Mathematical Modeling of Carbon Monoxide Exposures from Anesthetic Breakdown

Effect of Subject Size, Hematocrit, Fraction of Inspired Oxygen, and Quantity of Carbon Monoxide

Harvey J. Woehlck, M.D., David Mei, M.D., Ph.D.,† Marshall B. Dunning III, Ph.D.,‡ Franklin Ruiz, M.D.§

Background: Carbon monoxide (CO) is produced by reaction of isoflurane, enflurane, and desflurane in desiccated carbon dioxide absorbents. The inspiratory CO concentration depends on the dryness and identity of the absorbent and anesthetic. The adaptation of existing mathematical models to a rebreathing circuit allows identification of patient factors that predispose to more severe exposures, as identified by carboxyhemoglobin concentration.

Methods: From our companion study, the authors used quantitative *in vitro* CO production data for 60 min at 7.5% desflurane or 1.5% isoflurane at 1 l/min fresh gas flow. The carboxyhemoglobin concentration was calculated by iteratively solving the Coburn Forster Kane equation modified for a rebreathing system that incorporates the removal of CO by patient absorption. Demonstrating good fit of predicted carboxyhemoglobin concentrations to published data from animal and human exposures validated the model. Carboxyhemoglobin concentrations were predicted for exposures of various severity, patients of different sizes, hematocrit, and fraction of inspired oxygen.

Results: The calculated carboxyhemoglobin concentrations closely predicted the experimental results of other investigators, thereby validating the model. These equations indicate the severity of CO poisoning is inversely related to the hemoglobin quantity of a subject. Fraction of inspired oxygen had the greatest effect in patients of small size with low hematocrit values, where equilibrium and not the rate of uptake determined carboxyhemoglobin concentrations.

Conclusion: This model predicts that patients with low hemoglobin quantities will have more severe CO exposures based on the attainment of a higher carboxyhemoglobin concentration. This includes patients of small size (pediatric population) and patients with anemia.

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* Associate Professor, Department of Anesthesiology, Medical College of Wisconsin and Froedtert Memorial Lutheran Hospital. † Resident, § Visiting Assistant Professor, Department of Anesthesiology, ‡ Associate Professor, Department of Medicine, Medical College of Wisconsin.

Address reprint requests to Dr. Woehlck: Froedtert Memorial Lutheran Hospital, 9200 West Wisconsin Avenue, Milwaukee, Wisconsin 53226. Address electronic mail to: hwoehlck@mcw.edu or rkost@fmlh.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

CARBON monoxide (CO) can be produced by the breakdown of isoflurane, enflurane, and desflurane in dried carbon dioxide absorbents. Despite evidence suggesting that CO dissolved in blood may be a better measure of toxicity than carboxyhemoglobin,[1,2] carboxyhemoglobin remains the most clinically useful and widely accepted measure of CO poisoning.[3] Intraoperative CO production and exposures have been studied,[4,5] revealing that subject size is inversely related to carboxyhemoglobin concentration.[6] Mathematical modeling of CO absorption, elimination, production, and carboxyhemoglobin concentration has been performed using the equation developed by Coburn, Forster, and Kane (CFK).[7–9] This equation predicts environmental exposures where the inspired CO concentration is constant.[8–10] However, CO exposures during anesthesia are unlike environmental exposures, because low-flow anesthesia through a circle breathing circuit constrains the exposure to a finite quantity of CO that is similar in magnitude to the oxygen binding capacity of the hemoglobin in an average adult human. Absorption of CO into the subject lowers the CO inspiratory concentration. We adapted the CFK model to account for these factors. We hypothesized that these calculations can predict the severity of reported exposures and identify patients of higher risk.

Methods

Mathematical Modeling

The CFK equation[9] was solved iteratively *via* an Excel spreadsheet (Microsoft Corporation, Cupertino, CA) to calculate the uptake of CO into carboxyhemoglobin, assuming constant concentrations of inspiratory CO. To accommodate the CO concentrations in a rebreathing circuit that change based on absorption by the subject, production, removal *via* the scavenger, and dilution by fresh gas, we segmented the 60-min study period into 1-min intervals assumed to have constant CO concentrations. A mass balance was performed incorporating these features in a circuit volume measured to be approximately 7 l, and after each iteration, the quantity of CO absorbed by the patient was removed from the gas phase, and new inspiratory CO concentrations were calculated. Satisfactory convergence of carboxyhemoglobin and gas-phase CO concentrations was obtained within 10 iterative cycles for each 1-min increment. At

the end of each 1-min interval, additional CO was added to the circuit based on the production data obtained in the absence of a subject,[11] which is summarized in the Web-based electronic supplement to this article.

Clinical validation of the model was performed using CO production data that most closely resembled those described in previous publications.[5,6,12] The carboxyhemoglobin concentration was calculated for clinically relevant conditions to demonstrate the predicted effects of absorbent drying, anemia, patient size, and fraction of inspired oxygen (F_{IO_2}) on simulated CO exposures. These assumed approximate 1.2–minimum alveolar concentrations of isoflurane or desflurane and 1 l/min fresh gas flow.

