 was used. Ambient CO concentration not during commuting time was 1 ppm and commuting CO concentration was 20 ppm. The graph illustrates the second day simulated under these conditions.

## 4.3. Absorption, Distribution, and Elimination

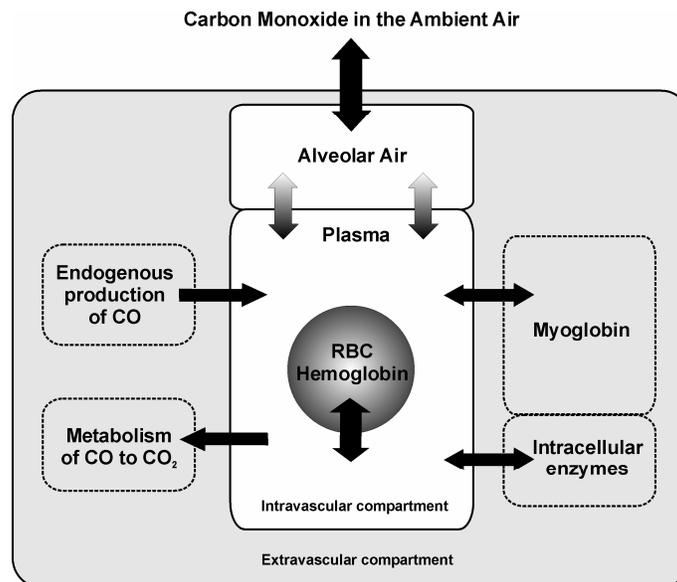
### 4.3.1. Pulmonary Absorption

Pulmonary uptake of CO accounts for all environmental CO absorption and occurs at the respiratory bronchioles and alveolar ducts and sacs. CO and O<sub>2</sub> share various physico-chemical properties, thus allowing for the extension of the knowledge about O<sub>2</sub> kinetics to those of CO despite the differences in the reactivity of the gases. The exchange of CO between the air and the body depends on a number of physical (e.g., mass transfer and diffusion), as well as physiological factors (e.g., alveolar ventilation and cardiac output), which are controlled by environmental conditions, physical exertion, and other processes discussed in Section 4.4. The ability of the lung to take up inhaled CO is measured by  $D_L\text{CO}$ , and CO uptake representing the product of  $D_L\text{CO}$  and the mean alveolar pressure ( $P_A\text{CO}$ ). The importance of dead space volume, gas mixing and homogeneity, and

ventilation/perfusion matching were discussed in depth in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)).

#### 4.3.1.1. Mass Transfer of Carbon Monoxide

Mass transfer refers to the molecular and convective transport of CO molecules within the body stores, driven by random molecular motion from high to low concentrations. CO enters through the airway opening (mouth and nose) and transfers in a gas phase to the alveoli. CO transport is due to convective flow, the mechanical action of the respiratory system, and diffusion in the acinar zone of the lung (Engel et al., 1973, [014336](#)). Then, CO diffuses across the air-blood interface into plasma and subsequently into red blood cells (RBC), binding RBC Hb. At environmental CO levels, CO uptake into RBC is limited by the reaction rate of binding of CO to O<sub>2</sub>Hb forming COHb. Pulmonary capillary RBC CO diffusion is rapidly achieved (Chakraborty et al., 2004, [193759](#); Gibson and Roughton, 1955, [193941](#); Reeves and Park, 1992, [193847](#); Roughton and Forster, 1957, [193862](#)). The formation rate and level of COHb depends upon pCO, pO<sub>2</sub> in the air, time of exposure, and the ventilation rate (Roughton and Forster, 1957, [193862](#)). Most of the body CO is bound to Hb; however, 10-15% of the total body CO is located in extravascular tissues primarily bound to other heme proteins (Coburn, 1970, [013916](#)). Considerable concentrations of CO have been measured in spleen, lung, kidney, liver, muscle, and heart (Vreman et al., 2005, [193786](#); Vreman et al., 2006, [098272](#)), whereas less CO is localized to fatty tissues, such as adipose and brain. The transfer of CO occurs by a partitioning of CO between Hb and tissue. Less than 1% of the total body CO stores appear as dissolved in body fluids, due to the insolubility and small tissue partial pressure of CO (Coburn, 1970, [013916](#)). Transport pathways and body stores of CO are shown in Figure 4-6.



Source: Adapted with Permission of Wiley-Blackwell from Coburn (1967, [011144](#))

Figure 4-6. Diagrammatic presentation of CO uptake and elimination pathways and CO body stores.

#### 4.3.1.2. Lung Diffusion of Carbon Monoxide

Lung diffusion of CO is an entirely passive process of gas diffusion across the alveolo-capillary membrane, through the plasma, across the RBC membrane and into the RBC stroma, where

CO binding to Hb rapidly occurs. Membrane and blood phase transfer are governed by physico-chemical laws, including Fick's first law of diffusion. The diffusing capacity of the lung for CO, represented as  $D_LCO$ , is a measurement of the partial pressure difference between inspired and expired CO. Due to the rapid binding of CO to Hb, a high pressure differential between air and blood exists when CO air levels are increased. Inhalation of CO-free air reverses the pressure differential (higher CO pressure on the blood side than the alveolar side), and then CO is released into the alveolar air. Since CO is also produced endogenously, CO release will also be affected by this production pressure. However, the air-blood gradient for CO is usually higher than the blood-air gradient; therefore, CO uptake will be a proportionately faster process than CO elimination.

A number of factors have been found to affect  $D_LCO$  including Hb concentration, cardiac output (Q), erythrocyte flow, COHb concentration,  $P_ACO_2$ , body position, exercise, time of day, age, etc. (Forster, 1966, [180430](#); Hsia, 2002, [193857](#)).  $D_LCO$  consistently decreases after intense bouts of exercise, likely due to the redistribution of blood volume to the periphery (Hanel et al., 1997, [193918](#); Manier et al., 1991, [193979](#)). However, in going from rest to exercise,  $D_LCO$  can increase linearly from: lung expansion leading to unfolding and distension of alveolar septa, opening and/or distension of capillaries as Q increases, increased capillary hematocrit, and more homogeneous distribution of capillary erythrocytes (Hsia, 2002, [193857](#)).  $D_LCO$  is less dependent upon lung volume at mid-range vital capacity, but at extreme volumes the diffusion rate is varied, higher than average at total lung capacity and lower at residual volume (McClellan et al., 1981, [012411](#)).

$D_LCO$  is also altered by a number of diseases. Decreased  $D_LCO$  is evident in patients with restrictive lung disease (i.e., decreased lung volumes) since a loss of lung tissue leads to a loss of functional lung units.  $D_LCO$  also shows a good correlation with the severity of restrictive lung disease (Arora et al., 2001, [186713](#)). Conditions affecting  $D_LCO$  vary and include chronic obstructive pulmonary disease (Terzano et al., 2009, [108046](#)), ulcerative colitis (Marvisi et al., 2000, [186703](#); Marvisi et al., 2007, [186702](#)), severe gastroesophageal reflux (Schachter et al., 2003, [186707](#)), beta thalassemia (Arora et al., 2001, [186713](#)), thoracic or abdominal aortic aneurysm (Sakamaki et al., 2002, [186706](#)), pulmonary arterial hypertension (Proudman et al., 2007, [186705](#)), and chemotherapy for breast cancer (Yerushalmi et al., 2009, [186711](#)). Diseases affecting CO kinetics and  $D_LCO$  are also discussed in Section 4.4.4.

## 4.3.2. Tissue Uptake

### 4.3.2.1. Respiratory Tract

The upper respiratory tract contributes little to the overall CO uptake. The lung has nearly constant exposure to CO; however, relatively little CO diffuses into the tissue except at the alveolar region en route to the circulation. No detectable uptake of CO was observed in the human nasal cavity or upper airway (Guyatt et al., 1981, [011196](#)) or in the monkey oronasal cavity after high CO exposure (Schoenfish et al., 1980, [011404](#)).

### 4.3.2.2. Blood

The blood is the largest reservoir for CO, where it reversibly binds to Hb. The chemical affinity of CO for adult human Hb is approximately 218 times greater than that of  $O_2$ , meaning one part CO and 218 (210-250) parts  $O_2$  would form equal parts of  $O_2Hb$  and  $COHb$  (Engel et al., 1969, [193914](#); Rodkey et al., 1969, [008151](#); Roughton, 1970, [013931](#)). This would happen when breathing air containing 21%  $O_2$  and 960 ppm CO. This concept was presented by Haldane and Smith (1895, [010538](#)) and later represented as the Haldane constant M (210-250) in the Haldane equation by Douglas, Haldane, and Haldane (1912, [013965](#)). M is relatively unaffected by changes in physiological pH,  $CO_2$ , temperature, or 2,3-diphosphoglycerate:

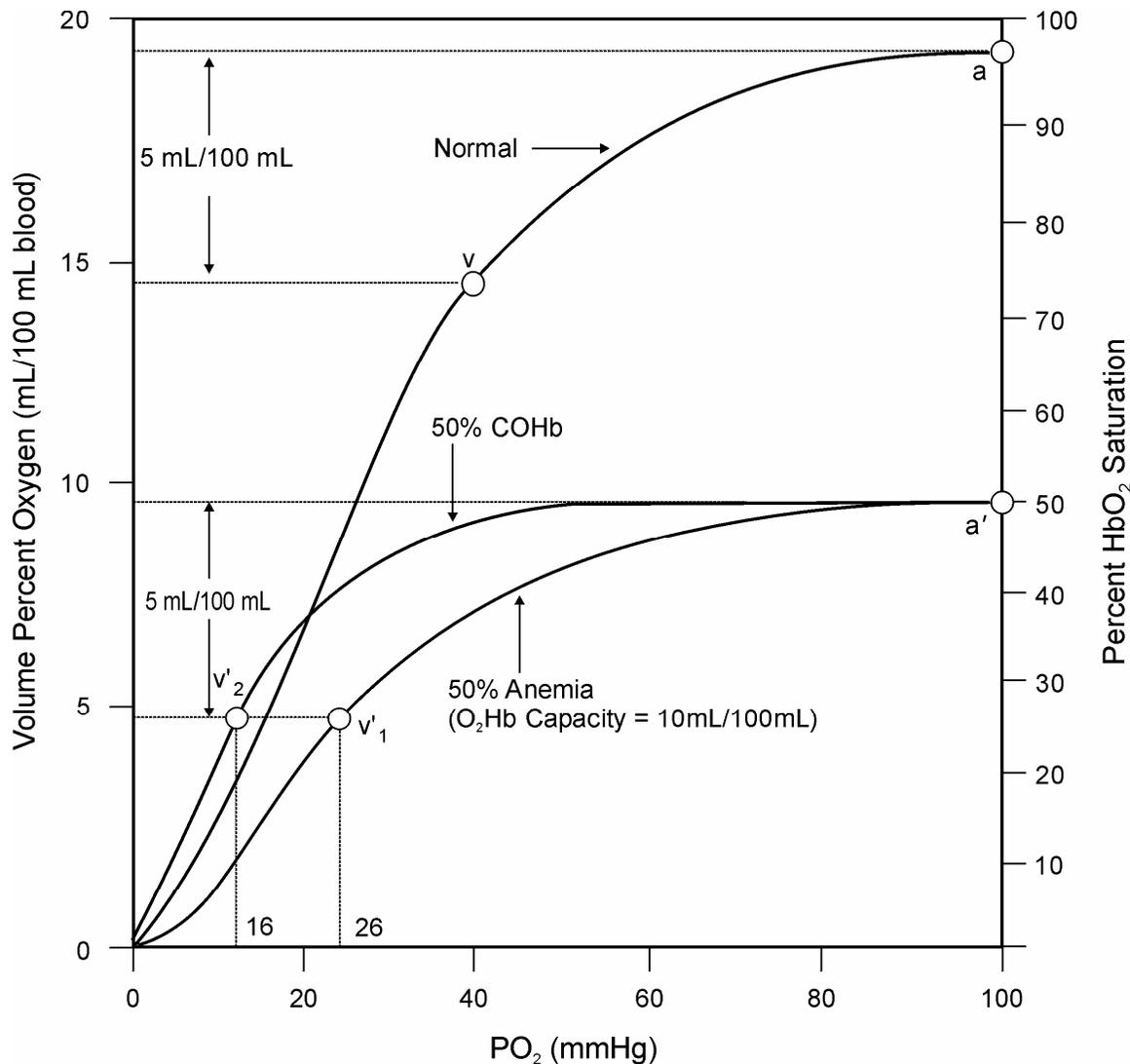
$$COHb \div O_2Hb = M \times (pCO \div pO_2)$$

Equation 4-3

The Hb association rate for CO is 10% slower than  $O_2$  and occurs in a cooperative manner (Chakraborty et al., 2004, [193759](#); Sharma et al., 1976, [193766](#)). Hb is composed of four globin

chains, each containing a heme group capable of binding CO or O<sub>2</sub>. The associative reaction rates become faster with successive heme binding, attributed to interactions within the protein and to strains imposed on the heme and its ligands (Alcantara et al., 2007, [193867](#)). More simply, the greater the number of heme sites bound to CO, the greater the affinity of free heme sites for O<sub>2</sub>, thus causing Hb to bind and retain O<sub>2</sub> that would normally be released to tissues. Cooperativity is greatly reduced in CO dissociation, but the rate of dissociation of CO from Hb is orders of magnitude slower than O<sub>2</sub> ( $k_{CO} = 4 \times 10^{-4} k_{O_2}$ ), which accounts for the high affinity values (Chakraborty et al., 2004, [193759](#)). The half-time of dissociation reaction is about 11 s at 37°C (Holland, 1970, [193856](#)). In general, CO uptake to COHb equilibrium is slower in humans and large animals, requiring 8-24 h, than in smaller species such as rats, which will equilibrate in 1-2 h (Penney, 1988, [012519](#)). Also, COHb equilibrium within the blood stream is not instantaneous. Men exposed to brief (~5 min) high-dose CO had an initial delay of 1-2 min in the appearance of venous COHb after the start of CO inhalation (Benignus et al., 1994, [013908](#); Smith et al., 1994, [076564](#)). Additionally, arterial COHb concentrations were considerably higher than venous concentrations during CO exposure; however, they converged within 2-10 min after the end of exposure, as venous and arterial blood mixed.

