APPENDIX: Description of the mathematical model

Except as noted below, all of the equations of the model are those that were presented previously (4). Changes to the previous model were motivated by the need to represent the effects of both moderate exercise and chronic anemia in order to predict the consequences of CO exposures on women in underdeveloped countries.

Exercise is represented in the model by an increase in the metabolic rate of oxygen consumption (MRO_2) in the muscle tissue compartments. MRO_2 in non-muscle tissues is assumed to remain at its resting level during exercise. With normal [Hb] and no CO present, blood flow to muscle is a function of muscle MRO_2. This function was determined (Figure A1) by fitting a quadratic curve to data from several studies on humans (14, 17, 18, 20) and one on rats (1).

In the model, minute ventilation at rest is either set to the measured value (if reported in the study being simulated) or is set to a value that yields a resting PaO_2 of ~100 Torr. Minute ventilation during exercise is calculated by multiplying resting ventilation by the metabolic rate ratio (MRR)—i. e., the ratio of whole body MRO_2 in exercise to that at rest. Resting cardiac output for normal subjects is calculated from a regression relationship on body weight and gender (reference 8, Eq. C.3). The change in cardiac output due to exercise is calculated using a linear approximation to the relationship presented in a previous model (reference 8, Eq. C.4). Cardiac output also increases in response to an increase in %HbCO (reference 8, Auxiliary Equations following Eq. B.2).

Once minute ventilation (V_E) is calculated, tidal volume (V_T) and dead space volume (V_D) are calculated from additional regression relationships for non-anemic subjects. For male subjects, data from Neder, *et al.*, (15) and Hey, *et al.*, (10) were combined and fit to

a straight line to yield the following equation: $\dot{V}_E = 28.0\ V_T - 10.4$. Similarly fitting data for females from Neder (15) gives $\dot{V}_E = 33.3\ V_T - 7.6$. Both equations are easily solved for V_T. For anemic subjects we use data from Sproule (19) to obtain: $\dot{V}_E = 51.15\ V_T - 23.13$. To estimate V_D we combined data from several studies of normal human subjects (6, 9, 12, 16, 19) and fit these data using a maximum likelihood method with a curvilinear function. The result is (Figure A2):

$$V_D = 0.05 + 0.3892 * 6.7691^{-2.3679} / \left(6.7691^{-2.3679} + V_T^{-2.3679}\right)$$

For anemic subjects, the only available data are from Sproule (19); a linear fit to these data provides the relationship $V_D = 0.2385 * V_T + 0.1587$.

When a specific anemic subject from the literature is simulated, measured cardiac output of that subject is used if it is available. Otherwise, on average in anemic subjects, resting cardiac output exhibits an increasing trend as [Hb] decreases, albeit with considerable between-subject variability. We combined data from Woodson et al., (21), Brannon et al., (3), and Duke and Abelmann (7) and estimated the average trend in cardiac output (Q_{dot}) as a power function of [Hb] using a maximum likelihood (MLE) method. The MLE fit for resting cardiac output in ml/min/kg (Figure A3) is

$$Q_{dot} = 51.40\left([Hb] - 0.0425\right)^{-0.2448}$$

In all cases, when Q_{dot} increases above its resting level (i. e., due to exercise, anemia, or CO), the increased flow is divided between muscle and nonmuscle tissues in proportion to their relative metabolic rates of O_2 consumption.

The shape of the oxygen dissociation curve changes in anemia, principally through an effect on 2,3-DPG concentration. To incorporate these changes, we estimated linear fits to data for P_{50} and Hill exponent, n, as functions of [Hb] (2).

Pulmonary shunt fraction (SF) decreases in exercise (5). Without this change in the model, it was necessary to increase ventilation more than linearly with whole-body MRO_2 in order to prevent a decrease in PaO_2. By trial and error we found that the following relationships between SF and fractional increase in Q_{dot} (dQ) from resting minimized changes in PaO_2 in exercise:

for normal subjects, $SF = 0.05 - 0.02 * dQ$

for anemic subjects, $SF = 0.045 - 0.01 * dQ$

All of the above effects of anemia were calculated in the model as functions of the deviation of [Hb] from a normal value. Thus, if in a simulation run the specified [Hb] value was normal, then all of the above effects due to anemia had magnitudes of zero.

In previous versions of our model it was assumed that CO in blood compartments binds to Hb first, then O_2 binds to Hb in an amount which satisfies the Haldane equation. For moderate exercise in anemia, the O_2 content of venous compartments becomes sufficiently low that this approximation yields errors in PO_2. Therefore, for venous compartments a different approach was utilized. The total O_2 and CO in a compartment are determined first from flux equations. Then PO_2 and HbO_2 are calculated so that dissolved O_2 plus HbO_2 equal the total O_2 content. Finally, a gradient search method is used to determine the COHb and Pco which yield an equivalent total pressure ($Peq = PO_2 + M_H * Pco$) and total bound Hb that satisfy the O_2 dissociation curve (whose parameters change with COHb). M_H

is the Haldane coefficient for blood. As noted above, dissolved CO content is ignored in all blood compartments.

The predicted effects of the combination of exercise with anemia were evaluated by performing two sets of simulations at various levels of exercise using the same subject-specific parameters (from subject LB of Brannon (3)) except for [Hb], which was set to 9.9 g/dl in anemia and 13 g/dl for the normal case. Note that some parameters and variables other than [Hb] would be different in the two cases because all of the effects ascribed to anemia would have magnitudes of zero when [Hb] equals 13. Furthermore, in this case the model calculate and removes the effects of anemia on cardiac output and ventilation since those effects were included in the experimental measurements. Figure A4 demonstrates that anemia generally results in lower PO_2 levels at any MRO_2, but the qualitative effects of changes in MRO_2 are rather similar at both [Hb] levels.

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Figure Legends

Figure A1. Variation of muscle blood flow (Qm) with muscle rate of oxygen consumption (VmO2). Squares: data from several experimental studies, as described in the text. Line: plot of the least squares regression fit to the data points given by

$$Q_m = -0.1246(V_mO_2)^2 + 7.596(V_mO_2) + 1.8631.$$

Figure A2. Variation of physiological dead space volume (VD) with tidal volume (VT) in normal subjects. Asterisks: data from multiple experimental studies, as described in the text. Line: plot of a maximum likelihood fit to the data, given by the equation

$$V_D = 0.05 + 0.3892 * 6.7691^{-2.3679} / \left(6.7691^{-2.3679} + V_T{}^{-2.3679}\right).$$

Figure A3. Variation of resting cardiac output (Qdot) with hemoglobin concentration ([Hb]). Diamonds: data from several experimental studies, as described in the text. Line: plot of a maximum likelihood fit to the data, given by the equation

$$Q_{dot} = 51.40\left([Hb] - 0.0425\right)^{-0.2448}.$$

Figure A4. Responses to exercise predicted by the model for an anemic subject with [Hb] of 9.9 g/dl and for the same subject if she had a normal [Hb] of 13 g/dl. A. arterial oxygen partial pressure (PaO2). B. oxygen partial pressure in the capillary blood compartment of muscle (PcapO2). C. Cardiac output and muscle blood flow (see key). D. PO2 in the arteriolar-venular (ar-ven) and capillary (cap,t) compartments of muscle tissue. In all cases the x-axis is whole-body oxygen consumption (MRO2)