CARBOXYHEMOGLOBIN FORMATION DUE TO TRANSIENT EXPOSURE TO HIGH LEVEL CARBON MONOXIDE: EXPERIMENTAL RESULTS AND AN EXPLANATORY MODEL

FINAL REPORT

Milan J. Hazucha[1], Marjolein V. Smith[2],

Vernon A. Benignus[3] and Phillip A. Bromberg[1]

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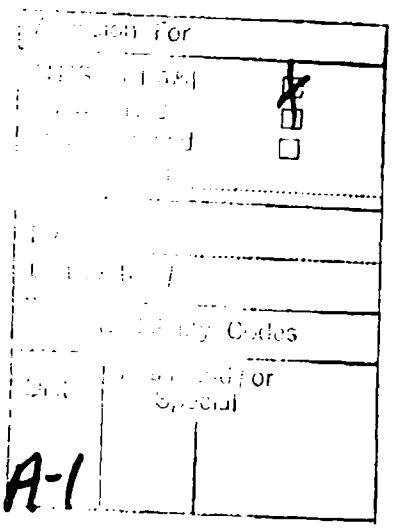

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Fifteen men were exposed to 6,683 ppm $C^{18}O$ for 3.1 - 6.6 min. Venous and arterial blood samples were drawn at one-min intervals beginning at the start of exposure and finishing 10 min later. Simultaneously, $\dot{V}_A$ was calculated from the measured values of $\dot{V}_E$ and deadspace. $\dot{V}_E$ was measured by integrating digitized continuous measures of inhaled and exhaled gas. All parameters of the nonlinear Coburn-Forster-Kane equation (CFKE) were measured on the individual subject except for the Haldane affinity ratio. Predictions of venous blood COHb in samples collected ca. two min after cessation of exposure were accurately predicted by the CFKE. Both venous and arterial COHb were inaccurately predicted during COHb formation, however. Venous levels were overpredicted during formation due to a delayed appearance of COHb. Individual subjects differed markedly in the delay of COHb appearance in venous blood. Arterial COHb was consistently underestimated either by the CFKE or by predictions based on venous blood samples. Thus, exposure of such organs as brain or heart to COHb can be higher than expected from previous knowledge when transient CO exposure is involved.

An explanation is suggested for the observed differences between arterial and venous COHb on the basis of the regional circulation of the forearm, where both samples were taken. Because regional circulation patterns are known to vary with physical training, the differences in physical training between subjects may account for the observed variation. An expanded model was derived from the Coburn-Forster-Kane equation that reflects the above hypothesis. Most of the parameter values for the expanded model were measured on individual subjects. Literature values were used for other parameters. Two parameters were estimated using five of the subjects and then used in the predictions of the expanded model for the remaining subjects.

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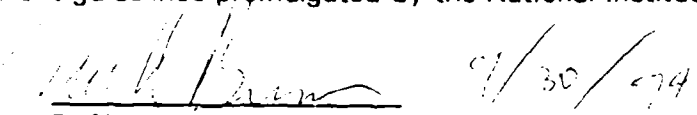

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EXECUTIVE SUMMARY

Military environments have sources of carbon monoxide (CO) to which personnel are exposed. The dangers of such exposure are well known, but, difficult to quantify. One of the problems of predicting the functional effect of CO exposure is the prediction of the amount of carboxyhemoglobin (COHb) formed as a result of the exposure. It is, therefore, desirable to be able to estimate COHb from CO exposure parameters.

The formation of COHb by CO exposure is a well-understood process when exposures are to low concentrations or for long periods of time. The prediction methods have not been well tested for cases of high-level, short-term exposures typical of military environments. In order to test the validity of the prediction equation an experiment must be conducted in which the physical and physiological parameters of the equation are carefully measured in each individual subject. The present report gives the results of such an experiment.

Fifteen men were exposed to 6,683 ppm $C^{18}O$ for 3.1 - 6.6 min. Venous and arterial blood samples were drawn at one-min intervals beginning at the start of exposure and finishing 10 min later. Simultaneously, $\dot{V}_A$ was calculated from the measured values of $\dot{V}_E$ and V_D. $\dot{V}_E$ was measured by integrating digitized continuous measures of inhaled and exhaled gas. All parameters of the nonlinear Coburn--Forster-Kane equation (CFKE), for prediction of COHb, were measured on the individual subject except for the Haldane affinity ratio.

Predictions from the CFKE depend on the homogeneous mixing of COHb in arterial and venous blood. Such mixing requires 2-7 min after cessation of high-level CO exposure. For this reason, an a priori hypothesis was formed and tested regarding four min of data, collected beginning two min after the end of CO exposure. The equation's prediction of average venous and arterial COHb in samples collected beginning two min after cessation of exposure were accurately predicted by the equation.

Even mean values of both venous and arterial COHb were, however, inaccurately predicted during exposure. Venous blood was overpredicted during formation due to a delayed appearance of COHb. Individual subjects differed markedly in the delay of COHb appearance in venous blood. Similarly, arterial COHb during exposure was consistently underestimated either by the equation or by predictions based on venous blood samples. Thus, exposure of such organs as brain or heart to COHb can be higher than expected from previous knowledge when transient CO exposure is involved.

An explanation is suggested for the observed differences between arterial and venous COHb on the basis of the regional circulation of the forearm, where both samples were taken. Because regional circulation patterns are known to vary with physical training, the differences in physical training between subjects may account for the observed variation. An expanded model was derived from the Coburn-Forster-Kane equation (CFKE) that reflects the above hypothesis. Most of the parameter values for the expanded model were measured on individual sub-

jects. Literature values were used for other parameters. Two parameters were estimated using five of the subjects and then used in the predictions of the expanded model for the remaining subjects. The model appeared to account for many of the individual differences in the data.

The conclusions from the present experiment can be enumerated as follows.

(1) When nonlinear CFKE parameters are measured on the individual subject the prediction of venous COHb becomes acceptable 2 - 5 min after cessation of exposure to high CO concentrations for short periods.

(2) Predictions are not accurate for either venous or arterial blood during the early phases of COHb formation during exposure to high CO concentrations. Mean venous levels are over predicted while mean arterial levels are underpredicted.

(3) The inaccurate predictions and large variation across subjects during COHb formation are primarily due to delay in the equilibration of arterial with venous blood. The delay in equilibration is described by an extended version of the CFKE model, which was constructed as a part of the present work.

(4) The arterial blood during exposure to transients of high concentration CO has considerably higher level of COHb than is predicted by the CFKE or would be estimated from a venous sample. It is possible that even higher (but shorter duration) transients occur in e.g. aortic blood and that these might produce clinically important effects.

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A-V diff	Arterial - venous difference (in some blood gas).
CO	Carbon monoxide, an invisible, odorless gas which is the product of incomplete combustion.
COHb	Carboxyhemoglobin, carbon monoxide bound to hemoglobin [% of total Hb].
df	Degrees of freedom (associated with a statistical test).
D_LCO	Diffusion capacity of lungs for CO [ml/min/mm Hg].
ECG	Electrocardiogram, a record of electrical activity emitted by the heart.
F_ICO	Fractional concentration of CO in inspired air [%].
FRC	Functional residual capacity [ml].
Hb	Hemoglobin concentration [g/(ml of blood)]
M	Haldane affinity ratio (245).
O_2Hb	Oxyhemoglobin, oxygen bound hemoglobin [ml/(100ml of blood)].
p	Probability of an event or outcome of a test of statistical significance.
P_B	Barometric pressure [mm Hg].
$\overline{P_CO_2}$	Average partial pressure of O_2 in lung capillaries [mm Hg].
P_ICO	CO partial pressure in inhaled air [mm Hg].
P_L	Dry gas pressure in lungs [mm Hg].
PPM	Parts per million.
$\dot{Q}$	Cardiac output [ml/min].
$\dot{Q}_c$	pulmonary capillary blood flow [ml/min].
r	Correlation coefficient (Pearson's product-moment).
SD	Standard deviation, a measure of variability around the mean.
SE	Standard error, a measure of variability of the estimate of the mean.
t	Student's t, a statistical test for significance.
T^2	Hotelling's T^2, a multivariate statistical test of significance.
$\dot{V}_A$	Alveolar ventilation rate [ml/min].
V_B	Total blood volume [ml].

$\dot{V}_{CO}$ Endogenous CO production rate [ml/min].

V_D Dead space (rebreathing) [ml].

V_i Volumes of the various compartments of the model, where i is the compartment number [ml].

CHAPTER 1

INTRODUCTION

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INTRODUCTION

Military environments have a number of sources of carbon monoxide (CO) to which personnel are frequently exposed. The dangers of such exposure are well known, but, difficult to quantify. One of the problems of predicting the functional effect of CO exposure is the prediction of the amount of carboxyhemoglobin (COHb) formed as a result of the exposure. While COHb can be measured from, e.g. blood samples, such methods are not practical to many non-laboratory situations. Thus, it becomes highly desirable to be able to estimate COHb from CO exposure parameters.

Formation of COHb as a result of endogenous CO production and low concentrations of inhaled CO was described by a differential equation (Coburn, Forster and Kane, 1965) which became known as the Coburn-Forster-Kane equation (CFKE). In deriving the CFKE it was assumed, among other things, that equilibration occurred instantly (a) between lung gases (b) in COHb concentrations between venous and arterial blood and (c) in COHb concentration between blood and extravascular tissues. When CO concentrations in inhaled air are low and exposures are long, as was the case during initial experiments (Coburn, Forster and Kane, 1965), the above conditions are approached.

The CFKE was derived under the assumption that the oxyhemoglobin concentration (O_2Hb) remained constant as COHb increased. This assumption, although not correct, is acceptable when COHb levels are low, because the

resultant error is negligible. However, as COHb becomes an appreciable portion of hemoglobin (Hb) the reduction in O_2Hb becomes greater and must be taken into account. Because of the assumption of constant O_2Hb and the consequent form of the model, the original version of the CFKE became known as the linear CFKE. A version of the CFKE which allows O_2Hb to vary with changing COHb became known as the nonlinear CFKE (Peterson and Stewart, 1975).

Military applications of the CFKE are questionable because the assumptions under which the derivation was made are almost always violated. A number of experiments have been done to test the adequacy of the CFKE as a predictor of COHb formation as a consequence of CO inhalation. Most of these studies employed exposure durations of 15 - 1440 min (Hauk and Neuberger, 1984; Jones et al., 1958; Peterson and Stewart, 1970, 1975). In all of these studies, many of the parameters of the CFKE were not measured on the individual. Either the values from normative data were used or the values were indirectly estimated from predictive formulae based on other physical characteristics of the subject, e.g. height and weight. The predicted COHb values from such studies were usually quite good, although the detail in the reporting was frequently insufficient to evaluate the results.

Studies of the adequacy of the CFKE for prediction of COHb formation after exposure to CO transients (less than 10 min) are rare. As part of a larger study (Hauk and Neuberger, 1984) one or two subjects were exposed to a series of CO transients and good agreement was obtained with nonlinear CFKE predictions.