CO binding to Hb also has effects on the O<sub>2</sub> dissociation curve of the remaining Hb by shifting the curve progressively to the left and altering the normal S-shaped curve to become more hyperbolic due to increased cooperative O<sub>2</sub> binding (Roughton, 1970, [013931](#)). This is referred to as the “Haldane effect” and causes tissues to have more trouble obtaining O<sub>2</sub> from the blood, even compared to the same extent of reduced Hb resulting from anemia. For example, Figure 4-7 (as explained in the 2000 CO AQCD) illustrates that in an acute anemia patient (50% of Hb) at a venous pO<sub>2</sub> of 26 mmHg ( $v'_1$ ), 5 vol % of O<sub>2</sub> (50% saturation) was extracted from the blood. In contrast, for a CO poisoned person with 50% COHb, the venous pO<sub>2</sub> will have to drop to 16 mmHg ( $v'_2$ ) to release the same 5 vol % O<sub>2</sub>. This more severe effect on O<sub>2</sub> pressure may lead to brain O<sub>2</sub> depletion and loss of consciousness if any higher demand of O<sub>2</sub> is needed (e.g., exercise).



Source: U.S. EPA (1991, [017643](#))

**Figure 4-7. O<sub>2</sub>Hb dissociation curve of normal human blood, of blood containing 50% COHb, and of blood with only 50% Hb because of anemia.**

### 4.3.2.3. Heart and Skeletal Muscle

Mb is a globular heme protein that facilitates O<sub>2</sub> diffusion from the muscle sarcoplasm to mitochondria, acting as an O<sub>2</sub> supply buffer to maintain adequate pO<sub>2</sub> for mitochondria when the O<sub>2</sub> supply changes, as in exercise. O<sub>2</sub> has a greater affinity for Mb than Hb, which allows small changes in tissue pO<sub>2</sub> to release large amounts of O<sub>2</sub> from O<sub>2</sub>Mb (Wittenberg et al., 1975, [012436](#)). Small reductions in O<sub>2</sub> storage capacity of Mb, due to CO binding, may have a profound effect on the supply of O<sub>2</sub> to the tissue.

Like Hb, Mb will undergo reversible CO binding, however the affinity constant is approximately eight-times lower than Hb (M = 20-40 versus 218, respectively) (Haab, 1990, [013359](#)). The association rate constant of CO and Mb is approximately 27 times lower than O<sub>2</sub>; however, the dissociation rate constant is approximately 630 times lower than O<sub>2</sub> (Gibson et al., 1986, [016289](#)), causing CO to be retained and possibly stored in the muscle. CO levels have been measured in human muscle and heart tissues with <2% COHb concentrations at background levels

(15 and 31 picomole [pmol] CO/mg ww, respectively) (Vreman et al., 2006, [098272](#)) (Table 4-2). Under conditions of CO asphyxiation, tissue concentrations increased 17-18 fold (265 and 527 pmol CO/mg ww muscle and heart tissue, respectively); however, heart tissue concentrations varied widely between individuals. Mouse muscle did not show this increase after exogenous CO exposure (Vreman et al., 2005, [193786](#)). This may be due to the fact that human muscle has a 15-fold higher concentration of myoglobin protein than mouse muscle (Weller et al., 1986, [187298](#)). The capacity for diffusion of CO into the muscle is represented by the coefficient  $D_mCO$  and is generally larger in males than in females, likely due to the differences in muscle mass and capillary density (Bruce and Bruce, 2003, [193975](#)). COMb concentrations in the heart and skeletal muscle increase with work load, due to a higher relative rate of CO binding to Mb relative to Hb. This causes an increase in COMb/COHb that is not seen at rest (Sokal et al., 1984, [011591](#)). Subjects with 2% COHb but not those with 20% COHb levels showed a significant uptake of CO from the blood to the muscle with increasing work intensity of the quadriceps muscle (Richardson et al., 2002, [037513](#)).

**Table 4-2. CO concentration in pmol/mg wet weight tissue and fold tissue CO concentration changes (normalized to background tissue concentrations) – human.**

Exposure	Adipose	Brain	Muscle	Heart	Kidney	Lung	Spleen	Blood	% COHb
Background	3 ± 1	3 ± 3	15 ± 9	31 ± 23	23 ± 18	57 ± 59	79 ± 75	165 ± 143	1.5 ± 1.2
Fire	5 ± 4 [1.7]	7 ± 5 [2.3]	24 ± 16 [1.6]	54 ± 33 [1.7]	27 ± 11 [1.2]	131 ± 127 [2.3]	95 ± 69 [1.2]	286 ± 127 [1.7]	3.8 ± 3.2 [2.5]
Fire + CO	18 ± 29 [6.0]	17 ± 14 [5.7]	168 ± 172 [11.2]	128 ± 63 [4.1]	721 ± 427 [31.3]	1097 ± 697 [19.2]	2290 ± 1409 [29.0]	3623 ± 1975 [22.0]	40.7 ± 28.8 [27.1]
CO asphyxiation	25 ± 27 [8.3]	72 ± 38 [24.0]	265 ± 157 [17.7]	527 ± 249 [17.0]	885 ± 271 [38.5]	2694 ± 1730 [47.3]	3455 ± 1347 [43.7]	5196 ± 2625 [31.5]	56.4 ± 28.9 [37.6]

Source: Reprinted with Permission of Wiley-Blackwell from Vreman et al. (2006, [098272](#))

#### 4.3.2.4. Other Tissues

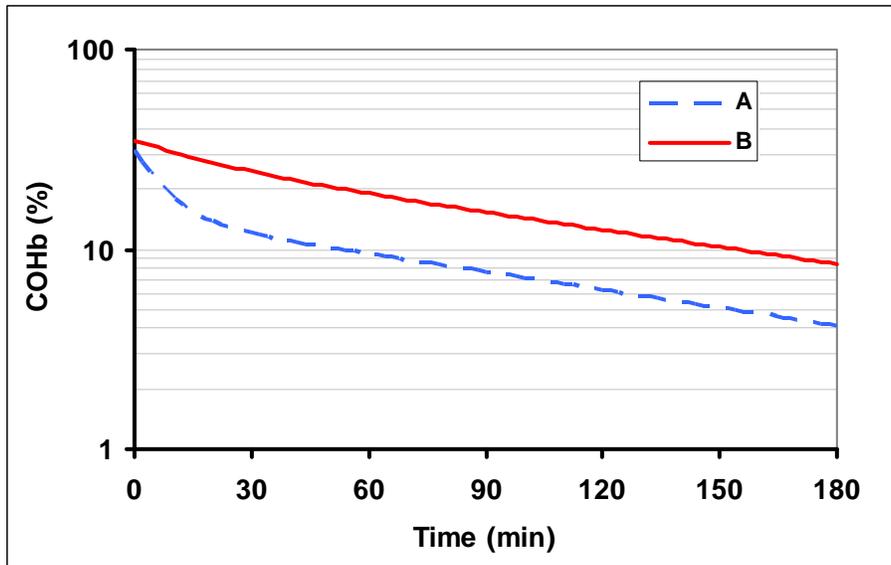
CO binds with other hemoproteins, such as cytochrome P450, cytochrome *c* oxidase, catalase, and peroxidase, but the possibility of this binding influencing CO-O<sub>2</sub> kinetics has not been established. CO transfers between COHb and tissue, the extent of which varies between organs. Blood-to-tissue flux causes less CO to be expired following CO exposure than what is lost from the blood in terms of COHb (Roughton and Root, 1945, [180418](#)). This value is estimated to be 0.3-0.4% min<sup>-1</sup> or 0.24 mL/min (Bruce and Bruce, 2003, [193975](#); Prommer and Schmidt, 2007, [180421](#)). The equilibration rate from blood to tissue is uncertain. Newly modeled CO trafficking kinetics shows that CO continues to be taken up by the muscle and extravascular tissues well beyond the end of exposure because of a less than instant equilibration (Bruce and Bruce, 2006, [193980](#)). Table 4-2 contains tissue CO concentrations from humans under different CO exposure conditions. The distribution of CO between the different human organs was shown to follow the same pattern versus percent of the blood CO concentration, irrespective of the level of blood CO (Vreman et al., 2006, [098272](#)). Consistently, the spleen, lung, and kidney had the highest measured CO concentration and the most dramatic increases over basal levels; the brain and adipose had the lowest CO concentrations. In addition to these fatty tissues, the muscular tissues including the heart and skeletal muscle had similarly low increases over background CO levels. This pattern was also found in rodents exposed to exogenous CO; however, increased endogenous CO produced after heme administration did not follow this pattern of uptake (Vreman et al., 2005, [193786](#)). Increased endogenous CO production led to moderately increased CO present in the lung, heart, liver, and spleen and no change in CO concentration in the testes, intestine, muscle, brain, and kidney. The spleen and liver have an abundance of HO-1 expression and are involved in the catabolism of heme, thus it is expected to have elevated CO concentrations in these organs after heme treatment. Also, elevated CO in the lung is not surprising since it is the site of CO excretion. The tissues analyzed in these studies were blanched before analysis; however, contamination of the tissue sonicates with blood from the vessels within each organ is a possible source of error. The measurements were presented by the authors as minimum tissue CO concentrations, due to the possibility of rapid loss of CO from blood and tissue exposed to the atmosphere, light, and elevated temperature (Chace et al., 1986, [012020](#); Ocak et al., 1985, [011641](#)). These results are not consistent with older papers,

suggesting that negligible retention of CO occurs in the liver or brain (Sokal et al., 1984, [011591](#); Topping, 1975, [193784](#)).

### 4.3.3. Pulmonary and Tissue Elimination

Blood COHb concentrations are generally considered to have a monotonically decreasing, second-order (logarithmic or exponential) elimination rate from equilibrium. However, more recent reports have presented evidence for a biphasic washout curve, especially after brief CO exposure (Figure 4-8) (Bruce and Bruce, 2006, [193980](#); Shimazu et al., 2000, [016420](#); Wagner et al., 1975, [010989](#)). This event is modeled by a two-compartment system where the initial rapid decrease is the washout rate from the blood, followed by a slower phase due to CO flux from the muscle and extravascular compartments back to the blood. Tissue elimination rates have been reported as slower than those for blood (Landaw, 1973, [010803](#)). The biphasic curve is more obvious after short-duration CO exposure (<1 h), whereas longer CO exposure ( $\geq 5$  h) results in a virtually monoexponential elimination, which could account for the historical findings. However, this elimination curve also follows a biphasic curve with a slightly higher rate of elimination initially (Shimazu et al., 2000, [016420](#)). Differences in elimination kinetics could also be a result of the variation in CO exposure duration (Weaver et al., 2000, [016421](#)).

The elimination of COHb is affected by a number of factors, including duration of exposure,  $P_aO_2$ , minute ventilation, the time post-exposure for analysis due to extravascular stores, as well as inter-individual variability (Bruce and Bruce, 2006, [193980](#); Landaw, 1973, [010803](#); Shimazu, 2001, [016331](#)). The elimination rate does not seem to be dependent upon the CO exposure source (e.g., fire, non-fire CO exposure) (Levasseur et al., 1996, [080895](#)). In addition, in a series of poisoning cases, the COHb elimination half-life was not influenced by gender, age, smoke inhalation, history of loss of consciousness, concurrent tobacco smoking, degree of initial metabolic acidosis (base excess), or the initial COHb level (Weaver et al., 2000, [016421](#)). On the contrary, in modeling the nonlinear kinetics of CO, a subject with a higher initial COHb will detoxify and eliminate CO more rapidly (Gosselin et al., 2009, [190946](#)). Similarly, it has been shown that the absolute elimination rates are associated positively with the initial concentration of COHb, however the relative rate of elimination, expressed as a percentage decline in COHb% after a measured time, is independent of the initial COHb concentration (Wagner et al., 1975, [010989](#)). COHb elimination half-life falls as the fractional inspired  $O_2$  concentration increases. While breathing air at sea level pressure, the expected half-life in adult males is approximately 285 min, but may be shorter in adult females. With inhalation of normobaric 40%  $O_2$ , the half-life falls to 75 min and further to 21 min when breathing 100%  $O_2$  because of greater competition for Hb by  $O_2$  (Landaw, 1973, [010803](#)). Another study reports the half-life falls to 74 min (mean) after breathing 100%  $O_2$ , although the range in this particular study was 26-148 min (Weaver et al., 2000, [016421](#)). In addition, COHb half-life will fall further after normocapnic hyperoxic hyperpnea (i.e., hyperventilation while maintaining normal  $CO_2$  pressure in high  $O_2$ ) (Takeuchi et al., 2000, [005675](#)).



