A mathematical model of ventilation response to inhaled carbon monoxide

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Submitted 10 January 2005; accepted in final form 26 January 2005

Stuhmiller, James H., and Louise M. Stuhmiller. A mathematical model of ventilation response to inhaled carbon monoxide. J Appl Physiol 98: 2033–2044, 2005.—A comprehensive mathematical model, describing the respiration, circulation, oxygen metabolism, and ventilatory control, is assembled for the purpose of predicting acute ventilation changes from exposure to carbon monoxide in both humans and animals. This Dynamic Physiological Model is based on previously published work, reformulated, extended, and combined into a single model. Model parameters are determined from literature values, fitted to experimental data, or allometrically scaled between species. The model predictions are compared with ventilation-time history data collected in goats exposed to carbon monoxide, with quantitatively good agreement. The model reaffirms the role of brain hypoxia on hyperventilation during carbon monoxide exposures. Improvement in the estimation of total ventilation, through a more complete knowledge of ventilation control mechanisms and validated by animal data, will increase the accuracy of inhalation toxicity estimates.

THE LEVEL OF VENTILATION and its change during acute exposures to toxic atmospheres has been shown to be an important factor in correctly predicting immediate incapacitation from the inhalation of fire gases (54). Fires generate many noxious gases, but carbon dioxide, carbon monoxide, and reduced oxygen are the most common and produce dramatic effects on ventilation that vary with gas composition, duration of exposure, and animal species. Being able to estimate these changes in terms of physiological processes is an important aspect of correctly extrapolating immediate incapacitation responses from animal to human.

A considerable amount of literature has been published concerning the modeling of breathing control in humans for the purposes of understanding how the biochemical and neurological systems maintain a sufficient ventilation to meet the body’s needs for oxygen. Although some transient breathing phenomena have been studied, the models are primarily aimed at understanding steady or slowly changing states. No attempt has been made to model breathing control in animals or to incorporate the effects of inhaling toxic gases.

Due to the inherent complexity of the process through which breathing is modulated, most mathematical simulations choose to model very specific responses (29). The majority of existing models have placed emphasis primarily on reflex response caused by blood chemistry changes sensed by central and peripheral chemoreceptors. There are three categories of sensor-based respiratory control mathematical models: models aimed at explaining the response to hypercapnia and hypoxia; models aimed at explaining the hyperventilation that accompanies exercise; and models aimed at explaining the occurrence of periodic breathing, sleep apnea, and the stability of respiration. This study is concerned with acute changes arising from inhaled carbon monoxide; this work does not deal with exercise or apnea.

In 1946, Gray (25) proposed the relationship between ventilation and chemical changes in the arterial blood that provided the first elegant mathematical approach to this interplay. In 1964, Grodins (26) combined the dynamics of the ventilatory response into a dynamic gas transport model composed of a lung and body tissue compartments. In 1967, Grodins et al. refined their mathematical analysis to include the effect of H+ ion concentration in the cerebrospinal fluid (CSF) at the central chemoreceptor, oxygen–carbon dioxide interaction at the peripheral chemoreceptors, and chemical buffering effects (27). Many of the modern models are based on the 1967 Grodins model. In 1972, Milhorn and coworkers (40) proposed a model that added a CSF compartment to Grodins’ steady-state model. Also in 1972, Duffin (20) proposed a mathematical model of the chemoreflex control of ventilation that assumed a central and peripheral controller, whereas, in 1980, Saunders et al. (51) reported an extended Grodins model, incorporating tidal volume (48). In 1997, Chiari et al. (16) developed a three-component model (lung, body tissue, and brain tissue) that incorporates a controller that adjusts alveolar ventilation and cardiac output dynamically. Chiari was the first to make use of modern simulation programming in solving the model equations.

In 2000, Duffin et al. (21), based on human experiments, introduced separate models for chemoreceptor drive and for ventilation response that determined both breathing frequency and tidal volume. This model not only provides a richer description of the nature of ventilation response, but also introduces critical thresholds for activation of these processes.

Finally, recently, Longobardo et al. (35–37) proposed a model of hypoxic depression in application to sleep apnea that is a fit of human data and, therefore, of limited applicability to animal tests or to understanding the acute exposures. More relevantly, in 2001, Ursino and colleagues (55, 56) developed models of the human ventilation control that include central ventilatory depression. These models describe the reduction of the response of the central neural system to the afferent peripheral chemoreceptor activity due to hypoxia of the brain tissue.

This paper presents a Dynamic Physiological Model (DPM) for estimating ventilation changes due to inhalation of carbon monoxide for the purpose of determining an acute exposure dose. This approach uses a composite of breathing control and blood chemistry models, drawing strongly on the previous research of Grodins, Chiari, Duffin, and Ursino. The parameters of the model equations are taken from the literature or are estimated based on allometric scaling. The model predictions are compared with ventilation and blood chemistry changes in goat exposed to carbon monoxide atmospheres. This physiologically based model can be used to improve estimates of inhaled dose of toxic gases.

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METHODS

This section summarizes the model equations used to estimate ventilation changes due to inhalation of carbon monoxide. The model consists of six subsets that are interconnected, according to the diagram contained in Fig. 1. The model equations are listed in the Appendix. The parameters of the model and their values are summarized in Tables 1 and 2.

Respiration System

The total ventilation is determined by the breathing frequency and tidal volume, whereas the volume of the dead space reduces the volume of air reaching the alveoli (39). Assuming that the external atmosphere is dry, then the humidification by the upper airway reduces the concentration inhaled in proportion to the partial pressure of water vapor to the atmospheric pressure. The transport and absorption of gas in the upper and lower airways follows Ref. 54 and other standard references. Equilibrium of partial pressures in the alveoli and blood leaving the lung capillaries is based on analysis of Hill et al. (28) and animal data (38). The respiration model equations are Eqs. A1–A8.