Tikuisis et al. (1987a) exposed 11 subjects (at rest) to two series of five transients of CO. The transients were 1 min at 7,500 ppm and 5 min at 1,500 ppm so that each delivered a dose of 37,500 ppm x min. CO transients were equally spaced such that exposure sequences lasted a total of 32 min for the 1-min transients and 36 min for the 5-min transients. The nonlinear CFKE was used with most parameters estimated from individual characteristics or norms. Only lung diffusion for CO (D_LCO) and minute ventilation rate ($\dot{V}_E$) were measured on each subject. By the end of the exposure sequences, the predicted COHb value lay within less than one standard error (SE) of the observed mean for each exposure scenario. Early in the scenario (for the first two transients or about the first 16 min) the predicted values of COHb were frequently more than one SE above the observed values. Mean errors of prediction were as high as 0.5% COHb for COHb values of ca. 5%, thus overpredicting by ca. 10% of the true value. The latter results were estimated from the graphs presented in the article (Tikuisis et al., 1987a). This might imply that the CFKE works less well for short exposures or until a certain level of COHb has been reached. Similar results were found in a second, smaller study (Tikuisis et al., 1987b). Measures of prediction errors were give graphically and appeared to increase as COHb increased. From the above studies it appears that even when all of the parameters of the CFKE are not measured on the individual subject, depending on the application, the predictions might be acceptable, except for exposures of only a few minutes (Tikuisis et al., 1987a,b).

Knowledge of the pharmacokinetics of COHb formation during short exposures to CO is important in more than a theoretical sense. In military settings, short duration, high level CO exposures are common (Tikuisis et al., 1987a,b). The COHb which is expected to form under such circumstances must frequently be estimated to set regulatory limits and make judgements about personnel safety. However, as reviewed above, the CFKE has not been adequately verified for transient CO exposures. In the two experiments in which CO transients were tested, the CFKE overpredicted the resultant COHb during the early exposure times (Tikuisis et al., 1987a,b). The interpretation of these results is clouded by the fact that some CFKE parameters were not measured on the individual subject. Thus the parameter values may have been slightly erroneous which may have resulted in prediction errors during the early part of exposure but not later (McCartney, 1990).

The present experiment was performed to test the CFKE during transient exposures to CO of ca. 5-min duration and high (ca. 6,700 ppm) concentrations. The goal was to measure as many of the parameters of the CFKE as possible on the individual subject. The results of the experiment were designed to be a test of the CFKE under optimum conditions, but under substantial violation of the assumption of equilibrium conditions which was made in the derivation of the original model. If the CFKE were to work well under such conditions, it would be considered robust for most other circumstances. If the CFKE were not to predict well under such circumstances, corrective procedures could be developed.

CHAPTER 2

METHOD

CHAPTER 2

METHOD

Pilot study.

Before the design of the main experiment, eight pilot subjects were tested in a simple procedure to determine the necessary sampling times for blood and the ventilation rates needed to bring blood COHb near target levels. In the pilot study, subjects breathed ca. 35 L of gas (6,115 ppm $C^{16}O$ in air) from a bag. The time required to empty the bag was ca. 5 min. and blood samples were taken at one-min intervals from the anticubital vein beginning one min before the exposure began. While $C^{16}O$ (normal CO) was used in the pilot study, $C^{18}O$ was used in the confirmatory experiment because the mass of the former is indistinguishable from the mass of the N_2 in the MGA and because $C^{18}O$ is not confounded with other possible sources of $C^{16}O$.

Subjects.

Subjects for the main experiment were 15 healthy young white or black males. They were screened for clinically normal routine chemical and hematological test before being accepted for the study. All subjects had been given extensive medical examinations, including a Bruce protocol exercise stress test to assure safety in exposure. Before signing the informed consent, subjects were briefed about experimental procedures, risks and safeguards. They were familiarized with the facilities and equipment before being trained to perform the required tests satisfactorily.

Procedure and Apparatus.

On the day prior to CO exposure, the subject's D_LCO, FRC, P_cO_2, Q_c and $\dot{V}_A$ were measured using a modified rebreathing technique (Sackner et al., 1980). Details of the measurement are in the section on the measurement of CFKE parameters. A 10 ml venous blood sample was also drawn to determine hematological values and COHb. The following day the subject's exposure was conducted. Within one wk following exposure, the subject's blood volume was measured by the Cr^{51} method (Sterling and Gray, 1950).

On the day of the experiment, an anesthesiologist inserted an arterial line (Redial AvA. Cath. set, Arrow Int., Inc.), under 1% lidocaine anesthesia, into radial artery of one forearm and a venous catheter (I.V. ext. set 7-SL, Abbott Inc.) into the contralateral anticubital vein. While seated, the subject breathed from a mouthpiece via a Hans-Rudolph 3700 series pneumotachometer connected to a three-way computer-controlled pneumatic balloon valve (Hans-Rudolph 2540 series). The three-way valve allowed the subject to breathe either room air, or bag gas (third port always closed). The bag gas (50 L of 6,683 ppm $C^{18}O$ with the balance of air) was delivered via a flutter valve (Hans-Rudolph PN 1408) so that the expired gas could be collected in a separate, previously evacuated, 100 L meteorological balloon. A gas sample line was led from the mouthpiece to a Perkin-Elmer model MGA-1100 mass spectrometer (MGA) for continuous sampling of both inspired and expired gas. $C^{18}O$ was used instead of the normal $C^{16}O$ because the mass of the latter is indistinguishable from the mass of the N_2 in the

MGA and because $C^{18}O$ is not confounded with other possible sources of $C^{16}O$.

The subject began breathing room air from the mouthpiece and after a short adaptation time (typically less than one min) a warning tone sounded to inform the phlebotomists that the valve would switch from room air to bag gas. The transition (time zero) came at the end of the first expiration after 30 sec from the warning tone had elapsed. The subject breathed from the supply bag until the supply line pressure sensor during inhalation reached a nominal preset point, indicating that the bag had been evacuated. At this point the valve automatically switched the inhaled gas back to room air. The subject was coached during bag breathing to attempt to evacuate the bag in 5 min. The subject continued to breathe room air from the mouthpiece until 10 min from time zero, after which he was allowed to breathe normally.

Gas sampling was continuous for the duration of mouthpiece breathing. The outputs of the MGA were digitized at the rate of 100 samples/sec using a 12-bit converter along with the gas flow rate output of the pneumotachometer and event signals. The gases monitored were $C^{18}O$, O_2 and CO_2. The analog signals were simultaneously plotted on a stripchart recorder (Astro-Med, model 8500). Digitized gas signals were stored beginning at time zero and ending at 10 min, i.e. 5 min following the end of exposure. Atmospheric pressure, relative humidity and room temperature were recorded just before and just after the 10-min mouthpiece breathing. Inhaled gas mixture was dry and exhaled gas was assumed to be water vapor saturated and body temperature at the gas sampling port. All gas volumes

were eventually converted to BTPS condition.

Arterial and venous blood samples (ca. 1 ml) were drawn simultaneously by a phlebotomist (venous sample) and an anesthesiologist (arterial sample) with 3 ml heparinized syringes, at 5 sec prior to exposure and at 30 sec and one min after exposure and on one-min intervals thereafter, continuing through 10 min. Shortly before a sample was to be drawn, catheters were flushed with saline. The first sample (containing saline and blood) was discarded and then another sample was drawn for analysis from the catheter which had been just filled with fresh blood. After the sample at min 10, further blood samples (venous only) were taken at 12, 16, 24, 40, 72, 136 and 264 min and thereafter as needed to monitor the subjects COHb elimination for safety reasons. Prior to each blood draw, the end-tidal CO concentration was measured by the breath holding technique (Jones et al., 1958) with the concentration measured by the MGA. All blood samples were put directly on ice. The subject was advised to remain in the facility for observation until his COHb fell below 10%.

Blood samples were analyzed on two IL-282 CO-oximeters (Instrumentation Laboratories, Inc.) within one hr after collection. Because IL-282 instruments are sometimes inaccurate at low COHb levels (U. S. Environmental Protection Agency, 1990), they were calibrated against a gas chromatographic (GC) method (Byron, model 104) in the present experiment. Blood samples ($n = 101$) from independent subjects were analyzed on both the IL-282 and the GC. COHb values ranged from 0.5 to 6.7% (CO-oximeter values). Regression analysis was performed to deter-

mine the relationship between the instruments.

All events in the experiment were timed by a microcomputer program written for the purpose. Events involving human actions, e.g. blood drawing and subject maneuvers, were signaled by computer-presented tones and messages. Equipment control actions and data collection were under control of the same computer program.

The CFKE and its Parameters.

The linear CFKE (Tikuisis et al., 1987a,b) may be written as

$$\frac{d(COHb)_t}{dt} = \frac{\dot{V}_{CO}}{V_B} + \frac{1}{V_B \cdot A}\left[P_I CO - (COHb)_t \frac{PCO_2}{(O_2Hb)\,M}\right] \qquad [1]$$

Where;

$$A = \frac{1}{D_L CO} + \frac{(P_B - 47)}{\dot{V}_A}. \qquad [2]$$

The terms of Equations [1 and 2] are defined in the Table of Abbreviations.

To convert the linear CFKE [1] into the nonlinear CFKE, the reduction in O_2Hb may be accounted for (Peterson and Stewart, 1975) by subscripting the O_2Hb term in [1] and solving as follows:

$$(O_2Hb)_t = 1.38 \cdot Hb - (COHb)_t \qquad [3]$$

where Hb is hemoglobin concentration in g/(ml blood).

Measurement of CFKE Parameters.

On the day before the CO exposure several parameters were obtained by the rebreathing technique (Sackner et al., 1980). After the subjects end-tidal volume had stabilized at a paced rate of 40 breaths per min while breathing air through a mouthpiece assembly, he was switched to rebreathe from a bag filled with a gas mixture (0.3% $C^{18}O$, 9.0% He, 21.0% O_2, 0.6% C_2H_2, balance N_2). The rebreathing bag volume was twice his tidal volume. The C_2H_2 and He were included in the mix to simultaneously measure other physiological variables. Rebreathing commenced at the paced rate and continued for 20-30 sec. Bag contents were sampled continuously by the MGA and gas temperature was sensed by a thermistor in the flow stream. D_LCO was then calculated from the bag gas concentrations after He concentrations became equilibrated by applying appropriate equations (Sackner et al., 1980). P_cO_2 was the minimum O_2 concentration measured by the MGA at end expiration during the rebreathing measurement of D_LCO.

During the CO exposure experiment P_ICO was calculated from the $C^{18}O$ concentration in ppm in the inhaled gas. $\dot{V}_A$ was calculated from the measured $\dot{V}_A$ and $\dot{V}_D$. Calculation of $\dot{V}_E$ was performed by integrating the digitized measures of flow rate for each minute. Thus a measure of $\dot{V}_A$ was available for each minute of the experiment. V_D was calculated for each minute by the $C^{18}O$ washout method (Petrini et al., 1982). Hb and O_2Hb were calculated from the total hemoglobin as measured by the IL-282 CO-oximeter using the control (time zero) blood samples. $\dot{V}_B$ was calculated from the red-cell volume as measured by the $Na_2{}^{51}CrO_4$ dilution

method (Sterling and Gray, 1950) about one wk after the CO exposure.

Data Analysis.