Source: Adapted with Permission of Lippincott Williams & Wilkins from Shimazu et al. (2000, [016420](#))

**Figure 4-8.** Changes in blood COHb after exposure to CO for a few minutes (A) or several hours (B), representing the biphasic nature of CO elimination. Note: y-axis is log-scale.

#### 4.3.4. COHb Analysis Methods

Blood COHb saturation can be analyzed using numerous methods with various benefits and limitations. The most popular current techniques include gas chromatography (GC) and spectrophotometry, specifically using CO-oximeters. CO-oximeters are commonly used because they require little sample preparation and simultaneously measure COHb, O<sub>2</sub>Hb, methemoglobin, and total hemoglobin concentration. However, at low concentrations of COHb relevant to ambient exposure (<5%), CO-oximeters overestimate COHb levels determined by GC (Mahoney et al., 1993, [013859](#); Widdop, 2002, [030493](#)). Conversely, at higher COHb levels (>5%), CO-oximeters will underestimate COHb concentrations. In addition to the inaccuracy of the CO-oximeters, some studies report considerable imprecision in the results. Also, numerous substances or conditions can interfere with CO-oximeter measurements (i.e., temperature, bilirubin, fetal hemoglobin). Alternatively, GC is an accurate, precise, highly specific analysis method and is generally used as the reference method for COHb analysis. GC requires the CO incorporated into blood or tissue samples to first be released using a liberating agent such as potassium ferricyanide or sulfosalicylic acid (Vreman et al., 2005, [193786](#); Vreman et al., 2006, [098272](#)), and then measured directly or indirectly. This methodology is more complex and time-consuming than spectrophotometry. In either analysis method, it is important to remember that COHb measured at one site in the body does not necessarily represent whole body CO distribution.

CO can also be measured directly in air or breath samples by using an electrochemical sensor that depends on the electrical signal generated by the oxidation of CO. There are conflicting reports on the correlation of exhaled CO (COex) with COHb. Multiple reports present positive correlation coefficients (r) ranging from 0.92 and 0.98 in smoking subjects (Jarvis et al., 1980, [011813](#); Jarvis et al., 1986, [012043](#); Landaw, 1973, [010803](#)). Positive linear correlations have also been shown in diseased patients with increased COHb (De las Heras et al., 2003, [194087](#)). Others have reported no correlation between low level COHb and COex and have suggested less correlation exists at the lower levels of COex relevant to ambient exposures (Horvath et al., 1998, [087191](#); Scharte et al., 2000, [194112](#)). Finally, CO is endogenously produced in the nose and paranasal sinus which may contribute to COex concentrations (Andersson et al., 2000, [011836](#)).

## 4.4. Conditions Affecting Uptake and Elimination

### 4.4.1. Physical Activity

Exercise is an important determinant of CO kinetics and toxicity due to the extensive increase in gas exchange. O<sub>2</sub> consumption can increase more than 10 fold during exercise. Similarly, ventilation, membrane and lung diffusing capacity, pulmonary capillary blood volume, and cardiac output increase proportional to work load. Also, exercise will improve the ventilation/perfusion ratio in the lung and mobilize RBC reserves from the spleen. The majority of these changes facilitate CO uptake and transport, by increasing gas exchange efficiency. Likewise, the COHb elimination rate increases with physical activity, causing a decrease in COHb half-life (Joumard et al., 1981, [011330](#)). During a transition period from rest to exercise while exposed to CO (500 ppm/10 min), the diffusing capacity and CO uptake were reported to rise faster than O<sub>2</sub> consumption for each exercise intensity (Kinker et al., 1992, [086328](#)). The two physiological variables that are most influential in the formation of COHb are alveolar ventilation and cardiac output. However, exercise did not affect the ability of the CFK equation to predict COHb saturation as long as appropriate variables were used for model analysis (Tikuisis et al., 1992, [013592](#)).

### 4.4.2. Altitude

Increased altitude changes a number of factors that contribute to the uptake and elimination of CO. The relationship between altitude and CO exposure has been discussed in depth in the 2000 CO AQCD and other documents (U.S. EPA, 1978, [086321](#)). In an effort to maintain proper O<sub>2</sub> transport and supply, physiological changes occur as compensatory mechanisms to combat the decreased barometric pressure and resulting altitude induced hypobaric hypoxia (HH). HH, unlike CO hypoxia, causes humans to hyperventilate, which reduces arterial blood CO<sub>2</sub> (hypocapnia) and increases alveolar partial pressure of O<sub>2</sub>. Hypocapnia will lead to difficulty of O<sub>2</sub> dissociation and decreased blood flow, thus reducing tissue O<sub>2</sub> supply. HH increases blood pressure (BP) and cardiac output and leads to redistribution of blood from skin to organs and from blood vessels to extravascular compartments. Generally these changes will favor increased CO uptake and COHb formation, as well as CO elimination. In hypoxic conditions both CO and O<sub>2</sub> bind reduced Hb through a competitive-parallel reaction (Chakraborty et al., 2004, [193759](#)). Sea level residents exposed to high altitude (3,658-5,800 m) for short or long visits (<1 year) experience negligible or minor changes in D<sub>L</sub>CO, although these changes in D<sub>L</sub>CO can be accounted for by polycythemia or increased red blood cell count and by the increased rate of reaction of carbon monoxide with hemoglobin due to hypoxia (West, 1962, [199513](#))(Guleria et al., 1971, [199518](#)). Breathing CO (9 ppm) at rest at altitude produced higher COHb compared to sea level (McGrath et al., 1993, [013865](#)), whereas high altitude exposure with exercise caused a decrease in COHb levels versus similar exposure at sea level (Horvath et al., 1988, [012725](#)). This decrease could be a shift in CO storage or suppression of COHb formation, or both. Altitude also increases the baseline COHb levels by inducing endogenous CO production. Initial HH increased lung HO-1 protein and activity, whereas chronic HH induced endogenous CO production in nonpulmonary sites (see Section 4.5) (Carraway et al., 2000, [021096](#)).

As the length of stay increases at high altitude, acclimatization occurs, inducing hyperventilation, polycythemia, and increased tissue capillarity and Mb content in skeletal muscle, which could also favor increased CO uptake. The D<sub>L</sub>CO of sea level natives who are long-term residents at altitude (3,100 m) increases from sea level values (Cerny et al., 1973, [199736](#)). Additionally, natives of high altitude (3,100-3,658 m) have increased D<sub>L</sub>CO compared to natives of sea level or sea level natives that stay at high altitude (DeGraff et al., 1970, [199737](#)) (Guleria et al., 1971, [199518](#)). This has been attributed to high pulmonary capillary blood volume and membrane diffusing capacity, and altered lung structure. Most of the early adaptive changes gradually revert to sea level values after individuals return to sea level. However, differences in people raised at high altitude persist even after reacclimatization to sea level (Hsia, 2002, [193857](#)). For example, altitude natives (3,658 m) staying at sea-level still have increased D<sub>L</sub>CO compared to sea level natives which suggests a permanent change in the lung structure resulting in a larger diffusing surface area (Guleria et al., 1971, [199518](#)).

### 4.4.3. Physical Characteristics

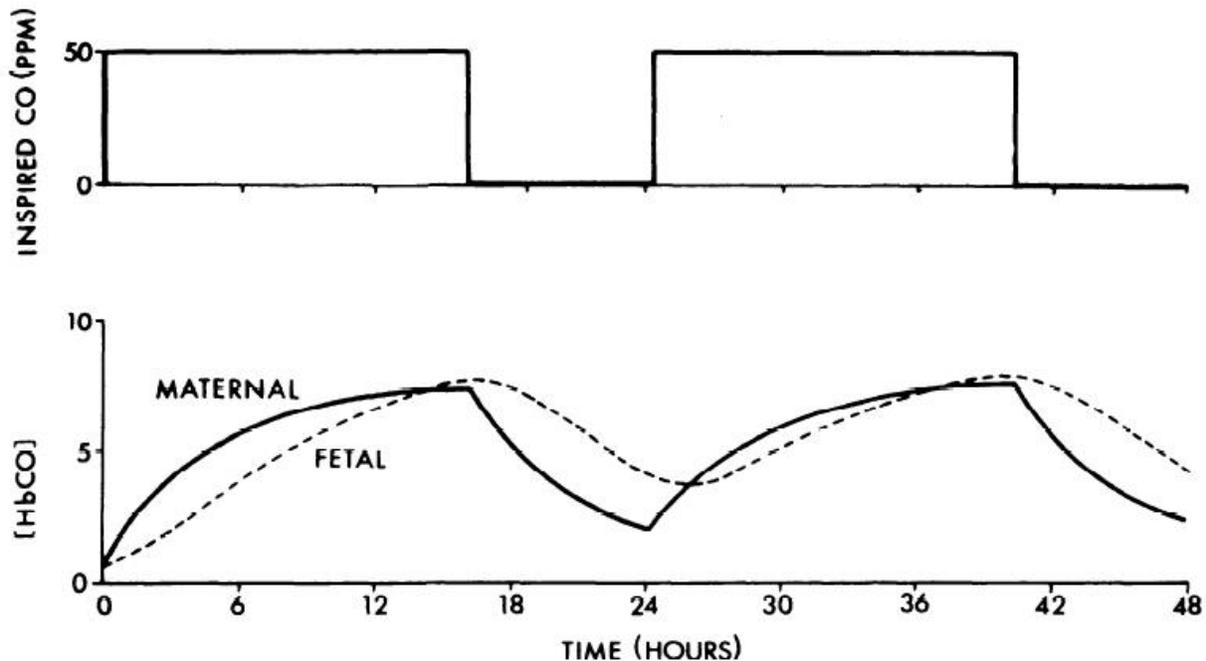
Certain physical characteristics (e.g., age, sex, pregnancy) can alter the variables that influence the uptake, distribution, and elimination of CO. Values of CO uptake and elimination change with age. Young children eliminate COHb more rapidly than adults after CO exposure (Joumard et al., 1981, [011330](#); Klasner et al., 1998, [087196](#)). After infancy, the COHb half-life increases with age, nearly doubling between 2 and 70 yr (Joumard et al., 1981, [011330](#)). The rate of this increase in CO elimination is very rapid in the growing years (2-16 yr of age), but slows beyond adolescence. Alveolar volume and  $D_LCO$  increase with increasing body length of infants and toddlers (Castillo et al., 2006, [193234](#)), suggesting a further degree of lung development and faster CO uptake. After infancy, increasing age decreases  $D_LCO$  and increases  $V_A/Q$  mismatch, causing it to take longer to both load and eliminate CO from the blood (Neas and Schwartz, 1996, [079363](#)).

COHb concentrations are generally lower in female subjects than in male subjects (Horvath et al., 1988, [012725](#)), and the COHb half-life may be longer in healthy men than in women of the same age, which may be partially explained by differences in muscle mass or the slight correlation between COHb half-life and increased height (Joumard et al., 1981, [011330](#)). However, women do have a higher rate of endogenous production while in the progesterone phase of the menstrual cycle and during pregnancy (Section 4.5). The rate of decline of  $D_LCO$  with age is lower in middle-aged women than in men; however, it evens out towards older age (Neas and Schwartz, 1996, [079363](#)). Women also tended to be more resistant to altitude hypoxia (Horvath et al., 1988, [012725](#)).

Ethnicity does alter physiological variables that determine CO uptake and kinetics. Lung volumes are 10-15% less in both Asian and African-American populations when compared to Caucasians. This causes a reduced alveolar surface area (20% less than estimated values) for gas exchange, leading to a 13% difference in  $D_LCO$  (Pesola et al., 2004, [193842](#); Pesola et al., 2006, [193855](#)). Certain factors, such as socioeconomic status (SES), were not controlled for in these studies. SES has been shown to affect pulmonary function, including decreasing  $D_LCO$  (Hegewald and Crapo, 2007, [193923](#)).

#### 4.4.3.1. Fetal Pharmacokinetics

Inhaled CO by pregnant animals quickly passes the placental barriers and enters the fetal circulation (Longo, 1977, [012599](#)). Fetal CO pharmacokinetics do not follow the same kinetics as maternal CO exposure, making it difficult to estimate fetal COHb based on maternal levels. Fetal COHb will vary as a function of maternal exposure but will also depend upon the rate of endogenous fetal CO production (Section 4.5), placental diffusing capacity of CO, the relative affinity of fetal Hb for CO compared to  $O_2$ , and the affinity of fetal blood for  $O_2$  (Longo, 1970, [013922](#)). Human fetal Hb has a higher affinity for CO than adult Hb, where the ratio of fetal COHb to maternal COHb at steady state in humans is approximately 1.11 (Longo, 1970, [013922](#))(Di Cera et al., 1989, [193998](#))(Hayde et al., 2000, [201602](#)). Maternal and fetal COHb concentrations have been modeled as a function of time using a modified CFK equation (Hill et al., 1977, [011315](#)). At steady-state conditions, the fetal COHb is up to 10-15% higher than the maternal COHb levels. For example, exposure to 30 ppm CO results in a maternal COHb of 5% and a fetal COHb of 5.75%. The fetal CO uptake lags behind the maternal for the first few hours but later may overtake the maternal values (Figure 4-9). Fetal COHb equilibrium may not be reached for 36-48 h after exposure. Similarly, during washout, the fetal COHb levels are maintained for longer, with a half-life of around 7.5 h versus the maternal half-life of around 4 h (Longo and Hill, 1977, [010802](#)).