Ventilation Control

Chemoreceptor response. The precise biochemical pathway and even the location of the chemoreceptive tissues are still a subject of active research. The reader is referred to the prolific work of Nattie et al. (42) and Dempsey (18) for discussions of these complex issues from a sleep apnea perspective. Despite these uncertainties, we have selected the most appropriate mathematical models for hypoxic and hypercapnic response currently available. The chemoreceptor response is based on the model of Duffin et al. (21), rearranged to allow the parameters to be determined for other species and modified to include elements from other breathing control models. The peripheral response, which is altered by some reactive oxygen species (1), is modeled in terms of unsaturation hemoglobin (15), rather than oxygen pressure, because this form produces better agreement with animal data (11) and human data (17) and does not produce a mathematical singularity at low oxygen pressure. The form of the central response, probably situated in the superficial tissues of the ventral medulla oblongata (34), is modified to reflect changes in CSF pH to reflect the role of CSF acidity on respiration response (32, 45). The model equations are Eqs. A9–A15.

Brain activity response. Following the central ventilatory depression model of Ursino and colleagues (55, 56), the central control system is attenuated as the oxygen supply is compromised. This attenuation produces a corresponding decrease in ventilation, primarily due to frequency reduction (8). Again, following Ursino, we assume that the reduction of oxygen consumption lags the reduction in oxygen supply from the blood and is described by a first-order,
low-pass dynamic equation. The dynamics of brain metabolism and its effect on ventilation are found in Eqs. A16–A19.

Combined ventilatory response. The ventilation changes due to chemoreceptor drive and reduced brain activity are assumed to combine as independent factors described by Eqs. A20 and A21.

Table 1. Model parameters that are independent of animal species

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Description</th>
<th>Value (reference no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patm (mmHg)</td>
<td>Atmospheric pressure</td>
<td>760 (273.16 + Temp)</td>
</tr>
<tr>
<td>Temp (°C)</td>
<td>Body temperature</td>
<td>37 (57)</td>
</tr>
<tr>
<td>Pcrit (mmHg)</td>
<td>Water vapor pressure at body temperature</td>
<td>47.07 [Data D190 (58)]</td>
</tr>
<tr>
<td>βw (meq/pH unit)</td>
<td>Plasma buffering capacity</td>
<td>6 (28)</td>
</tr>
<tr>
<td>βb (meq/pH unit)</td>
<td>Blood buffering capacity</td>
<td>23 (28)</td>
</tr>
<tr>
<td>βl (meq/pH unit)</td>
<td>Lactate buffering capacity</td>
<td>21.3 (based on data of Ref. 50)</td>
</tr>
<tr>
<td>Kf</td>
<td>Equilibrium constant for lactate buffering</td>
<td>1.38 × 10⁹ (33)</td>
</tr>
<tr>
<td>La max (meq/l)</td>
<td>Maximum lactate concentration in brain</td>
<td>4.2 (based on data of Ref. 50)</td>
</tr>
<tr>
<td>RERb</td>
<td>Aerobic respiratory exchange ratio</td>
<td>0.8 (46)</td>
</tr>
<tr>
<td>RERa</td>
<td>Anaerobic respiratory exchange ratio</td>
<td>1.0 (46)</td>
</tr>
<tr>
<td>Ua</td>
<td>Absorption factor in upper airway</td>
<td>0 (54)</td>
</tr>
<tr>
<td>VSM (l/mol)</td>
<td>Standard molar volume</td>
<td>22.41 (273.16)</td>
</tr>
<tr>
<td>αO2 (mM/mmHg)</td>
<td>Solubility of oxygen in plasma</td>
<td>0.0012 (4)</td>
</tr>
<tr>
<td>αCO2 (mM/mmHg)</td>
<td>Solubility of carbon dioxide in plasma</td>
<td>0.0253 (4)</td>
</tr>
<tr>
<td>αCO (mM/mmHg)</td>
<td>Solubility of carbon monoxide in plasma</td>
<td>0.001 (47)</td>
</tr>
<tr>
<td>μ (mmol/l)</td>
<td>Standard molar concentration</td>
<td>μ = 1.000 ( \frac{V_M}{\text{Patm}} )</td>
</tr>
</tbody>
</table>

Sources of values: A, assumed to be same as human; B, assumed; C, based on ventilation depression of 0.10 is observed for goat following denervation (10); D, based on oxygen chemoreflex reported in Ref. 22; DD, based on a fractional ventilation increase of 0.327/mmHg reported in Ref. 31 and a ratio of tidal volume increase/frequency increase of 2.02 reported in Ref. 57; F, assumed to be the same as goat; G, based on 15 g/dl and conversion factor in Benignus et al. (9); H, based on observed oxygen concentration (19); I, based on 15.1 g/dl from Ref. 6 and conversion factor in Benignus reported in Ref. 31 and a ratio of tidal volume increase/frequency increase of 2.02 reported in Ref. 57; J, from Laboratory Animals (1993) quoted in WRAIR Investigator’s Handbook; K, based on the fourth ventricle being one-fourth of the volume of cerebrospinal fluid in brain ventricles or 0.5% of brain volume of 70-kg man; L, based on 0.5% of brain volume of 35-kg goat; M, based on 0.5% brain volume of 0.5-kg rat; N, taken from the central ventilatory depression model of Ursino et al. (55, 56); O, scaled from humans by \( M_{body} \) 0.25.