The nonlinear CFKE was used to predict COHb at the end of each minute, corresponding to the blood samples. The COHb at time zero was used as the starting value. The CFKE was solved numerically by a forth-order Runge-Kutta method with a 1/50th of a min time step. The value of $\dot{V}_A$ for each min was used in the prediction for that min, otherwise previously measured values were used.

The experiment's dependent variable for statistical analysis was the error of prediction at each min. This error is defined as

$$E_t = COHb(predicted)_t - COHb(observed)_t \quad [5]$$

where all terms are in percent COHb. Both arterial and venous blood samples were compared to prediction.

The hypothesis to be tested in the present experiment was $E_t = 0.0$ for $t = 7, 8, 9$ and 10 in venous blood. This hypothesis is that the error of prediction in venous blood for the last 4 min of mouthpiece breathing is zero. At seven min, the $C^{18}O$ exposure will have been ended by more than one min. The hypothesis was formed because (a) pilot data indicated that the CFKE would predict poorly during the exposure due to delayed appearance of COHb in venous blood (b) primary interest for regulatory purposes was in the end result of exposure and (c) venous blood is the usually sampled tissue. The hypothesis was evaluated with a Hotelling T^2 test, simultaneously testing the four values of E_t against a vector of

four zeros. Stepdown Student's t tests were conducted at each of the four mins. Statistical computations were done on a BMDP microcomputer system (Dixon, 1986).

Other data were analyzed on a strictly exploratory basis (Muller, Barton and Benignus, 1984). Means and SDs for E_t were computed for arterial blood and for venous blood before min seven and after min 10.

An Extended Model

In equation [1] the COHb concentration was assumed to be instantly equilibrated between all vascular compartments. Thus the circulation system of the body was modeled as a single compartment. The present work sought to predict COHb levels in both arterial and venous samples for individual subjects before the inhaled CO equilibrated. To this end the CFKE was extended by modeling the circulation system in greater detail, while not altering the mechanism of CO uptake or elimination via the lungs.

The data from the present study have been used to develop a model which predicts both arterial and venous COHb during and following a brief exposure to high concentrations of CO, before equilibration in the blood. The observed variability in A-V differences in COHb could be reproduced by modeling different degrees of capillary development of the muscles of the forearm, although other factors, such as skin blood flow may contribute. Such differences in capillary development could be the result of physical training. Although almost all of the parameters for the model presented were measured directly or deduced from the

literature, two parameters were estimated from the observed COHb levels in a subset of five subjects and then the model was tested in the remaining eight subjects.

The structure of the model was derived by looking qualitatively at all the data, so that a valid statistical test of the fit of the model was not possible. The unknown parameters were estimated using as few subjects as possible. The fit of the model to the rest of the subjects was then examined heuristically.

The structure of the expanded model is shown in Figure 1. The first "lung" compartment includes the pulmonary capillaries and veins and roughly half the average volume of the heart. The CO diffuses into the blood stream and rapidly binds to Hb in this compartment and is presumed to be mixed throughout as COHb. While mixing within the pulmonary circulation is not instantaneous, dividing this compartment into three sub-components did not meaningfully alter the results of the model. Since the physiological variables and mechanism of delivering CO to the blood stream are the same as those included in the CFKE, this compartment could be expected to behave similarly to the single compartment of the CFKE. The smaller size of the "lung" compartment and the existence of other compartments with lower COHb, however, ensure a much higher COHb concentration in the lung compartment during the uptake of CO.

Insert Figure 1 About Here

Because in the experiment the blood was sampled only from the arms, the rest of the systemic circulation system was modeled with very little detail. However, as the blood perfuses different regions of the body at different rates, regions with relatively low concentrations of COHb will develop during CO uptake. Such regions could affect the COHb concentrations in the arms. Hence the remainder of the blood circulation was modeled by compartments two (high perfusion) and three (low perfusion) with adjustable perfusion rates but without attempting to model any specific organs (Figure 1).

The modeling of the circulation of the arms (Compartments 4-8), although still necessarily simplified, reflects anatomical structure to a greater extent. In the forearm the radial and ulnar arteries carry blood from the heart to the hand. The arterial blood samples were taken from the radial artery at the wrist. Smaller arteries and arterioles branch from the radial artery, some leading to the capillary net that supplies the muscles of the forearm. This blood is returned via venules and small veins to the median vein of the forearm and the antecubital vein. The antecubital vein joins with the basilic vein beyond the sampling site. The junction of the cephalic and antecubital veins varies from subject to subject and may occur before or after the sampling site (see Grant (1956), plates 21 and 39).

In the present model, blood flow through both "arms" was assumed to be a total of 5% of the $\dot{Q}$ at rest (Middleman, 1972). Each compartment broadly includes all blood vessels having roughly the same COHb levels. Compartment four represents the blood sampled from the radial artery and is labeled "major arteries"

in Figure 1. It also includes most smaller arteries and even arterioles in the upper arm or the hand, neither of which are explicitly modeled. Similarly, compartment eight includes the two large veins starting from the hand and is labeled "large veins" in Figure 1. It also includes all the capillary and venous blood in the hand and is therefore connected to compartment four. All the non-arterial blood in the skin and upper arms is also represented by compartment eight, which holds at least 62% of the blood in the arms.

Compartments five and six represent the small vessels (arterioles, capillaries and venules) perfusing the muscles of the forearm. Compartment seven represents intermediate veins draining the muscles of the forearm and was used to predict the COHb concentration of the samples taken from the antecubital vein. From the arm the blood then moves into compartment nine, consisting of the right half of the heart and the pulmonary arteries. Finally, blood flows back from compartment nine to compartment one.

The differential equations for the model are shown in Table 1. The equations are numbered to correspond to the compartments in Figure 1. In each case, the solution of the equation refers to the concentration of COHb predicted for that compartment (y_i) expressed as percent of total saturation of Hb with CO. Information about the source of parameter values is summarized in Table 2. Almost all of the physiological parameters used in the model of CO uptake were directly measured on each subject separately from the exposure. Among these parameters only the Haldane coefficient (M) was taken directly from the literature.

Insert Tables 1 through 3 About Here

As many of the remaining parameter values as possible were taken from the literature. Often a value could be selected from an accepted range of values. In other cases, the necessary parameter values were computed from other information found in the literature (see Table 3). The computations are as follows.

The volume of the first compartment (V_1) was computed as follows. From West (1985), an average adult with a total blood volume (V_B) of 5 L and a cardiac output of about 6 L/min has a mean pulmonary capillary transit time of about 0.75 sec. Hence the volume of the pulmonary capillaries was estimated to be about 75 ml or $0.015*V_B$. The total blood volume of the pulmonary circulation system was taken to be $0.105*V_B$, which is within the range given by Fox (1956). The volume of the pulmonary system was divided into $0.015V_B$ for capillaries and $0.045V_B$ each for the pulmonary arteries and veins. From Fox (1965), the total volume of the heart was taken to be $0.08*V_B$. Then

$$V_1 = (0.015 + 0.045 + 0.04)V_B = 0.1*V_B,$$

and simultaneously

$$V_\theta = (0.045 + 0.04)V_B = 0.085*V_B.$$

From Bischoff (1967), the volume of the small vessels (arterioles, capillaries and venules), ($V_5 + V_6$), of both arms was computed as $0.0076V_B$, while the fractional contribution of all such vessels to the volume of the whole systemic circulation system was computed as 0.143. Thus $0.053*V_B$ was taken as the

total intravascular volume of both arms (.0076*V_B/0.143). The ranges provided by Fox (1965) and Vander et al. (1975) were used to select the estimate of 0.13 for the fraction of the volume of the systemic circulation attributable to the arteries. V_4 (arteries in arms) was then computed as 0.0069*V_B by using the same fraction with the total volume of the arms (0.13*0.053)V_B. The volume of the seventh compartment (V_7), referring to intermediate veins draining the forearm and used to predict the COHb level of the samples taken from the antecubital vein, was taken arbitrarily to be 0.0025*V_B. The combined volumes of compartments five, six, and eight was then 0.0436V_B. By subtraction, the total volume of compartments two and three (V_2 + V_3) was 0.762*V_B.

Finally, there were some parameters that could not be measured individually or found in the literature. In particular, the parameters involved with compartments two and three as well as those of compartments five, six, and eight were estimated using some of the measured COHb values.

The last two groups of parameters can be estimated separately by temporarily simplifying the model. Numerical experiments showed that the COHb values predicted for compartments one and four were very similar, with the peak values predicted by the first compartment being approximately 0.1% COHb higher. Therefore, compartment one (with a minor adjustment) could predict the peak arterial value for any subject. This allowed the combination of compartments four, five, six, seven, and eight into a single "arms" compartment of known volume .053*V_B, for the purpose of estimating $\dot{Q}_{12}$ and V_2 (See above). The notation $\dot{Q}_{ij}$

denotes blood flow from compartment i to compartment j.

The simplified model is shown in Figure 2. Only parameters $\dot{Q}_{12}$ and V_2 remained to be estimated, but they were not identifiable. That is, repeated numerical trials showed that there are many pairs of values for these two parameters that give substantially the same results. Therefore in this paper $\dot{Q}_{12}$ was arbitrarily set at $0.6\dot{Q}$. Subsequently, V_2 was so determined that compartment one provided the best prediction of the maximum observed arterial value of three subjects by the least squares criterion. Choosing larger or smaller values for $\dot{Q}_{12}$ would have led to smaller or larger values of V_2, respectively. As mentioned earlier, compartments two and three do not represent specific physiological structures, but only summarize the circulation of the organs in such a way that a venous return with a sufficiently high concentration of COHb matching the observed arterial peaks is produced. The same parameter values for $\dot{Q}_{12}$ and V_2 were used for all subjects with the full model.

Insert Figure 2 About Here

In the full model (Figure 1), the modeling of the arms was done in sufficient detail to include compartments representing the small vessels (including capillaries draining the muscles of the forearm) and the antecubital vein, where the venous samples were taken. It is known that physical training of a particular muscle group increases the total number of capillaries supplying those muscles and that the increase in capillary volume increases the mean transit time of blood through the

muscle mass. The total blood volume of the muscle group is not increased by physical conditioning, so that the increase in capillary blood volume comes at the expense of the blood volume in the larger muscle veins (Rowell, 1986).

The model accounts for this phenomenon by constraining the volumes of compartments five, six, and eight to a fixed total of $0.0436 * V_B$ (See above). A fraction, f, of that total represents V_8, the large veins; the remainder is divided between compartments five and six. Clearly, depending on the level of physical training, the fraction f represents a continuous quantity that varies inversely with the degree of capillary development associated with training. The model is structured so that varying f does not affect the COHb concentrations of the arterial blood in compartment four, but does affect the concentration of compartment seven, representing the venous samples.

The parameters $\dot{Q}_{45}$ (blood flow from the arteries to small vessels of the arm) and f were also not identifiable in the sense that many pairs of values for $\dot{Q}_{45}$ and . produced similar results. In this paper $\dot{Q}_{45}$ was set at $.005\dot{Q}$. The values of f were then determined by comparing the observed venous peak to the peak COHb value predicted in compartment seven using the least squares criterion.