Source: Reprinted with Permission of the American Physiological Society from Hill et al. (1977, [011315](#))

**Figure 4-9. Predicted maternal and fetal COHb during periodic exposure to CO (50 ppm for 16 h followed by 0 ppm for 8 h).**

#### 4.4.4. Health Status

Health status can influence the toxicity involved with CO exposure by influencing the severity of hypoxia resulting from CO exposure. Any condition that would alter the blood O<sub>2</sub> carrying capacity or content will result in a greater risk from COHb induced hypoxia and decreased tissue O<sub>2</sub> delivery. The severity of this effect depends upon the initial level of hypoxia.

Anemias are a group of diseases that result in insufficient blood O<sub>2</sub> or hypoxia due to Hb deficiency through hemolysis, hemorrhage, or reduced hematopoiesis. Anemia may result from pathologic conditions characterized by chronic inflammation, such as malignant tumors or chronic infections (Cavallin-Ståhl et al., 1976, [086306](#); Cavallin-Ståhl et al., 1976, [193239](#)). The bodies of people with anemia compensate, causing cardiac output to increase as both heart rate and stroke volume increase. The endogenous production of CO, thus COHb, is increased in patients with hemolytic anemia due to increased heme catabolism, causing an increased baseline COHb concentration. One of the most prevalent anemias arises from a single-point mutation of Hb, causing sickle cell diseases. The Hb affinity for O<sub>2</sub> and O<sub>2</sub> carrying capacity is reduced causing a shift to the right in the O<sub>2</sub> dissociation curve. It is well documented that African-American populations have a higher incidence of sickle cell anemia, which may be a risk factor for CO hypoxia.

Chronic obstructive pulmonary disease (COPD) is often accompanied by a number of changes in gas exchange, including increased deadspace volume (V<sub>D</sub>) and ventilation-perfusion ratio (V<sub>A</sub>/Q) inequality (Marthan et al., 1985, [086334](#)), which could slow both CO uptake and elimination. Patients with pulmonary sarcoidosis, a restrictive lung disease, may also have a decrease in lung volumes, a loss of D<sub>L</sub>CO, and gas exchange abnormalities during exercise, including decreased arterial oxygen pressure (P<sub>a</sub>O<sub>2</sub>) and increased alveolar-arterial oxygen pressure difference (Lamberto et al., 2004, [193845](#)).

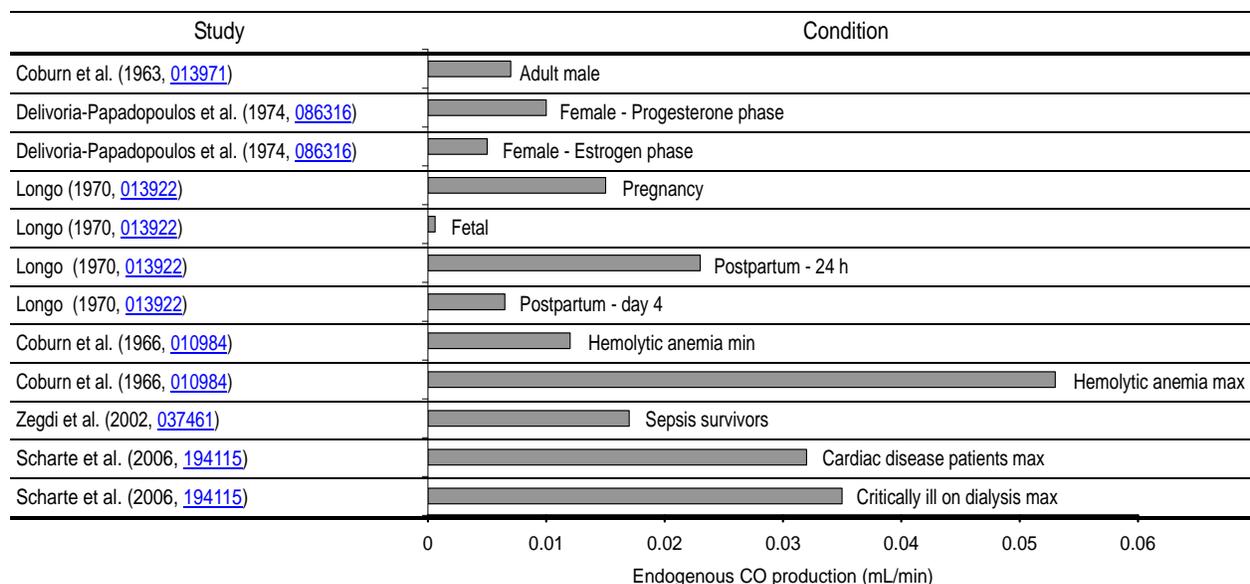
Individuals with heart disease may be at a greater risk from CO exposure since they may already have compromised O<sub>2</sub> delivery. Time to onset of angina was reduced after exposure to

100 ppm CO, compared to clean air (Kleinman et al., 1998, [047186](#)). Hyperlipidemic patients may have decreased CO diffusion capacity, a loss of  $V_A/Q$  gradient, and a decrease in  $P_aO_2$  (Enzi, 1976, [195794](#)) (Section 5.2).

## 4.5. Endogenous CO Production and Metabolism

Humans breathing air containing no environmental sources of CO will still have a low measurable level of circulating COHb due to endogenous CO production from heme protein catabolism. In the normal degradation of RBC Hb, the porphyrin ring of heme is broken at the  $\alpha$ -methene bridge by HO. HO is co-localized with NADPH-flavoprotein reductase and biliverdin reductase on the endoplasmic reticulum, where it catabolizes heme in an  $O_2$  and NADPH-dependent manner to biliverdin, ferrous iron, and CO. Biliverdin is then further broken down by biliverdin reductase into bilirubin, a powerful endogenous antioxidant. HO mediated metabolism functions as the rate-limiting enzyme step in heme degradation and endogenous CO production (Wu and Wang, 2005, [180411](#)). Three isoforms of HO exist, but HO-1 is the only inducible form (Maines and Kappas, 1974, [193976](#); Maines et al., 1986, [193978](#); McCoubrey et al., 1997, [016715](#)). Endogenous CO production can be increased by the up-regulation of HO-1 expression and activity by inducers such as oxidative stress, hypoxia, heavy metals, sodium arsenite, heme and heme derivatives, various cytokines, and also exogenous CO (Wu and Wang, 2005, [180411](#)).

The major site of heme catabolism, and thus the major organ of CO production, is the liver, followed by the spleen, brain, and erythropoietic system (Berk et al., 1976, [012603](#)). These rates of CO formation may be due to higher levels of HO activity in these tissues. The whole body production rate of CO is approximately 18.8  $\mu\text{mol/h}$  (0.42 mL/h or 0.007 mL/min) and produces between 400-500  $\mu\text{mol CO}$  per day (Coburn et al., 1963, [013971](#); Coburn et al., 1964, [013956](#); Coburn et al., 1966, [010984](#)) (Figure 4-10). The endogenous rate of production varied somewhat within individuals measured on multiple days ( $\pm 4.5 \mu\text{mol/h}$  and  $\pm 0.35\%$  COHb) (Coburn et al., 1966, [010984](#)). However, these measurements of day-to-day CO production variability were comparable to the equipment measurement error reported ( $\pm 3.1 \mu\text{mol/h}$ ). The endogenous rate of CO formation varies between different tissues, ranging from 0.029 nmol/mg protein/h in chorionic villi of term human placentas to 0.28 nmol/mg protein/h in cultured rat olfactory receptor neurons and rat liver perfusate (Marks et al., 2002, [030616](#)). However, these estimations are uncertain since CO is quickly scavenged in the cytosol of living cells. CO is endogenously produced in the nose and paranasal sinus which may contribute to exhaled CO concentrations (Andersson et al., 2000, [011836](#)). It is also important to note that increased endogenous CO production does not universally lead to an increase in COHb saturation.



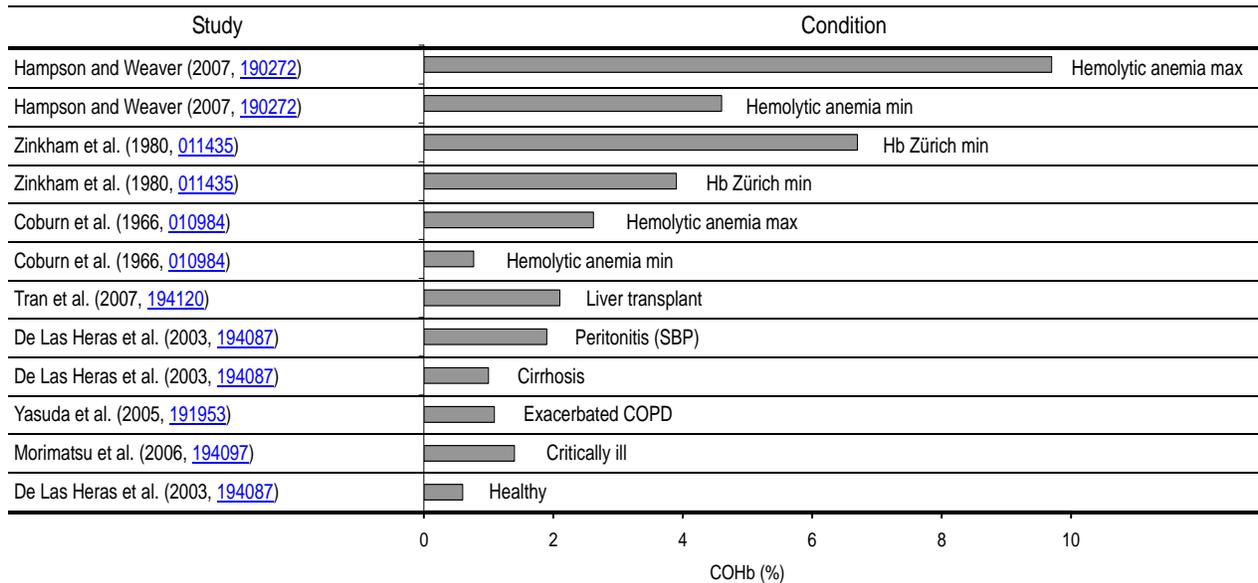
**Figure 4-10. Representative estimates of endogenous CO production rates resulting from various conditions and diseases.**

Not all endogenous CO production is derived from Hb breakdown. Other hemoproteins, such as Mb, cytochromes, peroxidases, and catalase, contribute 20-25% to the total amount of endogenous CO (Berk et al., 1976, [012603](#)). All of these sources result in a normal blood COHb concentration between 0.3 and 1% (Coburn et al., 1965, [011145](#)). The level of endogenous production can be changed by drugs or a number of physiological conditions that alter RBC destruction, other hemoprotein breakdown, or HO-1 expression and activity (Figure 4-10). Nicotinic acid (Lundh et al., 1975, [086332](#)), allyl-containing compounds (acetamids and barbiturates) (Mercke et al., 1975, [086303](#)), diphenylhydantoin (Coburn, 1970, [010625](#)), progesterone (Delivoria-Papadopoulos et al., 1974, [086316](#)), contraceptives (Mercke et al., 1975, [086308](#)), and statins (Muchova et al., 2007, [194098](#)) can increase CO production. Compounds such as carbon disulfide and sulfur-containing chemicals (parathion and phenylthiourea) will increase CO by acting on P450 system moieties (Landaw et al., 1970, [012605](#)). The P450 system may also cause large increases in CO produced from the metabolic degradation of dihalomethanes, leading to very high (>10%) COHb levels (Bos et al., 2006, [194084](#); Manno et al., 1992, [013707](#)) that can be further enhanced by prior exposure to hydrocarbons or ethanol (Pankow et al., 1991, [013551](#); Wirkner et al., 1997, [082642](#)). Minor sources of endogenous CO include auto-oxidation of phenols, flavonoids, and halomethanes, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids (Rodgers et al., 1994, [076440](#)).

Women experience fluctuating COHb levels throughout menstruation when endogenous CO production doubles in the progesterone phase (0.62 mL/h versus 0.32 mL/h in estrogen phase) (Delivoria-Papadopoulos et al., 1974, [086316](#); Mercke and Lundh, 1976, [086309](#)). Similarly, endogenous CO production increases during pregnancy (0.92 mL/h) due to contributions from fetal endogenous CO production (0.036 mL/h) and altered hemoglobin metabolism (Hill et al., 1977, [011315](#); Longo, 1970, [013922](#)).