Table 2. Model parameters that depend on species

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Description</th>
<th>Value (reference no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 (mmHg)</td>
<td>First drive threshold where slope changes</td>
<td>10.1 (21)</td>
</tr>
<tr>
<td>D2 (mmHg)</td>
<td>Second drive threshold where slope changes</td>
<td>19.3 (21)</td>
</tr>
<tr>
<td>FracPC</td>
<td>Fraction of response in peripheral chemoreceptors</td>
<td>0.131 (21)</td>
</tr>
<tr>
<td>fnorm (breaths/min)</td>
<td>Resting breathing frequency</td>
<td>12.5 (21)</td>
</tr>
<tr>
<td>G1 (1/mmHg)</td>
<td>First slope of tidal volume with PCO2</td>
<td>0.256 (21)</td>
</tr>
<tr>
<td>G2 (1/mmHg)</td>
<td>Second slope of tidal volume with PCO2</td>
<td>0.087 (21)</td>
</tr>
<tr>
<td>G3 (1/mmHg)</td>
<td>First slope of frequency with PCO2</td>
<td>0.063 (21)</td>
</tr>
<tr>
<td>G4 (1/mmHg)</td>
<td>First slope of frequency with PCO2</td>
<td>0.128 (21)</td>
</tr>
<tr>
<td>HbC</td>
<td>First coefficient in oxygen saturation curve</td>
<td>0.710 (24)</td>
</tr>
<tr>
<td>HbC2</td>
<td>Second coefficient in oxygen saturation curve</td>
<td>0.957 (24)</td>
</tr>
<tr>
<td>Hbrest (mmol/l)</td>
<td>Total hemoglobin concentration</td>
<td>8.19 (G)</td>
</tr>
<tr>
<td>LaFac (1/l)</td>
<td>Lactate factor</td>
<td>0.23 Eq. A61</td>
</tr>
<tr>
<td>Mnore</td>
<td>Haldane coefficient</td>
<td>234 (5)</td>
</tr>
<tr>
<td>Po2 (Tor)</td>
<td>Oxygen partial pressure at 50% saturation</td>
<td>26.5 (30)</td>
</tr>
<tr>
<td>Pco2/Patm</td>
<td>Threshold for chemoreceptors</td>
<td>0.0449 (21)</td>
</tr>
<tr>
<td>Qo2/Mbody (l/min·kg⁻¹)</td>
<td>Cardiac output/body mass</td>
<td>0.0834 (53)</td>
</tr>
<tr>
<td>Qo2/Mbody (l/min·kg⁻¹)</td>
<td>Normal brain blood flow per body mass</td>
<td>0.0107 (59)</td>
</tr>
<tr>
<td>Vblood/Mbody (l/kg)</td>
<td>Blood volume/body mass</td>
<td>0.0656 (53)</td>
</tr>
<tr>
<td>Vblood/Vblood</td>
<td>Fraction of blood volume in arteries</td>
<td>0.45</td>
</tr>
<tr>
<td>Vair/Vt</td>
<td>Dead space volume/tidal volume</td>
<td>0.32 (39)</td>
</tr>
<tr>
<td>Vresting/Vbody</td>
<td>Resting ventilation/body mass</td>
<td>0.112 (21)</td>
</tr>
<tr>
<td>Vblood/Mbody (ml/kg)</td>
<td>Volume of brain/body mass</td>
<td>21.3 (3)</td>
</tr>
<tr>
<td>VCSF (ml)</td>
<td>Volume of the CSF in the fourth ventricle</td>
<td>7.5 (K)</td>
</tr>
<tr>
<td>Vnorm/Mbody (mmol/min·kg⁻¹)</td>
<td>Normal oxygen consumption in brain</td>
<td>0.0221 (41)</td>
</tr>
<tr>
<td>tH (%)</td>
<td>Response time of hypoxic brain</td>
<td>5.0 (N)</td>
</tr>
<tr>
<td>tL (min)</td>
<td>Lactate clearing time</td>
<td>20.0 (13)</td>
</tr>
</tbody>
</table>

Blood Chemistry

Hemoglobin saturation. Using the formulation of Gomez (24), the fraction of hemoglobin sites bound to oxygen can be computed using Eqs. A22 and A23. The relation of West and Wagner (60) can be used...
to correct for the effects of temperature, pH, and Pco2 on the saturation curve (Eq. A24).

Oxygen-carbon monoxide partition. Oxygen and carbon monoxide compete for hemoglobin bonding sites. The so-called Haldane assumptions, described in Roughton and Darling (49), are used to determine that partitioning. The total concentrations of oxygen and carbon monoxide in the blood are partitioned between the portions dissolved in the plasma and the portions bound to hemoglobin. This partition is determined by Eqs. A25–A31.

Acid-base balance. In blood, pH changes arise from changes in carbon dioxide, generated by either metabolism or respiration, and are described by bicarbonate buffering. In the CSF, pH varies with concentration changes in both carbon dioxide and lactic acid. The acid-base balances are described by Eqs. A32–A39.

Carbon dioxide dissociation. Carbon dioxide is carried in the blood in three forms: 1) dissolved in the plasma; 2) as bicarbonate; and 3) bound to the amino groups of hemoglobin. The model Eqs. A40–A43 are based on standard blood chemistry relations and the relation of Hill et al. (28) for carbamino.

Circulatory System

In humans, the transit time of blood around the circulatory system is ~1 min on average and can be much longer for some circulatory subpaths (9, 52). Consequently, there is a time delay between the inhalation of gas and the chemical response of the ventilatory control sensors. This time delay affects the speed at which the ventilatory control system reacts to inhaled gases.