The medical records of each subject were examined for information about physical activities, particularly as related to the forearms. Most subjects completed a questionnaire describing their usual physical activity. However, some questionnaires had been completed as much as a year earlier than the experiment.

CHAPTER 3

RESULTS

CHAPTER 3

RESULTS

IL-282 Calibration.

The 101 COHb concentrations from the standardization sample ranged from 0.5% to 6.7% (IL-282 values). The regression equation fitted to correct the IL-282 values to the GC values was

$$COHb_{GC} = 0.99\,COHb_{CO\text{-}OX} + 0.146 \quad [6]$$

with correlation of 0.917. Considering the intercept and slope of the equation, it was decided to use uncorrected readings from the IL-282.

Pilot Study.

COHb in venous blood samples from pilot subjects did not begin to appear until after ca. 1 min following the onset of CO exposure. After this the COHb value increased and became stable 1 - 2 min following the cessation of exposure. It was reasoned that the time delay was due to the mixing of arterial blood into the venous return. The time delay would not be accounted for by the CFKE because the conditions for which it was derived assumed equilibration between all compartments. It was therefore decided to (a) test the CFKE only after such time that venous blood had reached maximum and only at such times that pulmonary measures were concurrently measured. The arterial blood was to be collected to explore its COHb concentration as a function of time, compared to venous blood.

Main Study.

Descriptive Results. Table 4 is a list of physical and hemodynamic measures for each subject. Figure 3 is a set of plots of arterial and venous COHb for each of the 15 subjects during exposure and the initial 10-13 min of recovery (total of 16 min per plot). The vertical dotted lines on each subject's plot mark the end of CO exposure. The highest arterial COHb was invariably observed near the end of exposure, ranging from 14.1% (Subject 109) to 20.5% (Subject 117). Venous peak COHb ranged from 11.9% (Subject 111) to 18.4 (Subject 107). COHb A-V diff began to increase immediately after exposure, reached a maximum somewhere between the middle and end of exposure and then began to decrease immediately after the end of exposure until the two values converged near the end of the plots. Maximum COHb A-V diff ranged from 2.3% (Subject 119) to 12.1 (Subject 117). Large differences also existed for the rate of convergence of arterial and venous COHb.

Figure 4 is a plot of the mean arterial and venous blood levels at each of 10 sampling times along with the mean CFKE prediction. The bars represent 90% confidence intervals. Errors of CFKE predictions of venous blood COHb levels (E_t) were computed for each of the 10 sample times for 15 subjects.

Insert Figures 3 and 4 and Tables 4 and 5 About Here

Significance Test. The Hotelling T^2 test was computed for the four times of measurement corresponding to the a priori hypothesis (the last four times). The

test was not statistically significant, $T^2 = 2.01$, $F \simeq 0.93$, $df = 2,13$, $p = 0.42$. Table 5 gives the mean and SD values for E_t along with the stepdown test results at each time. Errors of prediction, which were small and positive, were not statistically significantly at any of the four a times specified in the a priori hypothesis.

Exploratory Analyses. The early-exposure overprediction of venous COHb (see Figure 4) was apparently due to the time lag in the appearance of COHb in the venous compartment. The mean arterial blood COHb was higher than predicted and well overshot the mean venous blood by the end of exposure. The arterial blood mean COHb then began to decline and approach the mean venous value after exposure cessation.

To describe the overshoot of COHb in arterial blood, the error of estimation based on venous blood measures was calculated. This error was calculated by finding the peak arterial COHb value for individual subjects and subtracting from it the peak venous sample COHb for the same subject. This error is the smallest possible error which would have occurred if the venous blood had been sampled at peak and used as an estimate of the arterial blood level. There was a mean prediction error of 2.95% COHb, SD = 1.4, minimum = 1.1, maximum = 5.8.

The CFKE was derived under the assumption that the venous and arterial compartments were well equilibrated. Such equilibration was simulated by a weighted averaging of the venous and arterial blood COHb measures at each time point. Venous blood was weighted by 72% of blood volume while arterial blood was weighted by 28%. These values were calculated by apportioning capillary

(5% of total) and heart (7% of total) bloods equally into the venous and arterial compartments and by apportioning 75% of pulmonary blood (9% of total) to the arterial compartment (Guyton, 1986). The larger volume of pulmonary blood is venous but has already passed through the lungs and has therefore picked up more COHb and is added to the arterial compartment. Figure 5 is a plot of the weighted averaged arterial and venous blood measures and the predicted COHb via the CFKE. The bars represent the pooled 90% confidence intervals. The predicted values of COHb rarely fall outside the 90% confidence intervals for the weighted mean of the observed arterial and venous COHb at any time during either formation or the period shortly thereafter. The size of the prediction errors are small even when the are outside the confidence limits.

Insert Figure 5 About Here

Extended Model Results

The average CFKE prediction of COHb occurring four or five minutes after exposure ended corresponded very well with the average COHb measured at that time. However, individual predictions were in error by as much as 2.1% COHb. The fact that the averaged measured COHb values agreed well with the averaged CFKE predicted values suggests that the individual discrepancies were likely to be due to measurement error in some of the primary model parameters (Table 2). A 10% error in measurement of blood volume may, for example, account for an error of over 1% COHb. Whatever the source, the error of the CFKE prediction of COHb

for each subject is incorporated in the expanded model as well. Because the present model was not intended to improve the modeling of the uptake of CO, but only to provide an account of the distribution of COHb between arterial and venous blood during a period of rapid CO uptake, the data were adjusted to compensate for these errors.

In particular, the arterial and venous peak values were adjusted so that the difference between the observed and the adjusted peak values was the same as the difference between the observed and CFKE-predicted COHb values at minute 10 (i.e. after equilibration). Thus Table 6, for example, shows that the CFKE-predicted COHb value for subject 113 at 10 min (4-5 min post exposure) is 0.9% COHb less than was measured. The expanded model, incorporating this same error, therefore also underpredicts by 0.9% COHb. To compensate for this known error, 0.9% COHb was subtracted from both arterial and venous peak observations for subject 113, as shown in Table 6. The observed differences between arterial and venous COHb remain unaltered by this adjustment. These calculations were repeated for every subject (Table 6). The adjusted peak values were used for the fitting and predictions of the model.

Insert Table 6 about here.

Variability in the data is shown by the maximum difference between COHb values in simultaneous arterial and venous samples measured over all sampling times. In Table 7, the subjects are arranged according to decreasing observed

maximum A-V diff in COHb regardless of time (although this was usually at min 4 or 5 of the procedure). The subjects were grouped according to similar maximum A-V diff. In group I, examination of the medical records showed that subject 117 was an endurance athlete in training and was eliminated from further analysis because he would be likely to have atypical pulmonary and cardiovascular systems. Since only one member remained, the first group was not modeled.

Insert Table 7 About Here

The subjects 108 (group II), 107 (group III) and 119 (group IV) were chosen to estimate the parameter V_2 while taking into account the range of observed maximum A-V diff in COHb. Within each group, the subject chosen was the one with the best CFKE prediction for COHb levels 4 or 5 minutes after exposure ceased and therefore required the least adjustment. The estimated value $V_2 = 0.11V_B$ was then used in the complete model for all three groups.

The same value for the parameter f (inversely related to the degree of capillary development in the muscles of the forearm) was used for all members within each of the remaining three groups of subjects. Using subjects 108 and 112, the value of f was estimated to be 0.75 for group II; the corresponding sizes of the compartments were $V_5 = V_6 = 0.0055 * V_B$ and $V_8 = 0.0326 * V_B$. Using subjects 107 and 120 the value of f for group III was estimated to be 0.84 with corresponding compartment sizes of $V_5 = V_6 = 0.0035 * V_B$ and $V_8 = 0.0366 * V_B$. Subject 119 was used to estimate the value of f at 0.93 for group IV; the corresponding compartment sizes were $V_5 = V_6 = 0.0015 * V_B$ and $V_8 = 0.0406 * V_B$.

A graphical summary of the experimental results in comparison with predictions of both the model under discussion and the CFKE for the three groups of subject analyzed is shown in Figures 6 and 7. The parameters of the CFKE have the same values as the corresponding parameters in the expanded model.

Insert Figures 6 and 7 About Here

Figure 6 shows that the mean CFKE predictions overestimated the means of the measured values of the venous samples during the entire exposure period; however, the equation quickly became an excellent predictor after the exposure ended. Figure 7 indicates that the mean CFKE predictions underestimated the means of the measured values of the arterial samples during the exposure period and several minutes thereafter. The relative position of the values predicted by the two models corroborates the idea that improved modeling of regional circulation patterns is important to prediction during rapid uptake of CO.

The mean venous predictions made by the present model provided a good fit to the means of the venous observations, falling within one standard error at every point (Figure 6). The means of the arterial predictions were also good during the uptake of CO but decreased too quickly just after exposure ended, perhaps because the model did not take into account the continued uptake of CO during the period of CO washout from the alveolar air. As expected, the venous and arterial predictions converged to the CFKE-predicted values a minute or two after the exposures ended.

The highest mean prediction of the arterial values was within one standard error of the highest mean arterial measured values, and both occurred in the fifth minute (Figure 7). Note that both the arterial measured values and predictions made by the expanded model "overshot" the eventual equilibrium values, whereas the venous values approached the equilibrium values from below. Tikuisis et al. (1992) noted a similar "overshoot" in their measurements of arterialized venous blood. They hypothesized that the overshoot was the result of differing circulation times throughout the body.

Individual arterial peaks did not all occur on the fifth minute but come just after the CO exposure ended. This occurred as early as the third minute (subject 117) and as late as the seventh minute (subject 110). In all but one case, the predicted arterial peak and the observed peak occurred in the same minute (See Table 7).

In Table 7 the individual measured arterial and venous peak values (adjusted for the error in CO uptake) are compared with the corresponding predictions made by the expanded model presented in this paper. The arterial peak predictions were good, never differing by more than 0.7% COHb from the observations. The minute at which each peak occurred is given in parentheses in Table 7. Again, the time of arterial peak occurrence was accurately predicted, differing only once by one minute (subject 112).

The venous predictions were reasonably good, though somewhat less reliable. The venous peak value predictions differed by as much as 1% COHb for

only one subject (subject 120). The times at which the venous peaks occurred were not predicted as well. In group II the time of venous peak occurrence was predicted too early for three subjects. For group III the peak was predicted once too early and once too late.

These results are consistent with the hypothesis on which the model was based. If the venous COHb levels were affected by individual differences in regional circulation, then they would be more difficult to predict by any model. Modeling a capillary net using two (instantly mixed) compartments is a simplification that would be more likely to cause errors in the group assumed to have the greatest capillary development. It is also reasonable that these errors would result in predicting faster mixing, thereby producing an earlier peak.

The medical records provide some support for the role of the regional capillary compartment. In the final column of Table 7, the number of hours per week each subject reported playing tennis, racquetball, or weight lifting are shown. The average number of hours clearly decreases from group II to group IV. The correlation between the final column of Table 7 and the maximum A-V diff in COHb was 0.71. Note that this correlation did not include subjects 117 and 115 and that the average time was used for subjects with two reported training times. Interestingly, the correlation between the maximum A-V diff and general fitness as measured by the Bruce protocol was only 0.25.