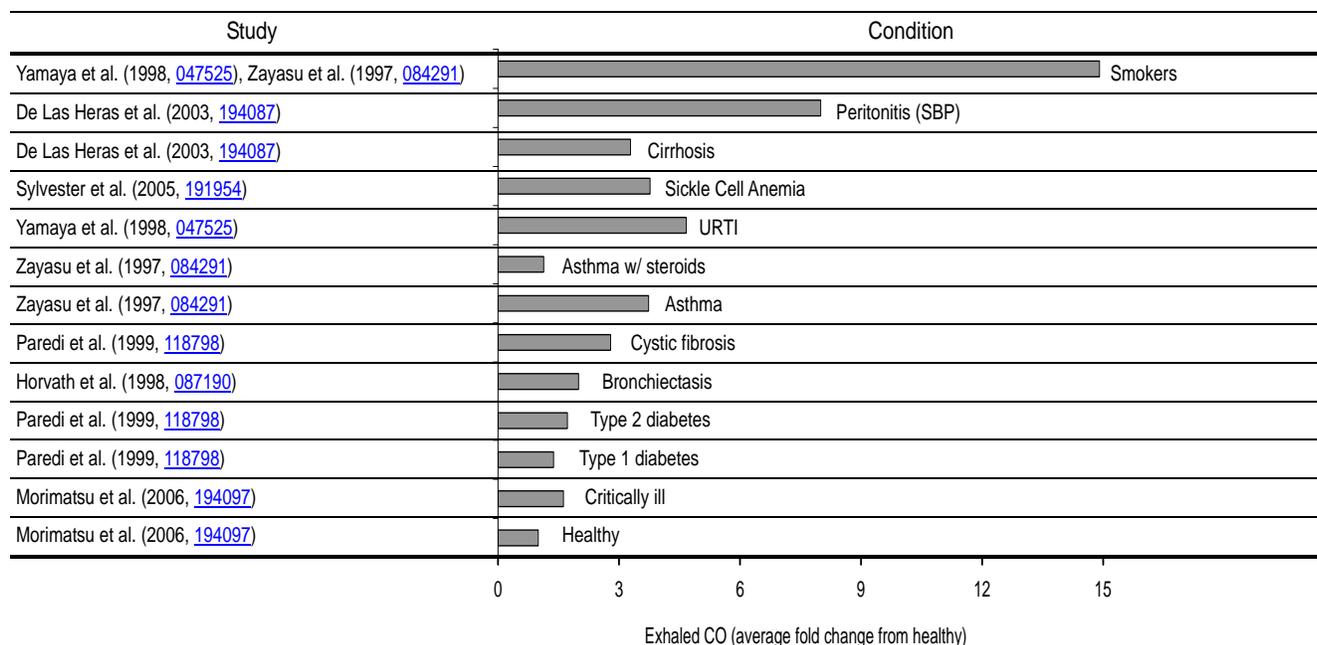
Any disturbance in RBC hemostasis by accelerated destruction of hemoproteins will lead to an increased production of CO (Figure 4-11 and Figure 4-12). Pathologic conditions such as anemias, hematomas, thalassemia, Gilbert's syndrome with hemolysis, and other hematological diseases and illness will accelerate CO production (Berk et al., 1974, [012386](#); Hampson and Weaver, 2007, [190272](#); Meyer et al., 1998, [047530](#); Solanki et al., 1988, [012426](#); Sylvester et al., 2005, [191954](#)). Patients with hemolytic anemia exhibit COHb levels at least two- to threefold higher than healthy individuals and CO production rates two- to eightfold higher (Coburn et al., 1966, [010984](#)). Recent studies report COHb levels measured by CO-oximeter that are elevated to levels between 4.6% and 9.7% due to drug-induced hemolytic anemia (Hampson and Weaver, 2007, [190272](#)) and between 3.9% and 6.7% due to an unstable hemoglobin disorder (Hb Zürich) (Zinkham et al., 1980, [011435](#)).

Endogenous CO production rate varied from 0.70 to 3.18 mL/h in anemic patients (Coburn et al., 1966, [010984](#)).



**Figure 4-11. Representative COHb saturation resulting from various diseases and conditions. Measurements of COHb taken using CO-oximeter, except in Coburn et al. (1966, [010984](#)), where COHb was measured using GC. SBP: Spontaneous bacterial peritonitis**

Critically ill patients exhale more CO and have higher endogenous CO production than healthy controls, likely due to both increased heme turnover as well as upregulation of the expression and activity of HO-1 (Morimatsu et al., 2006, [194097](#); Scharte et al., 2000, [194112](#); Scharte et al., 2006, [194115](#)) (Figure 4-12). CO production weakly correlates with the multiple organ dysfunction score (MODS), which estimates severity of organ dysfunction; however, it did not correlate with the Acute Physiology and Chronic Health Evaluation II score (APACHE II) (Scharte et al., 2006, [194115](#)) or the sequential organ failure assessment score (SOFA) (Morimatsu et al., 2006, [194097](#)). Critically ill patients that survived had a higher exhaled CO (COex) concentration than nonsurvivors (median 3.9 ppm versus 2.4 ppm) (Morimatsu et al., 2006, [194097](#)). Similarly, patients that survived severe sepsis had a higher CO production than those that did not survive ( $14.7 \pm 5.3$  versus  $8.5 \pm 3.3$   $\mu\text{l/kg/h}$ ) (Zegdi et al., 2002, [037461](#)).



**Figure 4-12. Representative exhaled CO concentrations (ppm) resulting from various conditions plotted as fold increases over healthy human controls from each study. SBP: Spontaneous bacterial peritonitis; URTI: Upper respiratory tract infection**

Diseases involving inflammation and infection result in increased endogenous CO production. For example, patients with severe sepsis or septic shock have a higher CO<sub>ex</sub> and endogenous CO production compared to control patients, which was reduced with treatment of the disease (i.e., antibiotics, surgery) (Zegdi et al., 2002, [037461](#)). Similarly, patients with pre-existing cardiac disease, as well as patients with renal failure who undergo dialysis, produced higher amounts of endogenous CO compared to other critically ill patients (Scharte et al., 2006, [194115](#)). High plasma COHb levels measured by CO-oximeter were found in nonsmoking patients evaluated for liver transplantation (mean 2.1%); however, this increase was not correlated with the Model for End Stage Liver Disease (MELD) score or the Child Turcotte Pugh score, used to assess the degree of liver impairment (Tran et al., 2007, [194120](#)). Further investigation in cirrhotic patients, with and without ascites, provided evidence for increased plasma CO concentrations, HO-1 activity in polymorphonuclear cells, exhaled CO, and blood COHb (De las Heras et al., 2003, [194087](#); Tarquini et al., 2009, [194117](#)). CO<sub>ex</sub>, plasma CO, and COHb levels were correlated with the Child-Pugh score, and thus the severity of disease. These parameters were significantly higher in patients with ascites or with spontaneous bacterial peritonitis (SBP) (COHb, healthy: 0.6 ± 0.1%; cirrhosis: 1.0 ± 0.1%; with ascites: 1.6 ± 0.2%; with SBP: 1.9 ± 0.2%; measured by CO-oximeter). Both CO<sub>ex</sub> and COHb levels decreased after resolution of the infection in patients with SBP, reaching values similar to noninfected patients within 1 mo (De las Heras et al., 2003, [194087](#)). Endotoxin concentration was correlated with plasma CO levels, suggesting a link between systemic endotoxemia and increased activity or expression of the HO/CO system (Tarquini et al., 2009, [194117](#)). CO<sub>ex</sub> concentrations are also elevated in patients with diabetes (Type 1: 4.0 ± 0.7 ppm; Type 2: 5.0 ± 0.4 ppm; healthy: 2.9 ± 0.2 ppm), and correlated with blood glucose levels and duration of disease (Paredi et al., 1999, [194102](#)). Likewise, obese Zucker rats, a model of metabolic syndrome with insulin resistance, have increased respiratory CO excretion and COHb levels compared to lean Zucker rats (3.9 ± 0.1% versus 3.0 ± 0.1% COHb), which is decreased by HO inhibition (Johnson et al., 2006, [193874](#)).

Endogenous CO is also increased in airway inflammatory diseases. Patients with upper respiratory tract infections exhaled higher CO concentrations than normal controls and this increase was attenuated after recovery (Yamaya et al., 1998, [047525](#)). Arterial COHb levels have been related

to disease severity in COPD patients (Yasuda et al., 2005, [191953](#)). Bronchiectasis patients had higher COex; however, anti-inflammatory treatment did not decrease the CO levels (Horvath et al., 1998, [087191](#)). Patients with cystic fibrosis had higher COex than normal controls ( $6.7 \pm 0.6$  ppm versus  $2.4 \pm 0.4$  ppm), and patients treated with steroids had a decrease in CO levels ( $8.4 \pm 1.0$  ppm versus  $5.1 \pm 0.5$  ppm) (Paredi et al., 1999, [118798](#)). Increased arterial COHb measured by CO-oximeter was reported in patients with bronchial asthma, pneumonia, idiopathic pulmonary fibrosis, pyelonephritis, and active rheumatoid arthritis (Yasuda et al., 2002, [035206](#); Yasuda et al., 2004, [191955](#)). Similarly, asthmatic patients exhibited an elevation of COex that decreased with corticosteroid therapy (nonsmoking controls:  $1.5 \pm 0.1$  ppm; asthmatics without corticosteroids:  $5.6 \pm 0.6$  ppm; with corticosteroids:  $1.7 \pm 0.1$  ppm; smoking controls:  $21.6 \pm 2.8$  ppm) (Zayasu et al., 1997, [084291](#)). These results were confirmed and associated with increased expression of HO-1 in airway macrophages (Horvath et al., 1998, [087190](#)). Also, COex was increased in patients with allergic rhinitis during the pollen season; however, their COex was similar to control subject levels out of season (Monma et al., 1999, [180426](#)). Similarly, endogenous CO production and HO-1 expression in nasal mucosa was correlated with allergic rhinitis in guinea pigs as described in Section 5.1 (Shaoqing et al., 2008, [192384](#)).

Altitude is also positively associated with baseline COHb concentrations (McGrath, 1992, [001005](#)) (McGrath et al., 1993, [013865](#)). This increase in COHb with altitude-induced hypoxia is associated in rats and cells with increases in the mRNA, protein, and activity of HO-1 leading to enhanced endogenous CO production (Carraway et al., 2002, [026018](#); Lee et al., 1997, [082641](#)). Whether other variables such as an accelerated metabolism or a greater pool of Hb, transient shifts in body stores, or a change in the elimination rate of CO, play a role has not been explored.

Because of the sensitivity of COHb to changes in the metabolic state, ranges of endogenous COHb levels in the population are uncertain. However, baseline levels of COHb, which reflect exposure to ambient and non-ambient CO and endogenous production of CO, have been measured in the population. COHb levels measured by CO-oximeter in packed red blood cell units reserved for use between 2004 and 2005 averaged  $0.78 \pm 1.48\%$ , with 10.3% of samples having COHb levels of 1.5% or greater and a maximum measurement of 12% (Ehlers et al., 2009, [194089](#)). This study reported a decrease from a study conducted in 1982-1983 in the number of units with elevated COHb; at that time, 49% of units had COHb levels  $>1.5\%$  (Aronow et al., 1984, [194083](#)) versus 10.3% in 2004-2005. Another study calculated that 23% of donated blood units had COHb levels exceeding 1.5%, with the highest measurement being 7.2% (Aberg et al., 2009, [194082](#)). Smoking is the main factor causing increased blood concentrations of CO. A dose-response relationship was shown to exist between COHb concentration and the number of cigarettes smoked a day (nonsmoker:  $1.59 \pm 1.72\%$ ; 1-5 cig/day:  $2.31 \pm 1.94\%$ ; 6-14 cig/day:  $4.39 \pm 2.48\%$ ; 15-24 cig/day:  $5.68 \pm 2.64\%$ ;  $\geq 25$  cig/day:  $6.02 \pm 2.86\%$  COHb). The mean baseline COHb value for former smokers was higher than that of never smokers in this prospective cohort study ( $1.96 \pm 1.87$  versus  $1.59 \pm 1.72\%$ ) (Hart et al., 2006, [194092](#)).

Endogenous CO is removed from the body mainly by expiration and oxidation. CO diffuses across the alveolar-capillary membrane and is exhaled. This event has been used as a noninvasive measurement of both endogenous and body load CO (Stevenson et al., 1979, [193767](#)). CO can also be oxidized to CO<sub>2</sub> by cytochrome *c* oxidase in the mitochondria (Fenn, 1970, [010821](#); Young and Caughey, 1986, [012091](#)). However, the rates of CO metabolism are much slower than the rates of endogenous CO production, with the rate of consumption representing only 10% of the rate of CO production in dogs (Luomanmäki and Coburn, 1969, [012319](#)).

## 4.6. Summary and Conclusions

CO elicits various health effects by binding with and altering the function of a number of heme-containing molecules, mainly Hb. The formation of COHb reduces the O<sub>2</sub>-carrying capacity of blood and impairs the release of O<sub>2</sub> from O<sub>2</sub>Hb to the tissues. Venous COHb levels have been modeled mainly by the CFK equation, but more recent models have included venous and arterial blood mixing and Mb and extravascular storage compartments, as well as other dynamics of CO physiology. The CFK equation remains the most extensively validated and applied model for COHb prediction. Recent models have indicated that CO has a biphasic elimination curve, due to initial washout from the blood followed by a slower flux from the tissues. The flow of CO between the

blood and alveolar air or tissues is controlled by diffusion down the pCO gradient. The uptake of CO is governed not only by this CO pressure differential, but also by physiological factors, such as minute ventilation and lung diffusing capacity, that can, in turn, be affected by conditions such as exercise, age, and health. Susceptible populations, including health compromised individuals and developing fetuses, are at a greater risk from COHb induced health effects due to altered CO kinetics, compromised cardiopulmonary function, and increased baseline hypoxia levels. Altitude may also significantly affect the kinetics of COHb formation. Compensatory mechanisms, such as increased cardiac output, compensate for the decrease in barometric pressure. Altitude also increases the endogenous production of CO through upregulation of HO-1. CO is considered a second messenger and is endogenously produced from the catabolism of heme proteins by enzymes such as HO-1. A number of diseases and conditions affect endogenous CO production, possibly causing a higher endogenous COHb level. Finally, CO is removed from the body by expiration or oxidation to CO<sub>2</sub>.