The gases enter the circulatory system across the blood-gas barrier, from the alveoli to the lung capillaries. The gases are carried in solution or bound to the hemoglobin along a circuit that begins at the lung capillaries, flows into the arteries, bifurcates into flows that go to the brain and to the rest of the body tissues, reunites as flow into the veins, and finally reenters the lung capillaries. In the lung, brain, and tissue capillaries, it is assumed that an equilibration between inflow, outflow, and tissue transfer occurs rapidly. In the veins and arteries, the transient changes in concentration are computed from the mass balance equations. These processes are described by Eqs. A44–A48.

Cardiac Output

The cardiac output leads to blood flow to the brain and to the rest of the body tissues. We assume that flow to the tissues remains constant, but that blood flow to the brain increases during hypoxia, based on the data of Ref. 50, shown in Fig. 2A. The equations governing cardiac output and its distribution are Eqs. A49 and A50.

Metabolic Effects

Oxygen metabolism. Under conditions that depress neural activity, oxygen consumption throughout the body is reduced linearly with activity from the normal resting value. Carbon dioxide generation is a fraction of the oxygen consumption rate. Under anaerobic conditions, carbon dioxide can be released from other body stores and produce a considerable increase in the exhaled carbon dioxide. The model does not contain this effect.

Oxygen transfer to the brain. Oxygen diffuses from the brain capillaries into the brain tissue at a rate that depends on the oxygen pressure differential between the capillaries and the tissue. When there is sufficient oxygen pressure, the transfer rate matches the normal oxygen consumption in the brain, but, as the oxygen pressure in the capillaries drops below a certain level, the transfer decreases until a point is reached at which no transfer occurs. Data collected by Doblar et al. (19) show this trend (see Fig. 2B), which is captured by the relationship in Eq. A54.

Lactic acid generation. When oxygen obtained from the bloodstream is inadequate to meet the energy demands of the brain, the deficit must be generated by anaerobic glycolysis. In aerobic glycolysis, 6 mmol of ATP are generated for every 1 mmol of oxygen consumed. In anaerobic glycolysis, the generation of 6 mmol of ATP will produce 6 mmol of lactate (59). Therefore, to replace the energy generated by 1 mmol/min of oxygen consumption in aerobic glycolysis, the brain will generate 6 mmol/min of lactate by anaerobic glycolysis. This increase in lactate is diluted in the volume of the CSF in the fourth ventricle, the ventricle that bathes the medulla oblongata. After the oxygen capacity returns to normal levels, the body clears the built-up lactate with a characteristic half-life time. The equations describing the lactic acid generation and clearing are Eqs. A56–A63.

Anaerobic limit. Based on studies in exercise metabolism, anaerobic glycolysis can only supply a portion of the energy production in muscle tissues at maximal exercise (14, 46), at which time venous lactate levels reach a maximum level (23). In goats suffering brain hypoxia from carbon monoxide exposure, lactate levels in the CSF reached an average peak of 4.2 meq/l (50). We assume that anaerobic glycolysis in the brain stops when lactate levels in the brain reach this maximum value.
Solution of the Model Equations

The model equations are solved using the MathWorks SIMULINK simulation program. Each simulation is initiated with an estimate of the normal blood concentrations of oxygen and carbon dioxide, consistent with the environmental conditions (altitude, temperature) and individual characteristics (species, body mass). When specific preexposure values of ventilation, metabolism, blood chemistry, or any other physiological variable are known, the initial concentrations are adjusted to reproduce those starting conditions. A typical simulation takes ~10–30 s on a desktop computer.

RESULTS

Researchers at the Rutgers Medical School have provided the most complete set of data describing the ventilatory and blood chemistry response to acute exposures of carbon monoxide (19, 50). Unanesthetized goats were exposed to single breaths of carbon monoxide, as well as continuous inhalation. The researchers measured blood chemistry changes in the brain and CSF and elucidated the origins of hyperventilation associated with carboxyhemoglobinemia.

In transient breathing tests, animals were exposed to 40% oxygen and then one or more breaths of either pure nitrogen or 1–2.5% carbon monoxide (50). The changes in ventilation and arterial oxygen saturation were recorded. The remarkable finding was that, even though both challenges produced significant reduction of arterial oxygen saturation, the nitrogen exposure led to large ventilation increases, whereas the carbon monoxide produces virtually no change. The results using the DPM are in substantial agreement with those results (Fig. 3).

The DPM offers an explanation for these results. The nitrogen exposure lowers the oxygen saturation and increases the fraction of free hemoglobin, which, in turn, increases the...
response of the peripheral chemoreceptors and increases the ventilation. In the carbon monoxide exposure, on the other hand, carbon monoxide displaces oxygen on the hemoglobin, lowering oxygen saturation, but does not produce any more free hemoglobin. Consequently, the hypoxic factor and ventilation are unchanged. Only when oxygen delivery to the brain is compromised, at \( \approx 60\% \) carboxyhemoglobin, is there a central chemoreceptor response.

In extended breathing tests, animals were exposed to 40% oxygen for 10 min, followed by a mixture of 40% oxygen and 1% carbon monoxide for 10 min (19). Data, averaged over all animals, were reported in 1-min intervals throughout the exposure. The animals displayed a rapid onset of hyperventilation when carboxyhemoglobin levels reached \( \approx 60\% \). This onset occurred at different times for different animals because of variations in body mass, in initial ventilation, and in blood chemistry states. Nonetheless, the salient features of the response are seen in the physiological quantities averaged over all of the animals.

The DPM simulation is initialized with the average preexposure conditions of the animals. Account was taken of the masks worn by the animals by increasing dead space volume from 32% of resting tidal volume to 50% (2). Adjustments are made to the initial bicarbonate concentrations to match the observed pH and \( \text{PCO}_2 \) values and to the initial cardiac output to match the observed brain blood flow rate. The predictions are compared with the average of the observed responses and with the extreme of the individual animal responses.