CHAPTER 4

DISCUSSION

CHAPTER 4

DISCUSSION

When the prediction for venous blood COHb values measured ca. two min after cessation of transient exposure is made with the nonlinear CFKE, the accuracy is remarkably good (see Figure 4 and Table 5). This seems to disagree with the data provided graphically by Tikuisis et al. (1987a,b) for the first two of a series of transient exposures. In the present experiment, all parameters of the CFKE, except the Haldane affinity ratio, were measured on the individual subject. This was not true for the experiment by Tikuisis et al. (1987a). It is therefore likely that the values which they did not measure were slightly incorrect. Such possible parameter error could have had more effect early in the exposure than later (McCartney, 1990) and thus the COHb resulting from the entire series of CO transients was correctly predicted while predictions for the very early part of the exposure were not. For transient exposures, accurate prediction of the venous blood COHb measured ca. two min after CO exposure cessation, therefore, may depend more upon accurate estimates of the CFKE parameters than for longer exposures.

The accuracy of the nonlinear CFKE for predicting either venous or arterial blood during early phases of CO exposure (while COHb is being rapidly formed) is poor (see Figure 4). This appears to be due to the fact that arterial and venous blood COHb had not equilibrated until after exposure cessation. If such equilibration is simulated by averaging the arterial and venous blood COHb measures, however, then the CFKE would appear to predict well (see Figure 5). It therefore

appears that the rather large inaccuracy of prediction by the CFKE during CO transient exposure is due, in large measure, to the arterial- venous differences in COHb appearance rate.

It is important to note that the arterial blood rises to a considerably higher value of COHb during exposure than would be indicated by the usual procedure of sampling venous blood. Peak arterial level would have been underestimated by an average of almost 3% COHb and in one subject the arterial COHb would have been underestimated by 5.8% COHb. At the COHb level involved, this was almost a 30% underestimate. Such organs as are exposed to fresh arterial blood, e.g. brain and heart, receive a short burst of a larger amount of COHb than would be expected from either the CFKE prediction or the venous blood observation. This difference becomes more extreme for short CO exposure to high CO concentrations. The consequences of the greater-than-expected COHb in the blood supplied to body organs is dependent on the amount of under estimation and the absolute COHb levels.

The underestimation of arterial blood COHb by peripheral venous sampling is probably more extreme than indicated in the present data. One-sec sampling of aortic blood in dogs artificially ventilated with 1.5 - 1.8% CO showed that transient COHb can, for several seconds, exceed 60% when superimposed on a baseline COHb of 20%, following a single breath of CO (Abboud et al., 1974). The sampling procedure used in the present protocol was not designed to detect such possible within-breath COHb transients. The figure in the paper does not

seem to specify the exact F_ICO of the single breath, but the range used was 1.5-7.5%.

Concern arose as to the possibility that subjects in the present study might have experienced levels of COHb in aortic blood approaching those reported for dogs by Abboud et al. (1974). Apart from the different experimental conditions, the minimum of their range is more than twice the 0.7% F_ICO used in the present experiment. Furthermore, even if F_ACO at the end of an inspiration were estimated as equal to F_ICO, and assuming V_A as $\approx$ 3600 ml [STPD], total available alveolar CO would be $\approx$ 25 ml [STPD]. Considering that $\dot{Q}_C$ is $\approx$ 100 ml/sec (cardiac output of 6 l/min) and that CO capacity of the blood is 20 ml/100 ml, a one-sec uptake of 9 ml CO, i.e., about 36% of the available CO would be required to achieve a one-sec transient elevation of arterial COHb from a worst-case "baseline" of 20% to a level of 60%. Even with a resting D_LCO as high as 1 ml/sec/mm Hg, and starting with a P_ACO of $\leq$ 5 mm Hg (0.7% x [760-47]), CO uptake should be $\leq$ 5 ml/sec; therefore, not even at the end of 5 min exposure, should the resulting arterial COHb transient exceed 45% (20% "baseline" + 25%). We therefore do not believe that the present subjects developed arterial COHb transients approaching 60%. The size of such transients should be investigated in humans because under certain adverse conditions, and especially with high F_ICO, COHb transients of such magnitude are of functional importance, particularly in military settings.

Before developing the extended CFKE model, several simple variants of Fick's law models with series compartments were tried. Based on observed rates

of CO uptake and previously-measured resting cardiac output, the predicted A-V diff from such models was about 3% COHb during uptake. None of the two-compartment series models could account for the much larger differences which we observed, unless physiologically unreasonable circulation times were used. More importantly, the series models could not account for the large individual differences which were observed.

Therefore, a more complicated model was constructed, involving several compartments whose characteristics were determined partly from measurements on the subjects and partly from the literature. The present more elaborate model of the circulatory system accurately predicted the individual peak or maximum values of arterial COHb during CO uptake. All but two of the parameters used by the model were measured individually or derived from the literature. The values of those two parameters were estimated by fitting the model to the observed (adjusted) venous and arterial peaks of five of the 13 subjects. The individual maximum venous and arterial COHb values of the remaining eight subjects were accurately predicted using the previously estimated parameters appropriate to the subject's "group placement" according to observed maximum COHb A-V diff and the subject's post-equilibration COHb and its COHb prediction. Although measuring the A-V diff would require taking arterial samples, a good correlation was found between the size of the maximum A-V diff and the history of exercise activities leading to forearm development.

The model presented in this paper could be further extended to investigate specific questions which have not been addressed. Thus, a more detailed model of the CO concentration in the lungs might be added to account for continued CO uptake during the early washout period. Shunted blood, bypassing the lungs and mixing with the O_2-enriched blood leaving the lungs, could be modeled by allowing a fraction of the blood leaving compartment nine (the heart on the way to the lungs) to enter blood flow leaving the "lung" (compartment one) directly.

Conclusions.

(1) When nonlinear CFKE parameters are measured on the individual subject and prediction of venous COHb is restricted to ca. two min after cessation of exposure to high CO concentrations for short periods, the predictions are accurate.

(2) Predictions are not accurate for either venous or arterial blood during the early phases of COHb formation during exposure to high CO concentrations. Venous levels are overpredicted while arterial are underpredicted.

(3) The inaccurate predictions and large variation across subjects during COHb formation are primarily due to delay in the equilibration of arterial with venous blood.

(4) The arterial blood during exposure to transients of high concentration CO has considerably higher level of COHb than is predicted by the CFKE or would be estimated from a venous sample.

(5) Transients of COHb in aortic blood, time-locked to respiration, may exceed the peripheral arterial blood by substantial amounts and could become clinically

important.

(6) The more elaborate model of the circulatory system presented in the present report accurately predicted the individual peak or maximum values of arterial COHb during CO uptake.

(7) The model presented in this paper could be further extended to investigate specific questions which have not been addressed, e.g., a more detailed model of the CO concentration in the lungs might be added to account for continued CO uptake during the early washout period and shunted blood, bypassing the lungs and mixing with the O_2-enriched blood leaving the lungs.

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TABLE 1

EQUATIONS FOR THE FULL MODEL (FIGURE 1)

1. $$V_1\frac{dy_1}{dt}=\dot{Q}(y_9-y_2)+\frac{100\,(P_ICO)\,(D_LCO)\,(\dot{V}_A)}{Hb[\dot{V}_A+(P_L)\,(D_LCO)]}-\frac{100\,(\overline{P_CO_2})\,(D_LCO)\,(\dot{V}_A)\,(y_1)}{M[\dot{V}_A+(P_L)\,(D_LCO)]\,Hb(100-y_1)}$$

2. $$V_2\frac{dy_2}{dt}=.60\dot{Q}(y_1-y_2)$$

3. $$V_3\frac{dy_3}{dt}=.35\dot{Q}(y_1-y_3)$$

4. $$V_4\frac{dy_4}{dt}=.05\dot{Q}(y_1-y_4)$$

5. $$V_5\frac{dy_5}{dt}=.005\dot{Q}(y_4-y_5)$$

6. $$V_6\frac{dy_6}{dt}=.005\dot{Q}(y_5-y_6)$$

7. $$V_7\frac{dy_7}{dt}=.005\dot{Q}(y_6-y_7)$$

8. $$V_8\frac{dy_8}{dt}=.045\dot{Q}(y_4)+.005\dot{Q}(y_7)-.05\dot{Q}(y_8)$$

9. $$V_9\frac{dy_9}{dt}=.60\dot{Q}(y_2)+.35\dot{Q}(y_3)+.05\dot{Q}(y_8)-\dot{Q}(y_9)$$

The solutions for y_i refer to the COHb predicted for the ith compartment.

TABLE 2

SOURCE OF PRIMARY MODEL PARAMETER[1] VALUES

PARAMETER	STATUS	REFERENCE
D_LCO	measured	This study
Hb	measured	This study
M	(literature)	Rowell, 1986
$\overline{P_CO_2}$	measured	this study
P_ICO	measured	This study
P_L	measured	
$\dot{V}_A$	computed from other observations	This study
V_B	calculated from measured red cell volume and hematocrit	This study

[1]See Table of Abbreviations for definition of parameter abbreviations.

TABLE 3

DEFINITION OF BLOOD FLOW AND VOLUME PARAMETERS[a] FOR MODEL EXTENSION

TERM	DEFINITION	STATUS	REFERENCE
$\dot{Q}$	cardiac output	measured	Middleman, 1972
$\dot{Q}_{12}$	from heart to quickly perfused compartment	$0.6\dot{Q}$ (arbitrary - see text)	
$\dot{Q}_{14}$	from heart to arteries of the arm	$0.05\dot{Q}$ (from literature)	Middleman, 1972
$\dot{Q}_{45}$	from the arteries to small arm vessels	$0.005\dot{Q}$ (arbitrary -see text)	
V_1	pulmonary capillaries & veins and 1/2 heart	$0.1V_B$ (see Method)	
V_2	quickly perfused compartment	$0.11V_B$ (see Method)	
V_3	slowly perfused compartment	$0.652V_B$ (see Method)	
V_4	major arteries in arms	$0.0069V_B$ (see Method)	
V_5, V_6	small vessels in arms	[b]varies with group (see text)	
V_7	intermediate veins in arms	$0.0025V_B$ (arbitrary - see Method)	
V_8	large veins in arms	[b]varies with group (see text)	
V_9	1/2 heart and pulmonary arteries	$0.085V_B$ (see Method)	

[a]All $\dot{Q}$ parameters are blood flows in ml/min.
All V parameters are blood volumes in ml.

[b]note that $V_5 + V_6 + V_8$ is considered to be a constant value, $0.0435V_B$.