# References

- Aberg AM; Sojka BN; Winsö O; Abrahamsson P; Johansson G; Larsson JE (2009). Carbon monoxide concentration in donated blood: Relation to cigarette smoking and other sources. *Transfusion*, 49: 347-353. [194082](#)
- Abi-Esber L; El-Fadel M (2008). In-vehicle CO ingestion: Validation through field measurements and mass balance simulations. *Sci Total Environ*, 394: 75-89. [190939](#)
- Abram SR; Hodnett BL; Summers RL; Coleman TG; Hester RL (2007). Quantitative circulatory physiology: An integrative mathematical model of human physiology for medical education. *Adv Physiol Educ*, 31: 202-210. [193859](#)
- Akland GG; Hartwell TD; Johnson TR; Whitmore RW (1985). Measuring human exposure to carbon monoxide in Washington, DC, and Denver, Colorado, during the winter of 1982-1983. *Environ Sci Technol*, 19: 911-918. [011618](#)
- Alcantara RE; Xu C; Spiro TG; Guallar V (2007). A quantum-chemical picture of hemoglobin affinity. *PNAS*, 104: 18451-18455. [193867](#)
- Andersson JA; Uddman R; Cardell L-O (2000). Carbon monoxide is endogenously produced in the human nose and paranasal sinuses. *J Allergy Clin Immunol*, 105: 269-273. [011836](#)
- Aronow WS; O'Donohue WJ Jr; Freygang J; Sketch MH (1984). Carboxyhemoglobin levels in banked blood. *Chest*, 85: 694-695. [194083](#)
- Arora M; Chandra J; Suri JC; Narayan S; Dutta AK (2001). Pulmonary function tests in beta thalassemia. *Indian J Pediatr*, 68: 239-242. [186713](#)
- Benignus VA; Coleman T; Eklund CR; Kenyon EM (2006). A general physiological and toxicokinetic (GPAT) model for simulating complex toluene exposure scenarios in humans. *Toxicol Mech Meth*, 16: 27-36. [151344](#)
- Benignus VA; Hazucha MJ; Smith MV; Bromberg PA (1994). Prediction of carboxyhemoglobin formation due to transient exposure to carbon monoxide. *J Appl Physiol*, 76: 1739-1745. [013908](#)
- Berk PD; Blaschke TF; Schar Schmidt BF; Waggoner JG; Berlin NI (1976). A new approach to quantitation of the various sources of bilirubin in man. *J Lab Clin Med*, 87: 767-780. [012603](#)
- Berk PD; Rodkey FL; Blaschke TF; Collison HA; Waggoner JG (1974). Comparison of plasma bilirubin turnover and carbon monoxide production in man. *J Lab Clin Med*, 83: 29-37. [012386](#)
- Bos PM; Zeilmaier MJ; van Eijkeren JC (2006). Application of physiologically based pharmacokinetic modeling in setting acute exposure guideline levels for methylene chloride. *Toxicol Sci*, 91: 576-585. [194084](#)
- Bruce EN; Bruce MC (2003). A multicompartment model of carboxyhemoglobin and carboxymyoglobin responses to inhalation of carbon monoxide. *J Appl Physiol*, 95: 1235-1247. [193975](#)
- Bruce EN; Bruce MC; Erupaka K (2008). Prediction of the rate of uptake of carbon monoxide from blood by extravascular tissues. *Respir Physiol Neurobiol*, 161: 142-159. [193977](#)
- Bruce MC; Bruce EN (2006). Analysis of factors that influence rates of carbon monoxide uptake, distribution, and washout from blood and extravascular tissues using a multicompartment model. *J Appl Physiol*, 100: 1171-1180. [193980](#)
- Carraway MS; Ghio AJ; Carter JD; Piantadosi CA (2000). Expression of heme oxygenase-1 in the lung in chronic hypoxia. *Am J Physiol*, 278: L806-L812. [021096](#)
- Carraway MS; Ghio AJ; Suliman HB; Carter JD; Whorton AR; Piantadosi CA (2002). Carbon monoxide promotes hypoxic pulmonary vascular remodeling. *Am J Physiol*, 282: L693-L702. [026018](#)
- Castillo A; Llapur CJ; Martinez T; Kisling J; Williams-Nkomo T; Coates C; Tepper RS (2006). Measurement of single breath-hold carbon monoxide diffusing capacity in healthy infants and toddlers. *Pediatr Pulmonol*, 41: 544-550. [193234](#)

---

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS)

- Cavallin-Ståhl E; Mercke C; Lundh B (1976). Carbon monoxide production in patients with breast carcinoma. *Br J Haematol*, 32: 177-182. [086306](#)
- Cavallin-Ståhl E; Mercke C; Lundh B (1976). Erythropoiesis and carbon monoxide production in Hodgkin's disease. *Br J Haematol*, 32: 167-175. [193239](#)
- Cerny FC; Dempsey JA; Reddan WG (1973). Pulmonary gas exchange in nonnative residents of high altitude. *J Clin Invest*, 52: 2993-2999. [199736](#)
- Chace DH; Goldbaum LR; Lappas NT (1986). Factors affecting the loss of carbon monoxide from stored blood samples. *J Anal Toxicol*, 10: 181-189. [012020](#)
- Chakraborty S; Balakotaiah V; Bidani A (2004). Diffusing capacity reexamined: relative roles of diffusion and chemical reaction in red cell uptake of O<sub>2</sub>, CO, CO<sub>2</sub>, and NO. *J Appl Physiol*, 97: 2284-2302. [193759](#)
- Chung SJ (1988). Formulas predicting carboxyhemoglobin resulting from carbon monoxide exposure. *Vet Hum Toxicol*, 30: 528-532. [012749](#)
- Coburn RF (1967). Endogenous carbon monoxide production and body CO stores. *Acta Med Scand Suppl*, 472: 269-282. [011144](#)
- Coburn RF (1970). Enhancement by phenobarbital and diphenylhydantoin of carbon monoxide production in normal man. *N Engl J Med*, 283: 512-515. [010625](#)
- Coburn RF (1970). The carbon monoxide body stores. *Ann N Y Acad Sci*, 174: 11-22. [013916](#)
- Coburn RF; Blakemore WS; Forster RE (1963). Endogenous carbon monoxide production in man. *J Clin Invest*, 42: 1172-1178. [013971](#)
- Coburn RF; Forster RE; Kane PB (1965). Considerations of the physiological variables that determine the blood carboxyhemoglobin concentration in man. *J Clin Invest*, 44: 1899-1910. [011145](#)
- Coburn RF; Williams WJ; Forster RE (1964). Effect of erythrocyte destruction on carbon monoxide production in man. *J Clin Invest*, 43: 1098-1103. [013956](#)
- Coburn RF; Williams WJ; Kahn SB (1966). Endogenous carbon monoxide production in patients with hemolytic anemia. *J Clin Invest*, 45: 460-468. [010984](#)
- Cronenberger C; Mould DR; Roethig HJ; Sarkar M (2008). Population pharmacokinetic analysis of carboxyhaemoglobin concentrations in adult cigarette smokers. *Br J Clin Pharmacol*, 65: 30-39. [194085](#)
- DeGraff AC Jr; Grover RF; Johnson RL Jr; Hammond JW Jr; Miller JM (1970). Diffusing capacity of the lung in Caucasians native to 3,100 m. *J Appl Physiol*, 29: 71-76. [199737](#)
- Delivoria-Papadopoulos M; Coburn RF; Forster RE (1974). Cyclic variation of rate of carbon monoxide production in normal women. *J Appl Physiol*, 36: 49-51. [086316](#)
- De las Heras D; Fernández J; Ginès P; Cárdenas A; Ortega R; Navasa M; Barberá JA; Calahorra B; Guevara M; Bataller R; Jiménez W; Arroyo V; Rodés J (2003). Increased carbon monoxide production in patients with cirrhosis with and without spontaneous bacterial peritonitis. *Hepatology*, 38: 452-459. [194087](#)
- Di Cera E; Doyle ML; Morgan MS; De Cristofaro R; Landolfi R; Bizzi B; Castagnola M; Gill SJ (1989). Carbon monoxide and oxygen binding to human hemoglobin F0. *Biochemistry*, 28: 2631-2638. [193998](#)
- Douglas CG; Haldane JS; Haldane JBS (1912). The laws of combination of haemoglobin with carbon monoxide and oxygen. *J Physiol*, 44: 275-304. [013965](#)
- Duci A; Chaloulakou A; Spyrellis N (2003). Exposure to carbon monoxide in the Athens urban area during commuting. *Sci Total Environ*, 309: 47-58. [044199](#)
- Ehlers M; Labaze G; Hanakova M; McCloskey D; Wilner G (2009). Alarming levels of carboxyhemoglobin in banked blood. *J Cardiothorac Vasc Anesth*, 23: 336-338. [194089](#)
- Engel LA; Wood LDH; Utz G; Macklem PT (1973). Gas mixing during inspiration. *J Appl Physiol*, 35: 18-24. [014336](#)
- Engel RR; Rodkey FL; O'Neal JD; Collison HA (1969). Relative affinity of human fetal hemoglobin for carbon monoxide and oxygen. *Blood*, 33: 37-45. [193914](#)

- Enzi G, Bevilacqua M, Crepaldi G (1976). Disturbances in pulmonary gaseous exchange in primary hyperlipoproteinemias. *Bull Europ Physiol Resp*, 12: 433-442. [195794](#)
- Fenn WO (1970). The burning of CO in tissues. *Ann N Y Acad Sci*, 174: 64-71. [010821](#)
- Forbes WH; Sargent F; Roughton FJW (1945). The rate of carbon monoxide uptake by normal men. *Am J Physiol*, 143: 594-608. [012850](#)
- Forster RE (1966). Diffusion of gases in the lungs. *Physiologist*, 9: 110-122. [180430](#)
- Gibson QH; Olson JS; McKinnie RE; Rohlf's RJ (1986). A kinetic description of ligand binding to sperm whale myoglobin. *J Biol Chem*, 261: 10228-10239. [016289](#)
- Gibson QH; Roughton FJ (1955). The kinetics of dissociation of the first oxygen molecule from fully saturated oxyhaemoglobin in sheep blood solutions. *Proc Biol Sci*, 912: 143. [193941](#)
- Gosselin NH; Brunet RC; Carrier G (2009). Determination of carboxyhaemoglobin in humans following low-level exposures to carbon monoxide. *Inhal Toxicol*, 21: 1077-1091. [190946](#)
- Guleria JS; Pande JN; Sethi PK; Roy SB (1971). Pulmonary diffusing capacity at high altitude. *J Appl Physiol*, 31: 536-543. [199518](#)
- Guyatt AR; Holmes MA; Cumming G (1981). Can carbon monoxide be absorbed from the upper respiratory tract in man? *Eur Respir J*, 62: 383-390. [011196](#)
- Haab P (1990). The effect of carbon monoxide on respiration. *Experientia*, 46: 1202-1206. [013359](#)
- Haldane J (1895). The action of carbonic oxide on man. *J Physiol*, 18: 430-462. [010538](#)
- Hampson NB; Weaver LK (2007). Carbon monoxide poisoning: a new incidence for an old disease. *Undersea Hyperb Med*, 34: 163-168. [190272](#)
- Hanel B; Teunissen I; Rabol A; Warberg J; Secher NH (1997). Restricted postexercise pulmonary diffusion capacity and central blood volume depletion. *J Appl Physiol*, 83: 11-17. [193918](#)
- Hart CL; Smith GD; Hole DJ; Hawthorne VM (2006). Carboxyhaemoglobin concentration, smoking habit, and mortality in 25 years in the Renfrew/Paisley prospective cohort study. *Heart*, 92: 321-324. [194092](#)
- Hayde M; Pollak A; Bernaschek G; Weiner CP; Vreman HJ; Stevenson DK; Widness JA (2000). Association of fetal and maternal carboxyhemoglobin levels in normal and Rh-alloimmune pregnancies. *Early Hum Dev*, 58: 205-212. [201602](#)
- Hegewald MJ; Crapo RO (2007). Socioeconomic status and lung function. *Chest*, 132: 1608-1614. [193923](#)
- Hill EP; Hill JR; Power GG; Longo LD (1977). Carbon monoxide exchanges between the human fetus and mother: A mathematical model. *Am J Physiol*, 232: H311-H323. [011315](#)
- Holland RA (1970). Reaction rates of carbon monoxide and hemoglobin. *Ann N Y Acad Sci*, 174: 154-171. [193856](#)
- Horvath I; Donnelly LE; Kiss A; Paredi P; Kharitonov SA; Barnes PJ (1998). Raised levels of exhaled carbon monoxide are associated with an increased expression of heme oxygenase-1 in airway macrophages in asthma: a new marker of oxidative stress. *Thorax*, 53: 668-672. [087190](#)
- Horvath I; Loukides S; Wodehouse T; Kharitonov SA; Cole PJ; Barnes PJ (1998). Increased levels of exhaled carbon monoxide in bronchiectasis: a new marker of oxidative stress. *Thorax*, 53: 867-870. [087191](#)
- Horvath SM; Bedi JF; Wagner JA; Agnew JW (1988). Maximal aerobic capacity at several ambient concentrations of carbon monoxide at several altitudes. *J Appl Physiol*, 65: 2696-2708. [012725](#)
- Hsia CC (2002). Recruitment of lung diffusing capacity: Update of concept and application. *Chest*, 122: 1774-1783. [193857](#)
- Jarvis MJ; Belcher M; Vesey C; Hutchison DCS (1986). Low cost carbon monoxide monitors in smoking assessment. *Thorax*, 41: 886-887. [012043](#)
- Jarvis MJ; Russell MAH; Saloojee Y (1980). Expired air carbon monoxide: a simple breath test of tobacco smoke intake. *Br Med J*, 281: 484-485. [011813](#)