The simulation reproduces the timing and magnitude of the mean changes to ventilation, breathing rate, and tidal volume (Fig. 4). The onset at \( \approx 4 \) min and the development of hyperventilation are closely reproduced in the simulation (Fig. 4A). This same response is seen in individual animals (Fig. 4D). After 10 min of exposure, data are reported for only one or two of the animals so that the variability grows rapidly.

Although not contained in the tabulated data, the researchers reported that all animals experienced rapid ventilatory depression within minutes following the peak of the observed hyperventilation (50). Furthermore, in experiments conducted by the same research group using anesthetized cats (43), the researchers found that, while lactic acidosis near the central chemosensitive regions produces stimulation of respiration during brain hypoxia, the overwhelming response to central lactic acidosis is respiratory depression. The model clearly shows this phenomenon (Fig. 4A).

The oxygen transport and consumption in the brain were shown by Doblar et al. (19) to be the controlling factor in the ventilation response, and these quantities are captured in the simulation (Fig. 5). Cerebral blood flow rises in response to the diminished oxygen delivery (Fig. 5A), whereas the oxygen content drops because of the buildup of carboxyhemoglobin (Fig. 5B). The net effect is a gradual drop in oxygen being

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**Fig. 5.** Oxygen delivery to and consumption by the brain. Data are from Ref. 19. Circles indicate mean values, whereas the lines indicate the high and low responses. The DPM reproduces the blood flow (A), oxygen concentration (B), and oxygen delivery rate (C). The blood flow increases in response to the lower oxygen content, but not fast enough to maintain oxygen delivery. D: the amount absorbed by the brain falls rapidly as the delivery rate decreases.
transported to the brain (Fig. 5C). As the oxygen content drops, oxygen transfer to the brain drops (Fig. 5D). This deficit leads to a generation of lactic acid in the CSF and an activation of the central chemoreceptors.

The simulation also predicts patterns in the arterial and venous blood chemistry that agree with observed data (Fig. 6). Carboxyhemoglobin levels build up at a rate of ~10%/min and then plateau around 70% near the end of the exposure (Fig. 6A). Initially, arterial carbon dioxide pressure rises slightly, due to release of carbon dioxide from the carbamino, but, at the onset of hyperventilation, the PCO₂ begins to fall (Fig. 6B). Doblare et al. (19) noted that the ratio of carbon dioxide production to oxygen consumption rose to values well above one and hypothesized that there might be additional releases from tissue stores that mitigate the drop in carbon dioxide pressure. This effect is not included in the simulation, so the model predicts a larger drop. The predicted venous oxygen saturation agrees with observation, rising during the course of the exposure (Fig. 6C).

Finally, we compare the blood chemistry in the venous side of the brain capillaries (Fig. 7). The oxygen pressure drops steadily throughout the exposure (Fig. 7A). The carbon dioxide pressure agrees with the magnitude and rate of change (Fig. 7B), but is offset by ~3 Torr. Just as in the case of the arterial blood chemistry, it is possible that there is an additional release of carbon dioxide from tissue stores that accounts for this difference. Nonetheless, the acidity levels are reproduced, being constant before hyperventilation occurs and then rising steadily afterwards (Fig. 7C).

Overall, the simulation agrees quantitatively with all 13 physiological parameters measured in these experiments. Most importantly, the magnitude and origin of the hyperventilation are captured.

**DISCUSSION**

A collection of models of respiration, circulation, and metabolism, along with models of the corresponding humeral and neural control systems, has been assembled into the DPM to provide a means of estimating ventilation response to inhaled carbon monoxide. The parameters of the model have been determined from previous modeling efforts, from experimental data, or from allometric scaling. In some cases, combining models that were developed for different purposes or in different contexts has required reformulation of the model equations.

The DPM provides a quantitative explanation of the hyperventilation and subsequent ventilation depression associated with acute carbon monoxide inhalation. The buildup of carboxyhemoglobin and corresponding reduction in oxygen de-
livery to the brain leads to anaerobic glycolysis and the observed lactate generation. Using buffering relations, the acidity changes are reproduced, and those changes, through the modified Duffin model, generate the observed hyperventilation. The continued reduced oxygen delivery leads to a decrease of central chemoreceptor response and the observed ventilation depression. The validity of this physiologically based explanation of carbon monoxide-induced hyperventilation is further supported by the agreement with other measured blood-gas quantities.

The DPM also provides a rational basis for extrapolation between species. Whereas exercise and sleep apnea studies can be made with human subjects, knowledge of immediate incapacitation and delayed lethality from inhaled gases must come from animal testing. A physiologically based ventilation response model allows the concepts developed for humans to be used to interpret animal tests and extrapolate those results accurately into human internal dose estimates.

There are many areas of uncertainty in the modeling of ventilation control, including the exact mechanism by which oxygen alters the peripheral chemoreceptor response and the details of how the central chemoreceptor senses and responds to the humoral properties. Further testing and theoretical investigations are warranted. A phenomenological model allows the possibility of using animal tests to explore these and other breathing control issues in a safer and more invasive manner than would be possible with human subjects.

The DPM model extends previous models that address hypoxic and hypercapnia environments to include carbon monoxide. These three gases occur universally in fire environments, and each significantly alters ventilation and, consequently, the uptake of all of the noxious gases. The extended model will allow better estimates of internal dose, thus improving the prediction of immediate incapacitation and delayed lung injury.

APPENDIX

The mathematical equations of the Total Physiological Model are given below.