TABLE 4

LIST OF PHYSICAL AND HEMODYNAMIC

MEASUREMENTS ON EACH SUBJECT

SUBJ ID	AGE (YR)	WEIGHT (KG)	HEIGHT (CM)	HEMO-GLOBIN (g/dl)	RBC (mil/ cu mm)	HEMATO-CRIT (%)	PRED. BLOOD VOL (l)	(RBC) BLOOD VOL (l)	PRED. CARDIAC OUTPUT (l/min)	OBS. CARDIAC OUTPUT (l/min)
106	31.1	81.8	180.3	14.4	1.6	41	5.4	4.1	5.8	6.4
107	21.1	74.1	185.4	16.3	1.9	44	5.3	4.5	6.2	6.3
108	24.8	60.5	172.7	15.8	1.6	41	4.4	4.0	6.0	7.5
109	30.1	82.7	185.4	15.3	2.3	47	5.6	5.2	6.0	7.3
110	31.3	75.0	177.8	15.9	1.9	42	5.1	4.8	5.9	6.1
111	21.7	81.8	182.9	15.5	2.7	42	5.5	6.6	6.2	7.1
112	23.3	100.0	191.8	16.2	2.1	42	6.4	5.3	6.2	6.7
113	33.7	68.2	177.8	15.0	1.8	40	4.9	4.7	5.8	6.7
114	36.0	84.1	188.0	16.4	2.4	38	5.7	6.5	6.7	6.8
115	26.9	75.0	180.3	15.1	2.1	43	5.2	5.1	6.0	6.6
116	19.3	63.6	170.2	15.5	1.5	38	4.5	4.2	6.0	6.2
117	35.4	65.9	179.1	17.1	1.9	42	4.8	4.8	5.8	5.1
118	21.0	52.7	161.0	15.8	1.4	43	3.8	3.5	6.3	5.1
119	18.7	89.0	185.0	15.6	2.5	38	5.8	6.9	6.2	6.9
120	23.9	72.7	179.1	14.5	1.5	36	5.1	4.4	6.1	5.8
MEAN	26.5	76.0	180.0	15.5	2.0	41	5.2	5.0	6.1	6.5

TABLE 5

MEANS, STANDARD DEVIATIONS AND STEPDOWN

TESTS FOR E_t^* FOR MINUTES 7-10

TIME	MEAN	SD	n	t	p
7	0.19	1.66	15	0.45	>0.5
8	0.09	1.39	15	0.26	0.8
9	0.00	1.30	15	0.01	>0.8
10	0.03	1.25	14	0.08	>0.8

*E_t is the error of prediction of the CFKE in %COHb

TABLE 6

INDIVIDUAL POST-EXPOSURE COHb (%) VALUES

SUBJ #	OBSERVED AV. COHb AT MIN 10	CFKE PREDIC-TION	OBSERVED ARTERIAL PEAK	ADJUSTED ARTERIAL PEAK	OBSERVED VENOUS PEAK	ADJUSTED VENOUS PEAK
117	14.8	15.2	20.5	20.9	15.5	15.9
115	12.3	12.3	16.6	16.6	12.4	12.4
113	16.2	15.3	18.4	17.5	16.2	15.3
108	15.0	15.7	17.9	17.9	14.9	15.6
116	15.6	14.6	18.5	17.5	15.5	14.5
109	12.4	14.0	15.0	16.6	12.1	13.7
118	12.5	13.8	15.0	16.3	12.4	13.7
112	13.5	14.3	15.8	16.6	14.2	15.0
111	14.2	12.0	16.2	14.0	15.4	13.2
120	14.9	14.5	17.7	17.3	14.7	14.3
107	17.0	16.6	19.9	19.5	18.4	18.0
106	16.2	16.9	19.3	20.0	17.4	18.1
110	18.1	17.4	19.6	18.9	18.8	18.1
114	13.5	12.1	16.9	15.5	15.2	13.8
119	12.6	12.4	14.1	13.9	13.8	13.6

TABLE 7

INDIVIDUAL OBSERVATIONS AND MODEL PREDICTIONS

SUBJ #	OBSERVED MAXIMUM A-V COHb DIFFERENCE	ADJUSTED OBSERVED ARTERIAL PEAK	PREDICTED ARTERIAL PEAK	ADJUSTED OBSERVED VENOUS PEAK	PREDICTED VENOUS PEAK	MIN PER WK IN TRAIN-ING
GROUP I						
117	12.1					
115	11.1					
GROUP II						
113	7.8	17.5 (5)[a]	17.6 (5)	15.3 (9)	15.6 (7)	0-120[b]
108[c,d]	7.4	17.9 (5)	17.5 (5)	15.6 (9)	16.1 (7)	360
116	7.1	17.5 (5)	17.2 (5)	14.5 (10)	14.9 (7)	450
109	6.6	16.6 (5)	16.3 (5)	13.7 (7-9)	14.4 (7)	240
118	6.6	16.3 (5)	16.5 (5)	13.7 (7-8)	14.2 (7)	260
112[d]	6.5	16.6 (4)	15.9 (5)	15.9 (7-8)	14.6 (7)	120-240[b]
GROUP III						
111	5.3	14.0 (4)	14.3 (4)	13.2 (5-6)	12.8 (6)	225
120[e]	5.3	17.3 (5)	17.8 (5)	14.3 (8-9)	15.3 (6)	120
107[c,e]	4.3	19.5 (5)	19.0 (5)	18.0 (5)	17.3 (6)	0
106	4.1	20.0 (4)	20.3 (4)	18.1 (4-5)	18.4 (5)	180-90[b]
110	4.0	18.9 (7)	19.0 (7)	18.1 (8-9)	18.0 (8)	0
GROUP IV						
114	2.9	15.5 (4)	15.1 (4)	13.8 (5)	13.7 (5)	0
119[c,f]	2.3	13.9 (5)	14.6 (5)	13.6 (6)	13.7 (6)	0

[a]The number in the parentheses refers to the minute the peak occurred.
[b]Two numbers are given when the questionnaire was filled out twice.
[c]Subjects used to estimate V2.
[d]Subjects used to estimate f for group II.
[e]Subjects used to estimate f for group III.
[f]Subject used to estimate f for group IV.

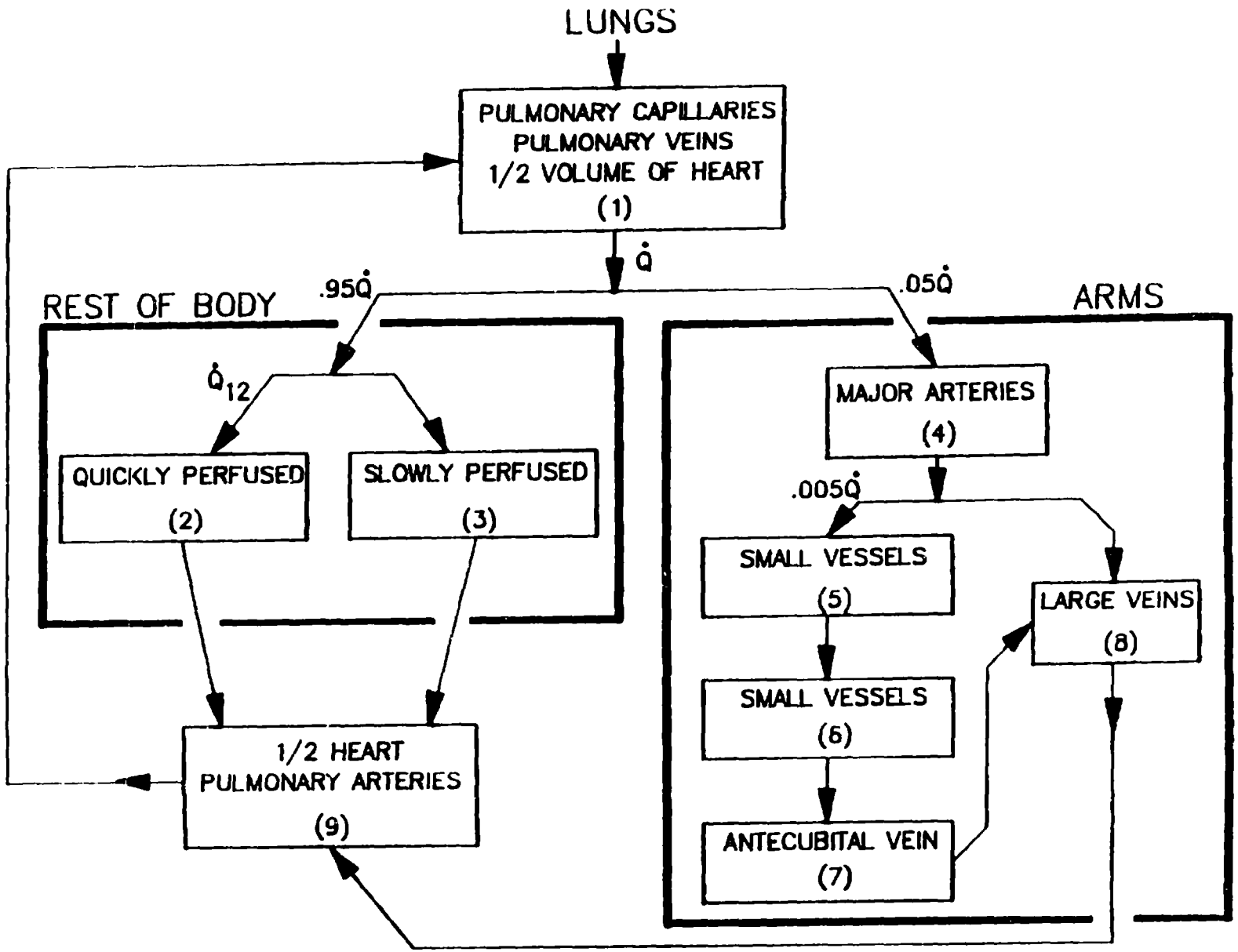

Figure 1. The structure of the full expanded COHb prediction model. The number of each compartment is given in parentheses.