- Johnson FK; Johnson RA; Durante W; Jackson KE; Stevenson BK; Peyton KJ (2006). Metabolic syndrome increases endogenous carbon monoxide production to promote hypertension and endothelial dysfunction in obese Zucker rats. *Am J Physiol Regul Integr Comp Physiol*, 290: 601-608. [193874](#)
- Joumard R; Chiron M; Vidon R; Maurin M; Rouzioux J-M (1981). Mathematical models of the uptake of carbon monoxide on hemoglobin at low carbon monoxide levels. *Environ Health Perspect*, 41: 277-289. [011330](#)
- Kinker JR; Haffor A-S; Stephan M; Clanton TL (1992). Kinetics of CO uptake and diffusing capacity in transition from rest to steady-state exercise. *J Appl Physiol*, 72: 1764-1772. [086328](#)
- Klasner AE; Smith SR; Thompson MW; Scalzo AJ (1998). Carbon monoxide mass exposure in a pediatric population. *Acad Emerg Med*, 5: 992-996. [087196](#)
- Kleinman MT; Leaf DA; Kelly E; Caiozzo V; Osann K; O'Niell T (1998). Urban angina in the mountains: effects of carbon monoxide and mild hypoxemia on subjects with chronic stable angina. *Arch Environ Occup Health*, 53: 388-397. [047186](#)
- Klimisch HJ; Chevalier HJ; Harke HP; Dontenwill W (1975). Uptake of carbon monoxide in blood of miniature pigs and other mammals. *Toxicology*, 3: 301-310. [010762](#)
- Lamberto C; Nunes H; Le Toumelin P; Duperron F; Valeyre D; Clerici C (2004). Membrane and capillary blood components of diffusion capacity of the lung for carbon monoxide in pulmonary sarcoidosis: relation to exercise gas exchange. *Chest*, 125: 2061-2068. [193845](#)
- Landaw SA (1973). The effects of cigarette smoking on total body burden and excretion rates of carbon monoxide. *J Occup Environ Med*, 15: 231-235. [010803](#)
- Landaw SA; Callahan EW Jr; Schmid R (1970). Catabolism of heme in vivo: comparison of the simultaneous production of bilirubin and carbon monoxide. *J Clin Invest*, 49: 914-925. [012605](#)
- Lee PJ; Jiang B-H; Chin BY; Iyer NV; Alam J; Semenza GL; Choi AMK (1997). Hypoxia-inducible factor-1 mediates transcriptional activation of the heme oxygenase-1 gene in response to hypoxia. *J Biol Chem*, 272: 5375-5381. [082641](#)
- Levasseur L; Galliot-Guilley M; Richter F; Scherrmann JM; Baud FJ (1996). Effects of mode of inhalation of carbon monoxide and of normobaric oxygen administration on carbon monoxide elimination from the blood. *Hum Exp Toxicol*, 15: 898-903. [080895](#)
- Longo LD (1970). Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. *Ann N Y Acad Sci*, 174: 313-341. [013922](#)
- Longo LD (1977). The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. *Am J Obstet Gynecol*, 129: 69-103. [012599](#)
- Longo LD; Hill EP (1977). Carbon monoxide uptake and elimination in fetal and maternal sheep. *Am J Physiol*, 232: H324-H330. [010802](#)
- Lundh B; Cavallin-Ståhl E; Mercke C (1975). Nicotinic acid and the endogenous production of carbon monoxide. *J Intern Med*, 197: 173-176. [086332](#)
- Luomanmäki K; Coburn RF (1969). Effects of metabolism and distribution of carbon monoxide on blood and body stores. *Am J Physiol*, 217: 354-363. [012319](#)
- Mahoney JJ; Vreman HJ; Stevenson DK; Van Kessel AL (1993). Measurement of carboxyhemoglobin and total hemoglobin by five specialized spectrophotometers (CO-oximeters) in comparison with reference methods. *Clin Chem*, 39: 1693-1700. [013859](#)
- Maines MD; Kappas A (1974). Cobalt induction of hepatic heme oxygenase; with evidence that cytochrome P-450 is not essential for this enzyme activity. *PNAS*, 71: 4293-4297. [193976](#)
- Maines MD; Trakshel GM; Kutty RK (1986). Characterization of two constitutive forms of rat liver microsomal heme oxygenase. Only one molecular species of the enzyme is inducible. *J Biol Chem*, 261: 411-419. [193978](#)
- Manier G; Moinard J; Techoueyres P; Varene N; Guenard H (1991). Pulmonary diffusion limitation after prolonged strenuous exercise. *Respir Physiol*, 83: 143-153. [193979](#)
- Manno M; Rügge M; Cocheo V (1992). Double fatal inhalation of dichloromethane. *Hum Exp Toxicol*, 11: 540-545. [013707](#)

- Marks GS; Vreman HJ; McLaughlin BE; Brien JF; Nakatsu K (2002). Measurement of endogenous carbon monoxide formation in biological systems. *Antioxid Redox Signal*, 4: 271-277. [030616](#)
- Marthan R; Castaing Y; Manier G; Guenard H (1985). Gas exchange alterations in patients with chronic obstructive lung disease. *Chest*, 87: 470-475. [086334](#)
- Marvisi M; Bassi E; Bonassi R; Civardi G; Delsignore R (2007). DLCO correlates with intestinal inflammation in ulcerative colitis, but albuminuria does not. *Minerva Gastroenterol Dietol*, 53: 321-7. [186702](#)
- Marvisi M; Borrello PD; Brianti M; Fornarsari G; Marani G; Guariglia A (2000). Changes in the carbon monoxide diffusing capacity of the lung in ulcerative colitis. *Eur Respir J*, 16: 965-8. [186703](#)
- McCartney ML (1990). Sensitivity analysis applied to Coburn-Forster-Kane models of carboxyhemoglobin formation. *AIHA J*, 51: 169-177. [013162](#)
- McClellan PA; Duguid NJ; Griffin PM; Newth CJL; Zamel N (1981). Changes in exhaled pulmonary diffusing capacity at rest and exercise in individuals with impaired positional diffusion. *Eur Respir J*, 17: 179-186. [012411](#)
- McCoubrey WK Jr; Huang TJ; Maines MD (1997). Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase-3. *FEBS J*, 247: 725-732. [016715](#)
- McGrath JJ (1992). Effects of altitude on endogenous carboxyhemoglobin levels. *J Toxicol Environ Health*, 35: 127-133. [001005](#)
- McGrath JJ; Schreck RM; Lee PS (1993). Carboxyhemoglobin levels in humans: Effects of altitude. *Inhal Toxicol*, 5: 241-249. [013865](#)
- Mercke C; Cavallin-Ståhl E; Lundh B (1975). Carbon monoxide production and reticulocyte count in normal women: effect of contraceptive drugs and smoking. *Acta Med Scand*, 198: 155-160. [086308](#)
- Mercke C; Cavallin-Stahl E; Lundh B (1975). Heme catabolism during short-term treatment with phenobarbital, diazepam and oxazepam. *Acta Med Scand*, 198: 149-154. [086303](#)
- Mercke C; Lundh B (1976). Erythrocyte filterability and heme catabolism during the menstrual cycle. *Ann Intern Med*, 85: 322-324. [086309](#)
- Meyer J; Prien T; Van Aken H; Bone H-G; Waurick R; Theilmeyer G; Booke M (1998). Arterio-venous carboxyhemoglobin difference suggests carbon monoxide production by human lungs. *Biochem Biophys Res Commun*, 244: 230-232. [047530](#)
- Monma M; Yamaya M; Sekizawa K; Ikeda K; Suzuki N; Kikuchi T; Takasaka T; Sasaki H (1999). Increased carbon monoxide in exhaled air of patients with seasonal allergic rhinitis. *Clin Exp Allergy*, 29: 1537-1541. [180426](#)
- Morimatsu H; Takahashi T; Maeshima K; Inoue K; Kawakami T; Shimizu H; Takeuchi M; Yokoyama M; Katayama H; Morita K (2006). Increased heme catabolism in critically ill patients: Correlation among exhaled carbon monoxide, arterial carboxyhemoglobin, and serum bilirubin IXalpha concentrations. *Am J Physiol Lung Cell Mol Physiol*, 290: L114-L119. [194097](#)
- Muchova L; Wong RJ; Hsu M; Morioka I; Vitek L; Zelenka J; Schröder H; Stevenson DK (2007). Statin treatment increases formation of carbon monoxide and bilirubin in mice: A novel mechanism of in vivo antioxidant protection. *Can J Physiol Pharmacol*, 85: 800-810. [194098](#)
- NCHS; Radford EP; Drizd TA (1982). Blood carbon monoxide levels in persons 3-74 years of age: United States, 1976-80; Advance Data from Vital and Health Statistics, No 76. National Center for Health Statistics; Office of Health Research, Statistics, and Technology; Public Health Service; U.S. Department of Health and Human Services. Hyattsville, MD. DHHS Pub. No. (PHS) 82-1250. [011442](#)
- Neas LM; Schwartz J (1996). The determinants of pulmonary diffusing capacity in a national sample of US adults. *Am J Respir Crit Care Med*, 153: 656-664. [079363](#)
- Neto CA; Yanagihara JI; Turri F (2008). A carbon monoxide transport model of the human respiratory system applied to urban atmosphere exposure analysis. *J Braz Soc Mech Sci & Eng*, 30: 253-260. [194672](#)
- Ocak A; Valentour JC; Blanke RV (1985). The effects of storage conditions on the stability of carbon monoxide in postmortem blood. *J Anal Toxicol*, 9: 202-206. [011641](#)
- Ott WR; Mage DT (1978). Interpreting urban carbon monoxide concentrations by means of a computerized blood COHb model. *J Air Waste Manag Assoc*, 28: 911-916. [011124](#)

- Pankow D; Matschiner F; Weigmann H-J (1991). Influence of aromatic hydrocarbons on the metabolism of dichloromethane to carbon monoxide in rats. *Toxicology*, 68: 89-100. [013551](#)
- Paredi P; Biernacki W; Invernizzi G; Kharitonov SA; Barnes PJ (1999). Exhaled carbon monoxide levels elevated in diabetes and correlated with glucose concentration in blood: A new test for monitoring the disease? *Chest*, 116: 1007-1011. [194102](#)
- Paredi P; Shah PL; Montuschi P; Sullivan P; Hodson ME; Kharitonov SA; Barnes PJ (1999). Increased carbon monoxide in exhaled air of patients with cystic fibrosis. *Thorax*, 54: 917-20. [118798](#)
- Penney DG (1988). A review: Hemodynamic response to carbon monoxide. *Environ Health Perspect*, 77: 121-130. [012519](#)
- Pesola GR; Huggins G; Sherpa TY (2006). Abnormal predicted diffusion capacities in healthy Asians: an inequality with a solution. *Respiration*, 73: 799-807. [193855](#)
- Pesola GR; Sunmonu Y; Huggins G; Ford JG (2004). Measured diffusion capacity versus prediction equation estimates in blacks without lung disease. *Respiration*, 71: 484-492. [193842](#)
- Peterson JE; Stewart RD (1970). Absorption and elimination of carbon monoxide by inactive young men. *Arch Environ Occup Health*, 21: 165-171. [012416](#)
- Peterson JE; Stewart RD (1975). Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. *J Appl Physiol*, 39: 633-638. [010696](#)
- Prommer N; Schmidt (2007). Loss of CO from the intravascular bed and its impact on the optimised CO-rebreathing method. *Eur J Appl Physiol*, 100: 383-391. [180421](#)
- Proudman SM; Stevens WM; Sahhar J; Celmajer D (2007). Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. *J Intern Med*, 37: 485-94. [186705](#)
- Reeves RB; Park HK (1992). CO uptake kinetics of red cells and CO diffusing capacity. *Respir Physiol*, 88: 1-21. [193847](#)
- Richardson RS; Noyszewski EA; Saltin B; Gonzalez-Alonso J (2002). Effect of mild carboxy-hemoglobin on exercising skeletal muscle: Intravascular and intracellular evidence. *Am J Physiol*, 283: R1131-R1139. [037513](#)
- Riediker M; Williams R; Devlin R; Griggs T; Bromberg P (2003). Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars. *Environ Sci Technol*, 37: 2084-2093. [043761](#)
- Rodes C; Sheldon L; Whitaker D; Clayton A; Fitzgerald K; Flanagan J; DiGenova F; Hering S; Frazier C (1998). Measuring concentrations of selected air pollutants inside California vehicles [final report]. California Environmental Protection Agency, Air Resources Board; South Coast Air Quality Management District. Sacramento, CA. <http://www.arb.ca.gov/research/abstracts/95-339.htm>. [010611](#)
- Rodgers PA; Vreman HJ; Dennery PA; Stevenson DK (1994). Sources of carbon monoxide (CO) in biological systems and applications of CO detection technologies. *Semin Perinatol*, 18: 2-10. [076440](#)
- Rodkey FL; O'Neal JD; Collison HA (1969). Oxygen and carbon monoxide equilibria of human adult hemoglobin at atmospheric and elevated pressure. *Blood*, 33: 57-65. [008151](#)
- Roughton FJ; Forster RE (1957). Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. *J Appl Physiol*, 11: 290-302. [193862](#)
- Roughton FJW (1970). The equilibrium of carbon monoxide with human hemoglobin in whole blood. *Ann N Y Acad Sci*, 174: 177-188. [013931](#)
- Roughton FJW; Root WS (1945). The fate of CO in the body during recovery from mild carbon monoxide poisoning in man. *Am J Physiol*, 145: 239-252. [180418](#)
- Sakamaki F; Oya H; Nagaya N; Kyotani S; Satoh T; Nakanishi N (2002). Higher prevalence of obstructive airway disease in patients with thoracic or abdominal aortic aneurysm. *J Vasc Surg*, 36: 35-40. [186706](#)
- Schachter LM; Dixon J; Pierce RJ; O'Brien P (2003). Severe gastroesophageal reflux is associated with reduced carbon monoxide diffusing capacity. *Chest*, 123: 1932-8. [186707](#)
- Scharte M; Bone HG; Van Aken H; Meyer J (2000). Increased carbon monoxide in exhaled air of critically ill patients. *Biochem Biophys Res Commun*, 267: 423-426. [194112](#)