Respiration Model

Total ventilation.

\[ V_E = f \cdot V_T \]  

(A1)

where \( V_E \) is ventilation (l/min), \( f \) is breathing frequency (breaths/min), and \( V_T \) is tidal volume (l/breath).

Alveolar ventilation.

\[ V_A = f \cdot (V_T - V_D) \]  

(A2)

where \( V_A \) is alveolar ventilation (l/min) and \( V_D \) is dead space volume (liters).
Humidification.

\[
[X]_{\text{inh}} = \frac{\text{Patm} - P_{\text{H}_{2}\text{O}}}{\text{Patm}} [X]_{\text{sat}} \tag{A3}
\]

where \([X]\) is inhaled concentration of substance \(X\) (mmol/l), \(\text{inh}\) is inhaled, and \(\text{ext}\) is external atmosphere. See Tables 1 and 2 for definitions of terms not defined in APPENDIX.

Absorption in dead space.

\[
\dot{m}_{\text{dead space}} - \text{tissue} = U_{1} V_{E} [X]_{\text{inh}} \tag{A4}
\]

where \(\dot{m}\) is mass transfer between regions (mmol/min).

Transport to alveoli.

\[
\dot{m}_{\text{dead space}} - \text{alveoli} = V_{A} [(1 - U_{1}) [X]_{\text{inh}} - [X]_{\text{alv}}] \tag{A5}
\]

where \(\text{alv}\) is alveoli.

Mass balance in alveoli.

\[
\dot{m}_{\text{alveoli}} - \text{lung cap} = \dot{m}_{\text{dead space}} - \text{alveoli} \tag{A6}
\]

Alveolar concentration.

\[
[X]_{\text{alv}} = \frac{P X_{\text{alv}}}{\text{Patm}} \tag{A7}
\]

where \(P X_{\text{alv}}\) is alveolar partial pressure of \(X\).

Equilibrium at lung tissue.

\[
P X_{\text{alv}} = P X_{\text{lung cap}} \tag{A8}
\]

where \(P X_{\text{lung cap}}\) is lung capillary partial pressure of \(X\).

Ventilation Control

Total chemoreceptor drive.

\[
D = \cdot D_{p} + D_{C} \tag{A9}
\]

where \(D\) is the chemical drive, \(D_{p}\) is peripheral chemoreceptor drive, and \(D_{C}\) is chemoreceptor drive.

Peripheral drive.

\[
D_{p} = \text{FracPC} \cdot \text{Hyp} \cdot (\text{PCO}_{2}^{\text{CSF}} - \text{PCO}_{2}^{\text{th}}) \tag{A10}
\]

where \(\text{FracPC}\) is the fraction of the ventilation response due to peripheral chemoreceptors, \(\text{Hyp}\) is hypoxic factor, and \(\text{PCO}_{2}^{\text{CSF}}\) is \(\text{PCO}_{2}\) at the peripheral chemoreceptor.

Hypoxic factor.

\[
\text{Hyp} = \frac{1 - \text{Sat}^{\text{art}}}{1 - \text{Sat}^{\text{art}, \text{norm}}} \tag{A11}
\]

where \(\text{Sat}^{\text{art}}\) is unsaturated hemoglobin fraction at the peripheral receptor, and \(\text{Sat}^{\text{art}, \text{norm}}\) is normal \(\text{Sat}^{\text{art}}\).

Central drive.

\[
D_{C} = (1 - \text{FracPC}) \cdot (\text{PCO}_{2}^{\text{CSF}} - \text{PCO}_{2}^{\text{th}}) \tag{A12}
\]

where \(\text{PCO}_{2}^{\text{CSF}}\) is \(\text{PCO}_{2}\) in the cerebrospinal fluid (CSF).

CSF buffering.

\[
\text{PCO}_{2}^{\text{CSF}} = \text{PCO}_{2}^{\text{norm}} - \frac{P_{u}}{\alpha_{\text{CO}_{2}}} (\text{pH}_{\text{CSF}} - \text{pH}_{\text{norm}}) \tag{A13}
\]

where \(\text{PCO}_{2}^{\text{norm}}\) is normal \(\text{PCO}_{2}\), \(\text{pH}_{\text{CSF}}\) is CSF pH, and \(\text{pH}_{\text{norm}}\) is normal pH.

Ventilation response to chemoreceptor drive.

\[
\left( \frac{V_{T}}{V_{T}^{\text{norm}}} \right)^{\text{drive}} = 1 + \begin{cases} 
0, & D < D_{1} \\
G_{11} \cdot (D - D_{1}), & D_{1} < D < D_{2} \\
G_{12} \cdot (D_{2} - D_{1}) + G_{12} \cdot (D - D_{2}), & D_{2} < D
\end{cases} \tag{A14}
\]

where \(V_{T}^{\text{norm}}\) is normal resting \(V_{T}\).

\[
\left( \frac{f}{f_{\text{norm}}} \right)^{\text{drive}} = 1 + \begin{cases} 
0, & D < D_{1} \\
G_{21} \cdot (D - D_{1}), & D_{1} < D < D_{2} \\
G_{22} \cdot (D_{2} - D_{1}) + G_{22} \cdot (D - D_{2}), & D_{2} < D
\end{cases} \tag{A15}
\]

where \(f_{\text{norm}}\) is normal resting \(f\).

Brain activity.

\[
A_{b} = \frac{V_{\text{brain}}}{V_{\text{brain}, \text{norm}}} \tag{A16}
\]

where \(A_{b}\) is brain activity.