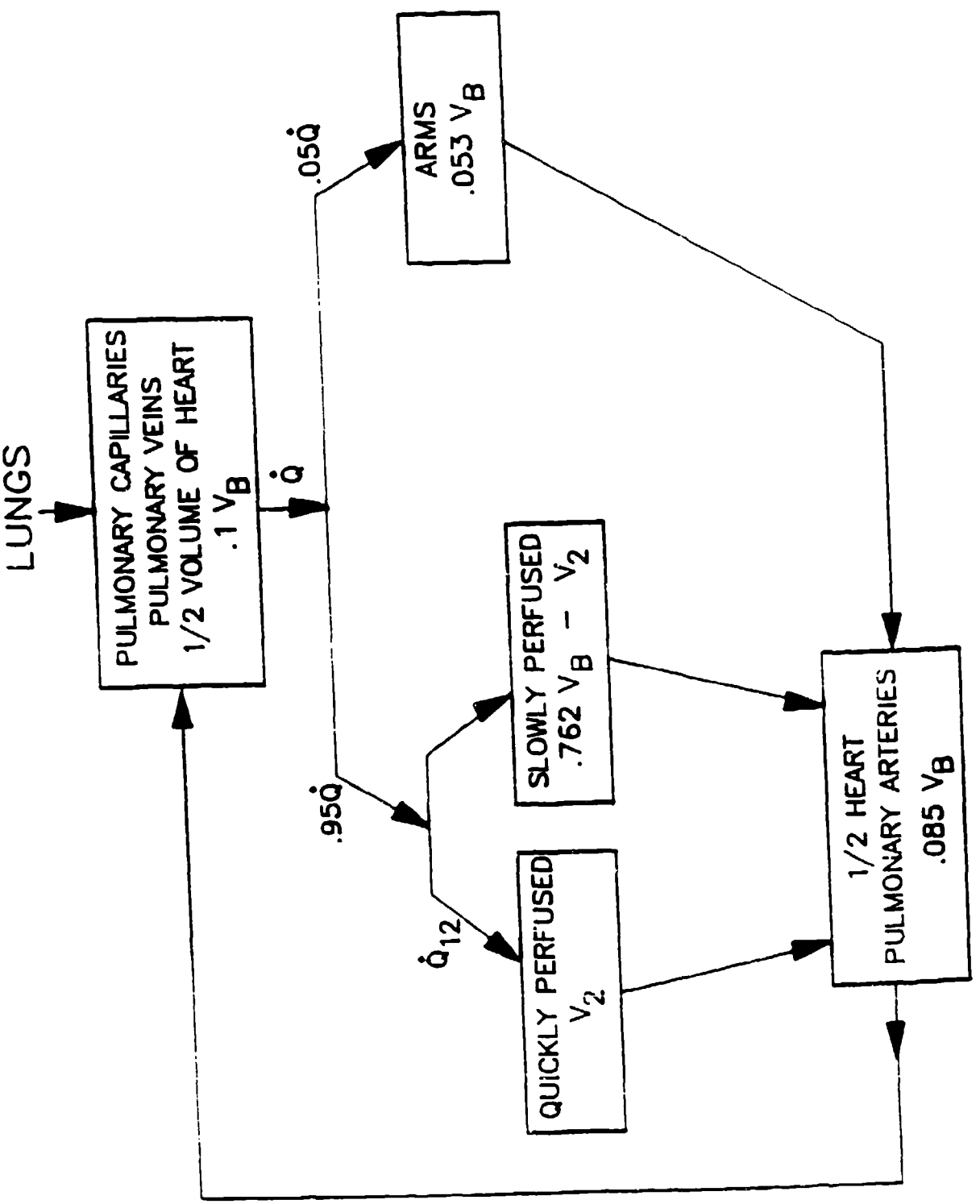

Figure 2. The structure of the simplified version of the expanded COHb predic tion model.

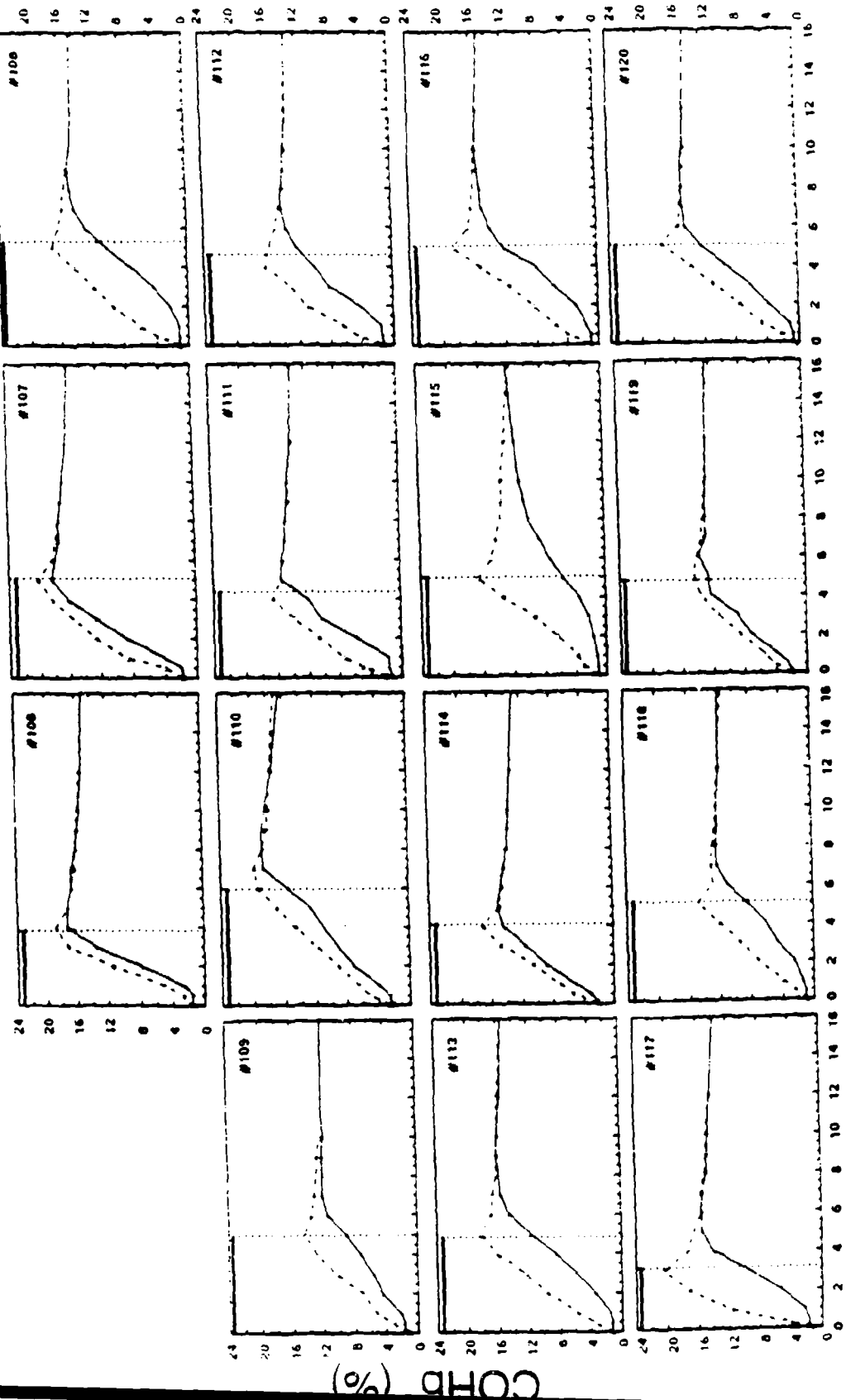

Figure 3. Plots of venous (solid line) and arterial (dashed line) COHb for each subject in the study. The dark horizontal bar and the vertical dotted lines indicate the bag-breathing (exposure) period for each subject.

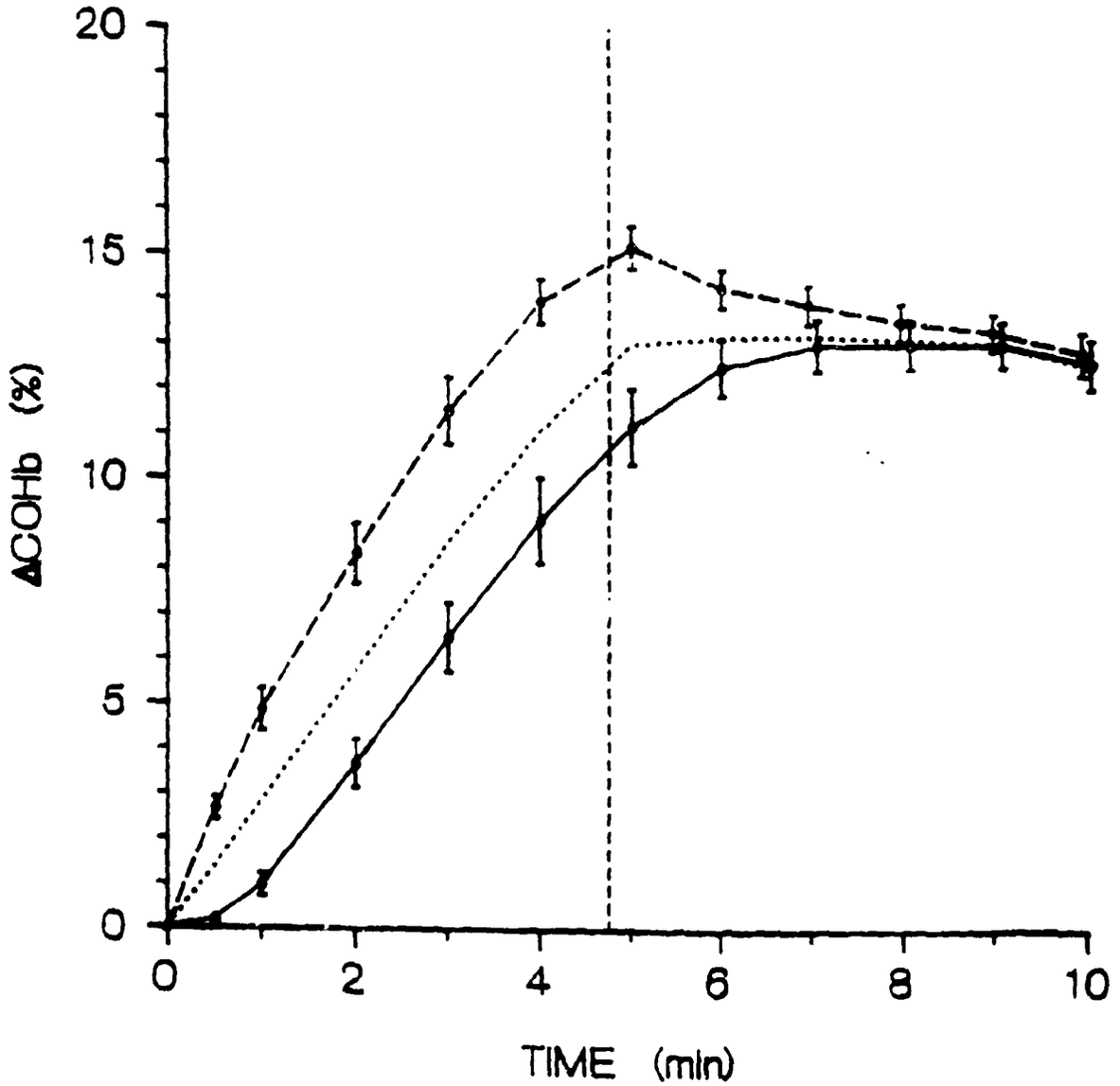

Figure 4. Mean *and* ± one SE of observed venous, arterial and CFKE-predicted ΔCOHb. Dashed line = arterial, solid line = venous, dotted line = CFKE prediction. The vertical dashed line indicates the mean end of exposure.