- Scharte M; von Ostrowski TA; Daudel F; Freise H; Van Aken H; Bone HG (2006). Endogenous carbon monoxide production correlates weakly with severity of acute illness. *Eur J Anaesthesiol*, 23: 117-122. [194115](#)
- Schoenfisch WH; Hoop KA; Struelens BS (1980). Carbon monoxide absorption through the oral and nasal mucosae of cynomolgus monkeys. *Arch Environ Health*, 35: 152-154. [011404](#)
- Selvakumar S; Sharan M; Singh MP (1992). Mathematical model for the exchange of gases in the lungs with special reference to carbon monoxide. *Med Biol Eng Comput*, 30: 525-532. [013750](#)
- Shaoqing Y; Ruxin Z; Yinjian C; Jianqiu C; Chunsheng Z; Jiangfeng T; Genhong L (2008). Possible contribution of endogenous carbon monoxide to the development of allergic rhinitis in guinea pigs. *J Inflamm*, 5: 23. [192384](#)
- Sharan M; Selvakumar S (1999). A mathematical model for the simultaneous transport of gases to compute blood carboxyhaemoglobin build-up due to CO exposures: application to the end-expired breath technique. *Environ Pollut*, 105: 231-242. [194673](#)
- Sharan M; Selvakumar S; Singh MP (1990). Mathematical model for the computation of alveolar partial pressure of carbon monoxide. *Int J Bio Med Comput*, 26: 135-147. [003798](#)
- Sharma VS; Schmidt MR; Ranney HM (1976). Dissociation of CO from carboxyhemoglobin. *J Biol Chem*, 251: 4267-4272. [193766](#)
- Shimazu T (2001). Half-life of blood carboxyhemoglobin. *Chest*, 119: 661-663. [016331](#)
- Shimazu T; Ikeuchi H; Sugimoto H; Goodwin CW; Mason AD Jr; Pruitt BA Jr (2000). Half-life of blood carboxyhemoglobin after short-term and long-term exposure to carbon monoxide. *J Trauma*, 49: 126-131. [016420](#)
- Singh MP; Sharan M; Selvakumar S (1991). A mathematical model for the computation of carboxyhaemoglobin in human blood as a function of exposure time. *Proc Biol Sci*, 334: 135-147. [013583](#)
- Smith MV (1990). Comparing solutions to the linear and nonlinear CFK equations for predicting COHb formation. *Math Biosci*, 99: 251-263. [013164](#)
- Smith MV; Hazucha MJ; Benignus VA; Bromberg PA (1994). Effect of regional circulation patterns on observed HbCO levels. *J Appl Physiol*, 77: 1659-1665. [076564](#)
- Sokal JA; Majka J; Palus J (1984). The content of carbon monoxide in the tissues of rats intoxicated with carbon monoxide in various conditions of acute exposure. *Arch Toxicol*, 56: 106-108. [011591](#)
- Solanki DL; McCurdy PR; Cuttitta FF; Schechter GP (1988). Hemolysis in sickle cell disease as measured by endogenous carbon monoxide production: A preliminary report. *Am J Clin Pathol*, 89: 221-225. [012426](#)
- Stevenson DK; Ostrander CE; Johnson JD (1979). Effect of erythrocyte destruction on the pulmonary excretion rate of carbon monoxide in adult male Wistar rats. *J Lab Clin Med*, 94: 649-654. [193767](#)
- Stewart RD; Peterson JE; Baretta ED; Bachand RT; Hosko MJ; Herrmann AA (1970). Experimental human exposure to carbon monoxide. *Arch Environ Health*, 21: 154-164. [013972](#)
- Stewart RD; Peterson JE; Fisher TN; Hosko MJ; Baretta ED; Dodd HC; Herrmann AA (1973). Experimental human exposure to high concentrations of carbon monoxide. *Arch Environ Occup Health*, 26: 1-7. [012428](#)
- Sylvester KP; Patey RA; Rafferty GF; Rees D; Thein SL; Greenough A (2005). Exhaled carbon monoxide levels in children with sickle cell disease. *Eur J Pediatr*, 164: 162-165. [191954](#)
- Takeuchi A; Vesely A; Rucker J; Sommer LZ; Tesler J; Lavine E; Slutsky AS; Maleck WA; Volgyesi G; Fedorko L; Iscoe S; Fisher JA (2000). A simple "new" method to accelerate clearance of carbon monoxide. *Am J Respir Crit Care Med*, 161: 1816-1819. [005675](#)
- Tarquini R; Masini E; La Villa G; Barletta G; Novelli M; Mastroianni R; Romanelli RG; Vizzutti F; Santosuosso U; Laffi G (2009). Increased plasma carbon monoxide in patients with viral cirrhosis and hyperdynamic circulation. *Am J Gastroenterol*, 104: 891-897. [194117](#)
- Terzano C; Conti V; Petroianni A; Ceccarelli D; De Vito C; Villari P (2009). Effect of Postural Variations on Carbon Monoxide Diffusing Capacity in Healthy Subjects and Patients with Chronic Obstructive Pulmonary Disease. *Respiration*, 77: 51-57. [108046](#)
- Tikuisis P (1996). Modeling the uptake and elimination of carbon monoxide. In Penney DG (Ed.), *Carbon Monoxide* (pp. 45-67). Boca Raton, FL: CRC Press, Inc / Lewis Publishers. [080960](#)

- Tikuisis P; Buick F; Kane DM (1987). Percent carboxyhemoglobin in resting humans exposed repeatedly to 1,500 and 7,500 ppm CO. *J Appl Physiol*, 63: 820-827. [012219](#)
- Tikuisis P; Kane DM; McLellan TM; Buick F; Fairburn SM (1992). Rate of formation of carboxyhemoglobin in exercising humans exposed to carbon monoxide. *J Appl Physiol*, 72: 1311-1319. [013592](#)
- Tikuisis P; Madill HD; Gill BJ; Lewis WF; Cox KM; Kane DM (1987). A critical analysis of the use of the CFK equation in predicting COHb formation. *Am Ind Hyg Assoc J*, 48: 208-213. [012138](#)
- Topping DL (1975). Acute effects of carbon monoxide on the metabolism of perfused rat liver. *Biochem J*, 152: 425-427. [193784](#)
- Tran TT; Martin P; Ly H; Balfe D; Mosenifar Z (2007). Carboxyhemoglobin and its correlation to disease severity in cirrhotics. *J Clin Gastroenterol*, 41: 211-215. [194120](#)
- Tyuma I; Ueda Y; Imaizumi K; Kosaka H (1981). Prediction of the carbonmonoxyhemoglobin levels during and after carbon monoxide exposures in various animal species. *Jpn J Physiol*, 31: 131-143. [011226](#)
- U.S. Census Bureau (2008). American Housing Survey for the United States: 2007. U.S. Government Printing Office. Washington, DC. [194013](#)
- U.S. EPA (1978). Altitude as a factor in air pollution. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA-600/9-78-015. [086321](#)
- U.S. EPA (1991). Air quality criteria for carbon monoxide. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA/600/8-90/045F. <http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=3000554R.txt>. [017643](#)
- U.S. EPA (2000). Air quality criteria for carbon monoxide. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA 600/P-99/001F. [000907](#)
- Vreman HJ; Wong RJ; Kadotani T; Stevenson DK (2005). Determination of carbon monoxide (CO) in rodent tissue: effect of heme administration and environmental CO exposure. *Anal Biochem*, 341: 280-289. [193786](#)
- Vreman HJ; Wong RJ; Stevenson DK; Smialek JE; Fowler DR; Li L; Vigorito RD; Zielke HR (2006). Concentration of Carbon Monoxide (CO) in Postmortem Human Tissues: Effect of Environmental CO Exposure. *J Forensic Sci*, 51: 1182-1190. [098272](#)
- Wagner JA; Horvath SM; Dahms TE (1975). Carbon monoxide elimination. *Respir Physiol Neurobiol*, 23: 41-47. [010989](#)
- Weaver LK; Howe S; Hopkins R; Chan K (2000). Carboxyhemoglobin half-life in carbon monoxide-poisoned patients treated with 100% oxygen at atmospheric pressure. *Chest*, 117: 801-808. [016421](#)
- Weller PA; Price M; Isenberg H; Edwards YH; Jeffreys AJ (1986). Myoglobin expression: early induction and subsequent modulation of myoglobin and myoglobin mRNA during myogenesis. *Mol Cell Biol*, 6: 4539-4547. [187298](#)
- West JB (1962). Diffusing capacity of the lung for carbon monoxide at high altitude. *J Appl Physiol*, 17: 421-426. [199513](#)
- Widdop B (2002). Analysis of carbon monoxide. *Ann Clin Biochem*, 39: 378-391. [030493](#)
- Wirkner K; Damme B; Poelchen W; Pankow D (1997). Effect of long-term ethanol pretreatment on the metabolism of dichloromethane to carbon monoxide in rats. *Toxicol Appl Pharmacol*, 143: 83-88. [082642](#)
- Wittenberg BA; Wittenberg JB; Caldwell PRB (1975). Role of myoglobin in the oxygen supply to red skeletal muscle. *J Biol Chem*, 250: 9038-9043. [012436](#)
- Wu L; Wang R (2005). Carbon monoxide: endogenous production, physiological functions, and pharmacological applications. *Pharmacol Rev*, 57: 585-630. [180411](#)
- Yamaya M; Sekizawa K; Ishizuka S; Monma M; Mizuta K; Sasaki H (1998). Increased carbon monoxide in exhaled air of subjects with upper respiratory tract infections. *Am J Respir Crit Care Med*, 158: 311-314. [047525](#)
- Yasuda H; Sasaki T; Yamaya M; Ebihara S; Maruyama M; Kanda A; Sasaki H (2004). Increased arteriovenous carboxyhemoglobin differences in patients with inflammatory pulmonary diseases. *Chest*, 125: 2160-2168. [191955](#)
- Yasuda H; Yamaya M; Nakayama K; Ebihara S; Sasaki T; Okinaga S; Inoue D; Asada M; Nemoto M; Sasaki H (2005). Increased arterial carboxyhemoglobin concentrations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 171: 1246-1251. [191953](#)

- Yasuda H; Yamaya M; Yanai M; Ohru T; Sasaki H (2002). Increased blood carboxyhaemoglobin concentrations in inflammatory pulmonary diseases. *Thorax*, 57: 779-783. [035206](#)
- Yerushalmi R; Kramer MR; Rizel S; Sulkes A; Gelmon K; Granot T; Neiman V; Stemmer SM (2009). Decline in pulmonary function in patients with breast cancer receiving dose-dense chemotherapy: a prospective study. *Ann Oncol*, 20: 437-440. [186711](#)
- Young LJ; Caughey WS (1986). Mitochondrial oxygenation of carbon monoxide. *Biochemistry*, 239: 225-227. [012091](#)
- Zayasu K; Sekizawa K; Okinaga S; Yamaya M; Ohru T; Sasaki H (1997). Increased carbon monoxide in exhaled air of asthmatic patients. *Am J Respir Crit Care Med*, 156: 1140-1143. [084291](#)
- Zegdi R; Perrin D; Burdin M; Boiteau R; Tenaillon A (2002). Increased endogenous carbon monoxide production in severe sepsis. *Intensive Care Med*, 28: 793-796. [037461](#)
- Zinkham WH; Houtchens RA; Caughey WS (1980). Carboxyhemoglobin levels in an unstable hemoglobin disorder (Hb Zürich): effect on phenotypic expression. *Science*, 209: 406-408. [011435](#)