Ventilation depression due to brain activity.

\[
\left( \frac{V_{E}}{V_{E}^{\text{norm}}} \right)^{\text{brain}} = A_{b} \tag{A17}
\]

Partition of ventilation depression.

\[
\left( \frac{f}{f_{\text{norm}}} \right)^{\text{brain}} = A_{b} \tag{A18}
\]

Oxygen consumption in brain.

\[
\frac{d V_{\text{O}_{2}}^{\text{brain}}}{d t} = \frac{1}{\tau_{b}} (m_{\text{blood}} - V_{\text{O}_{2}^{\text{norm}}}) \tag{A19}
\]

Combined ventilation response.

\[
\left( \frac{V_{T}}{V_{T}^{\text{norm}}} \right)^{\text{drive}} \left( \frac{f}{f_{\text{norm}}} \right)^{\text{drive}} = A_{b} \tag{A20}
\]

Blood Chemistry

Gomez saturation formulation.

\[
\text{Sat} = \frac{u}{1 + u} \tag{A22}
\]

where \(u = (1 - \text{HbC}_{1}) \cdot \frac{P}{P_{50}} + (\text{HbC}_{1} - \text{HbC}_{2}) \cdot \left( \frac{P}{P_{50}} \right)^{2} + \text{HbC}_{2} \cdot \left( \frac{P}{P_{50}} \right) \tag{A23}
\]

where \(P\) is partial pressure of oxygen (Torr).
West pressure correction.
\[ P = P_O2 \cdot 10^{(0.024 \cdot (37 - \text{Temp}) + 0.4 \cdot (pH - 7.4)) \cdot \left( \frac{40}{P_CO2} \right)^{0.06}} \]  
(A24)

where Temp is blood temperature (C).

Haldane’s first assumption.
\[ HbO2 + HbCO = \text{Sat}(P) \cdot Hb_{tot} \]  
(A25)

where HbO2 is oxyhemoglobin, HbCO is carboxyhemoglobin, and Hb_{tot} is total hemoglobin.

Equivalent oxygen pressure.
\[ P = P_O2 + M_{CO} \cdot Pco \]  
(A26)

where \( M_{CO} \) is the Haldane coefficient for carbon monoxide, and Pco is carbon monoxide partial pressure.

Haldane’s second assumption.
\[ HbCO = \frac{M_{CO} \cdot Pco}{P_O2} \]  
(A27)

Oxygen partition.
\[ O_2 = [O_2]_{pl} + HbO2 \]  
(A28)

where \([O_2]_{pl}\) is total concentration of oxygen (mM), and \([O_2]_{pl}\) is plasma \([O_2]_{pl}\).

Carbon monoxide partition.
\[ [CO] = [CO]_{pl} + HbCO \]  
(A29)

where \([CO]_{pl}\) is total concentration of carbon monoxide (mM), and \([CO]_{pl}\) is plasma \([CO]_{pl}\).

Carbon monoxide solubility.
\[ [CO]_{pl} = \alpha_{CO} \cdot HbO2 \]  
(A30)

General buffering equation.
\[ \Delta(pH) = -\frac{1}{\beta_A} \Delta(\text{acid}) \]  
(A32)

where \(\Delta\) is change, and \(\beta_A\) is buffering capacity of acid-base pair (meq/pH unit).

Carbon dioxide plasma buffering equation.
\[ \Delta(pH) = -\frac{1}{\beta_A} \Delta[CO_2] \]  
(A33)

where \([CO_2]_{pl}\) is carbon dioxide concentration.

Carbon dioxide CSF buffering equation.
\[ \Delta(pH)^{CO_2}_{\text{CSF}} = -\frac{1}{\beta_P} \Delta[CO_2] \]  
(A34)

Lactate buffering equation.
\[ \Delta(pH)^{La}_{\text{CSF}} = -\frac{1}{\beta_L} \Delta[La^{\text{CSF}}] \]  
(A35)

where \([La^{\text{CSF}}]\) is CSF lactic acid concentration (meq/l).

Carbon dioxide solubility.
\[ [CO_2]_{pl} = \alpha_{CO} \cdot P_{CO2}^{\text{pl}} \]  
(A36)

Carbon dioxide equilibrium.
\[ P_{CO2}^{\text{pl}} = P_{CO2}^{\text{at}} \]  
(A37)

\( p \text{H changes in the CSF.} \)
\[ \Delta(pH)^{CSF} = -\frac{1}{\beta_P} \Delta[CO_2] - \frac{1}{\beta_L} \Delta[La^{\text{CSF}}] \]  
(A38)

Final relationship for the central chemoreceptor drive.
\[ D_C = (1 - \text{FracPC}) \cdot \left( P_{CO2}^{\text{pl}} + \frac{\beta_P}{\beta_L} \cdot \Delta[La^{\text{CSF}}] - P_{CO2}^{\text{at}} \right) \]  
(A39)

Carbon dioxide partition.
\[ [CO_2]_{pl} = \alpha_{CO} \cdot P_{CO2}^{\text{pl}} \]  
(A40)

Henderson-Hasselbach equation.
\[ [HCO_3^-] = [CO_2]_{pl} \cdot 10^{pH_{H2O}} \]  
(A41)

Hill’s relation.
\[ [carb] = Hb_{tot} \cdot \left( 0.2413 + \frac{\text{HalEff}}{1 - \text{Sat}O_2} \right) \]  
(A43)

where \(\text{HalEff}\) is the Haldane effect coefficient, and \(\text{Sat}O_2\) is oxygen saturation.

Circulation System

Mass balance in lung capillaries.
\[ Q \cdot [X]_{\text{lung cap}} = Q \cdot [X]_{\text{ven}} + m_{\text{ven}} - m_{\text{lung cap}} \]  
(A44)

where \(Q\) is total blood flow (l/min); lung cap is lung capillary, and ven is venous.