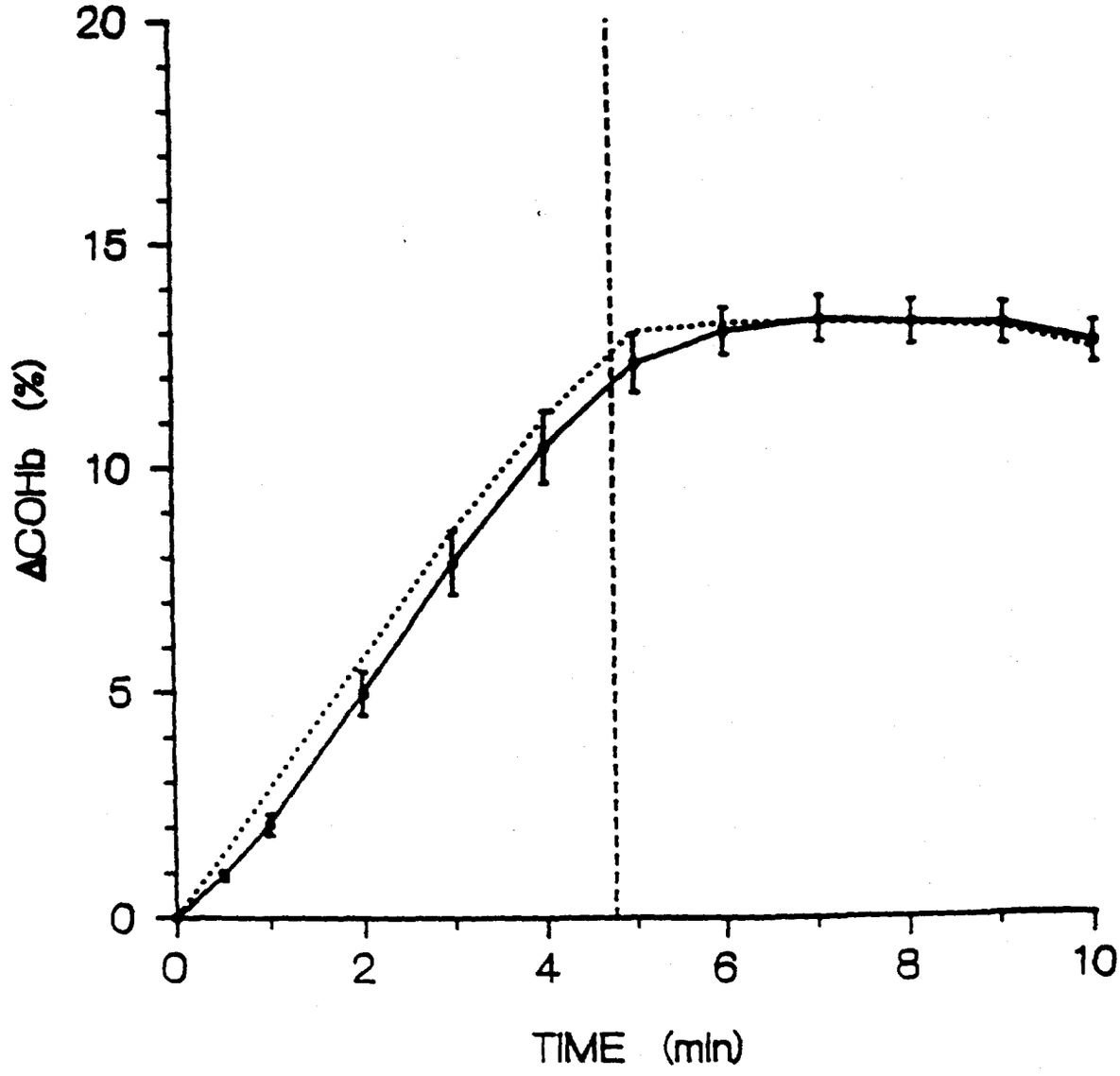

Figure 5. Comparison of mean predictions of the CFKE with the means of the weighted average of the observed arterial and venous ΔCOHb. Venous blood was weighted by 72% of blood volume while arterial blood was weighted by 28% (see Method). The bars represent ± one SE for the weighted means. Solid line = observed weighted average, dotted line = mean of CFKE predictions. The vertical dashed line indicates the mean end of exposure.

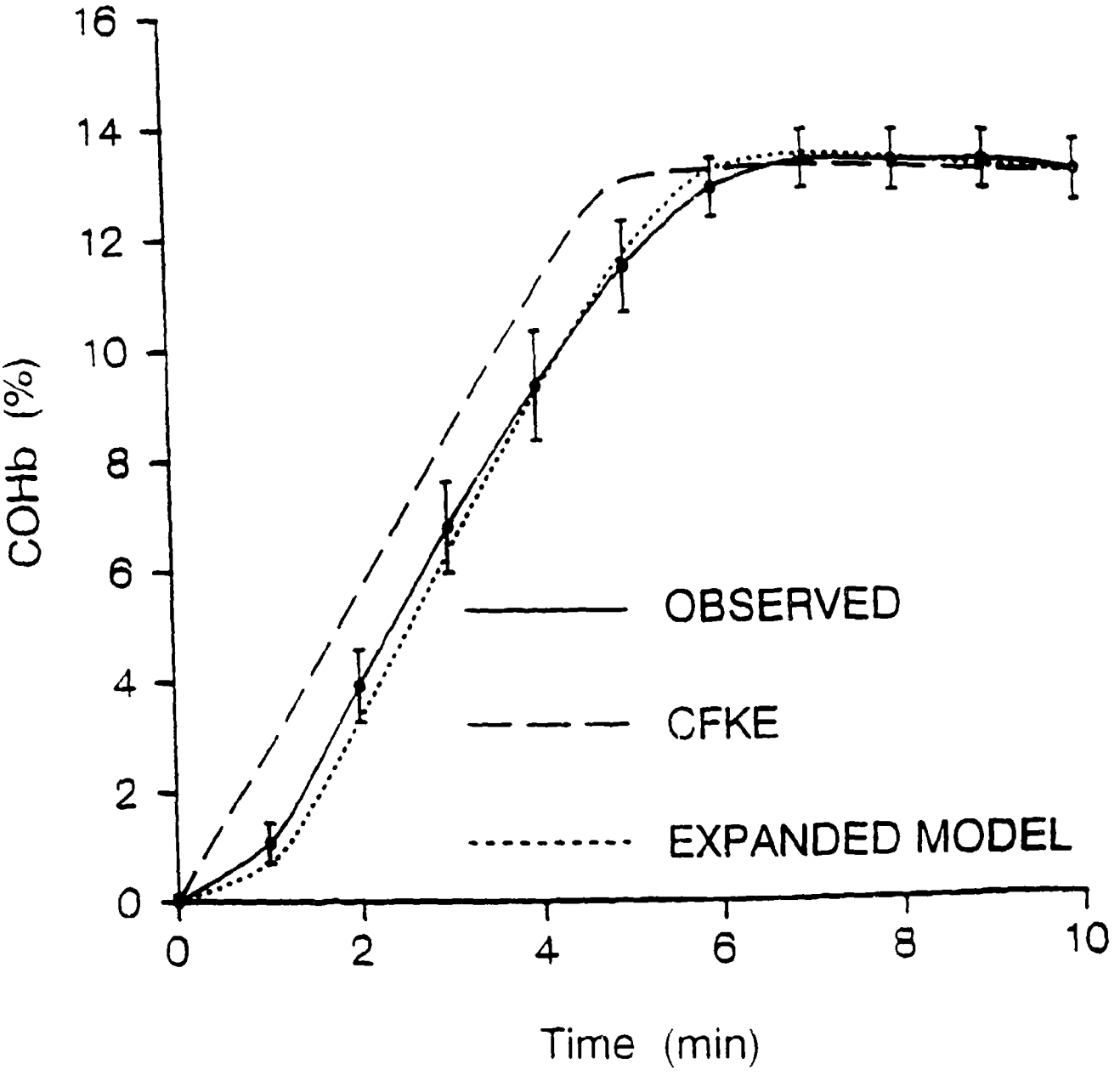

Figure 6. Venous group mean observations, CFKE predictions and expanded modal predictions of COHb for the 10-min observation period. Note that all COHb values represent increase in COHb over pre-exposure values.

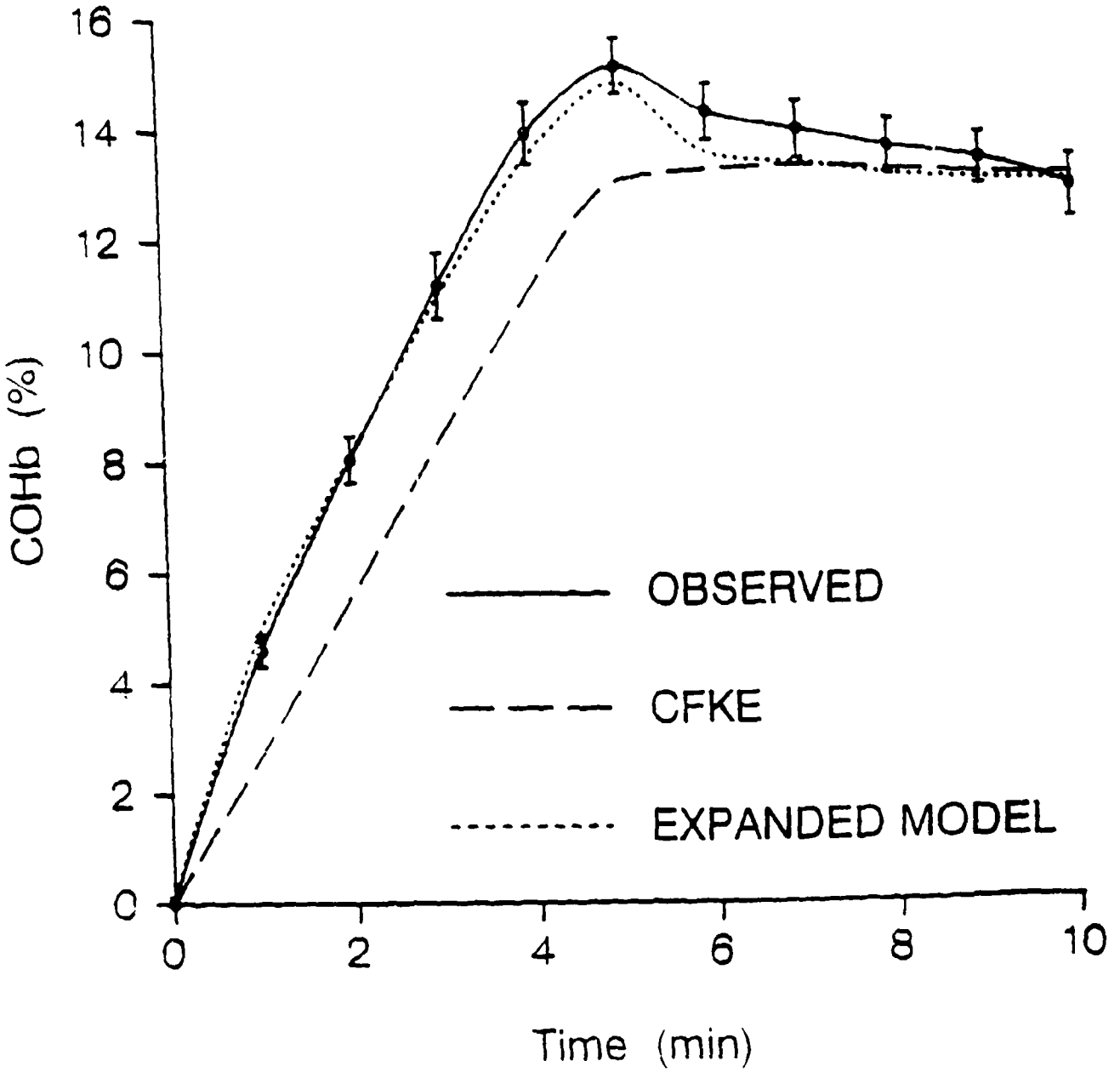

Figure 7. Arterial group mean observations, CFKE predictions and expanded model predictions of COHb for the 10-min observation period. Note that all COHb values represent increase in COHb over pre-exposure values.

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