Mass balance in arteries.
\[ V_{art} \frac{d[X]_{art}}{dr} = Q([X]_{\text{lung cap}} - [X]_{art}) \]  
(A45)

where art is artery, and V_{art} is volume of blood in the arteries (liters).

Mass balance in brain capillaries.
\[ Q_{\text{brain}} [X]_{\text{brain}} = Q_{\text{brain}} [X]_{\text{art}} + m_{\text{blood} \rightarrow \text{brain}} \]  
(A46)

where \(Q_{\text{brain}}\) is blood flow into the brain.

Mass balance in tissue capillaries.
\[ Q_{\text{tissue}} [X]_{\text{tissue cap}} = Q_{\text{tissue}} [X]_{\text{art}} + m_{\text{blood} \rightarrow \text{tissue}} \]  
(A47)

where \(Q_{\text{tissue}}\) is blood flow to body tissue, and tis cap is tissue capillaries.

Mass balance in veins.
\[ V_{ven} \frac{d[X]_{ven}}{dr} = Q_{\text{brain}} [X]_{\text{brain}} + Q_{\text{tissue}} [X]_{\text{tissue cap}} - Q[X]_{ven} \]  
(A48)

where V_{ven} is volume of blood in venous system (liters).

Cardiac Output and Distribution

Partition of cardiac output.
\[ Q = Q_{\text{brain}} + Q_{\text{tissue}} \]  
(A49)

\[ Q_{\text{brain}} = Q_{\text{brain}} \cdot \left( 1 + 1.2 \cdot \frac{[O_2]_{\text{at}}}{[O_2]_{\text{norm}}} - 1 \right) \]  
(A50)

Metabolic System

Oxygen consumption in tissues.
\[ V_{\text{tissue}}^{O_2} = V_{\text{tissue,norm}}^{O_2} \cdot A_b \] (A51)

where \( V_{\text{O}_2}^{\text{tissue}} \) is tissue oxygen consumption, and \( V_{\text{O}_2}^{\text{tissue,norm}} \) is normal \( V_{\text{O}_2}^{\text{tissue}} \).

**Oxygen uptake in tissues.**

\[ m_{\text{blood}}^{O_2} = V_{\text{tissue}}^{O_2} \] (A52)

**Aerobic carbon dioxide production.**

\[ V_{\text{CO}_2}^{aerobic} = \text{RER}_a \times V_{\text{O}_2}^{aerobic} \] (A53)

where \( \text{RER}_a \) is aerobic respiratory exchange ratio.

**Oxygen uptake in brain.**

\[ \frac{m_{\text{blood}}^{O_2}}{V_{\text{O}_2}^{\text{brain,norm}}} = \begin{cases} 1, & 30 < P_{O_2}^{\text{brain}} \\ \frac{P_{O_2}^{\text{brain}} - 10}{30 - 10}, & 10 < P_{O_2}^{\text{brain}} < 30 \\ 0, & P_{O_2}^{\text{brain}} < 10 \end{cases} \] (A54)

**Anaerobic glycolysis.**

\[ V_{\text{O}_2}^{\text{brain,an}} = V_{\text{O}_2}^{\text{brain}} - m_{\text{blood}}^{O_2} \] (A55)

where an is anaerobic glycolysis.

**Lactate Generation in Brain**

**Lactate generation.**

\[ \frac{d[\text{La}^-]}{dt} = 6 \cdot \frac{V_{\text{O}_2}^{\text{brain,an}}}{V_{\text{CSF}}^{4}} \] (A56)

where \([\text{La}^-]\) is lactate concentration.

**Lactate buffering.**

\[ K_s = \frac{[\text{La}^-]}{[\text{H}_2\text{O}] \times [\text{La}^-]} \] (A57)

**Henderson-Hasselbalch equation.**

\[ \text{pH} = 3.86 + \log \left( \frac{[\text{La}^-]}{[\text{La}^+] \cdot V_{\text{CSF}}^{4}} \right) \] (A58)

At a normal pH of 7.4:

\[ [\text{La}^-] = \frac{[\text{La}^-]}{3.467} \] (A59)

Combining Eqs. A62 and A59 produces the lactate generation relationship.

Combining Eqs. A56 and A59:

\[ \left( \frac{d[\text{La}^-]}{dt} \right)^{\text{an}} = \text{LaFac} \cdot \frac{V_{\text{O}_2}^{\text{brain,an}}}{V_{\text{CSF}}^{4}} \] (A60)

**Lactate generation factor.**

\[ \text{LaFac} = \frac{6}{3.467 \cdot V_{\text{CSF}}^{4}} \] (A61)

**Lactate clearing.**

\[ \left( \frac{d[\text{La}^-]}{dt} \right)^{\text{clearing}} = - \frac{1}{\tau_L} [\text{La}] \] (A62)

**Lactate dynamics.**

\[ \frac{d[\text{La}^-]}{dt} = \text{LaFac} \cdot \frac{V_{\text{O}_2}^{\text{brain,an}}}{V_{\text{CSF}}^{4}} - \frac{1}{\tau_L} [\text{La}] \] (A63)

**Limit of anaerobic glycolysis.**

\[ [\text{La}] \leq [\text{La}]^{\text{max}} \] (A64)

**ACKNOWLEDGMENTS**

The authors thank Diane Long of Jaycor/Titan for careful processing, organization, and analysis of the data that has made our model comparisons possible. The authors thank Professor James Duffin, University of Toronto, for providing additional materials and insight into his modeling efforts.

**GRANTS**

The authors thank Dr. Karl Friedl, Director of the Military Operational Medicine Research Program of the US Army Medical Research and Materiel Command, for support of the work under contract DAMD17-00-C-0031.

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