Statistical Analysis

Correlation coefficients and mean differences between experimental and calculated data were performed with StatView (Abacus Concepts, Berkeley, CA). No statistical analyses were performed for calculated data.

Results

Validation

Figure 1 demonstrates that the calculated carboxyhemoglobin concentrations show a good fit to the experimental data of Frink *et al.*[5] (n = 10; r^2 = 0.961; mean difference between calculated and experimental carboxyhemoglobin = 2.2%). For the exposure reported by

Berry *et al.*,[12] this model predicted carboxyhemoglobin within 2% of the measured value (n = 1) but also predicted a peak carboxyhemoglobin concentration of 42% before interventions to stop and treat the exposure. For the experiment by Bonome *et al.*[6] (not shown), the calculated and experimental data (n = 9) have an r^2 = 0.876 with a mean difference between calculated and experimental data of 6.9% carboxyhemoglobin.

Clinically Relevant Extrapolations

Figure 2 shows that, in an average-sized adult human, 24 h or more of absorbent drying results in carboxyhemoglobin concentrations that are associated with rapid development of severe poisoning, and 48 h or more of drying can result in lethal concentrations of CO with 7.5% desflurane. Similar but less severe trends exist with isoflurane, with later peak carboxyhemoglobin concentrations. Figures 3 and 4 show that the carboxyhemoglobin concentration is inversely related to hematocrit and patient size.

The effect of F_{IO_2} is shown in figure 5. This effect demonstrates that initially there is little difference in carboxyhemoglobin concentration during the first 15–20 min of exposure during these conditions, but later in the exposure there is considerable difference as a result of F_{IO_2}.
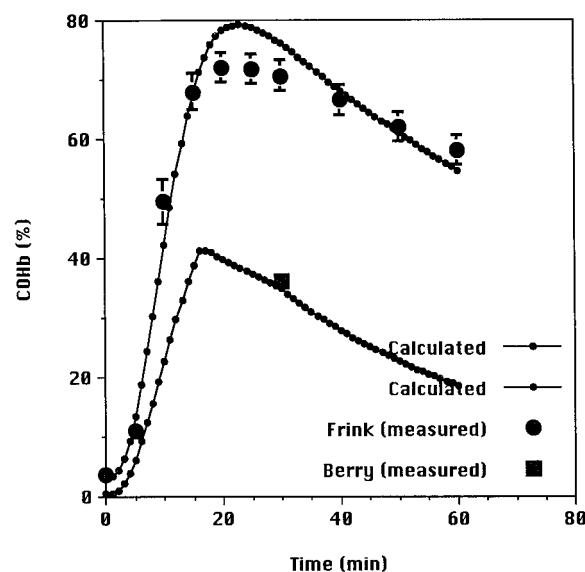

Fig. 1. Data used to validate the predicted carboxyhemoglobin (COHb) concentrations. These data show a good fit to the experimental data of Frink *et al.*[5] (n = 10; r^2 = 0.961; mean difference between calculated and experimental carboxyhemoglobin = 2.2%). For the exposure reported by Berry *et al.*,[12] this model predicted carboxyhemoglobin concentration within 2% of the measured value (n = 1) but also predicted a peak carboxyhemoglobin concentration of 42% before interventions to stop and treat the exposure.
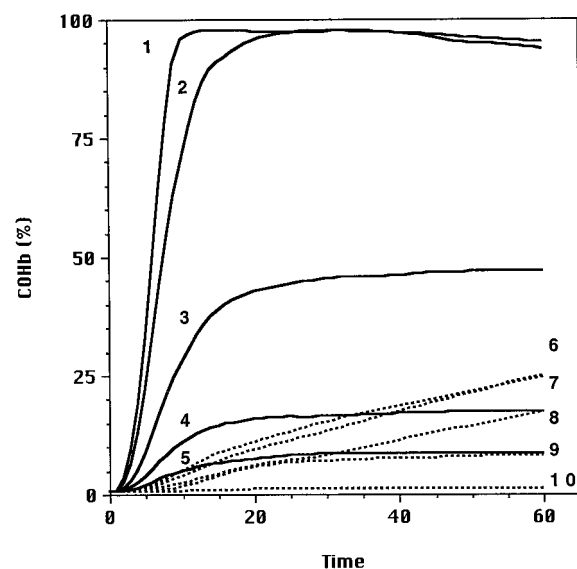

Fig. 2. The predicted effect of various barium hydroxide lime drying times on the carboxyhemoglobin (COHb) saturation in a 70-kg patient receiving an anesthetic at 1,000 ml/min fresh gas flow, a hematocrit of 42%, tidal volume of 15 ml/kg, respiratory rate of 10 breaths/min, and fraction of inspired oxygen of 40%. Solid lines 1, 2, 3, 4, and 5 represent complete desiccation, 66-, 48-, 24-, and 14-h drying time, respectively, at 10 l/min with 7.5% end-tidal desflurane. Note that highly dried absorbent rapidly produces carboxyhemoglobin concentrations in the lethal range. Dashed lines 6, 7, 8, 9, and 10 represent complete desiccation, 66-, 48-, 24-, and 14-h drying time, respectively, at 10 l/min with 1.5% end-tidal isoflurane.
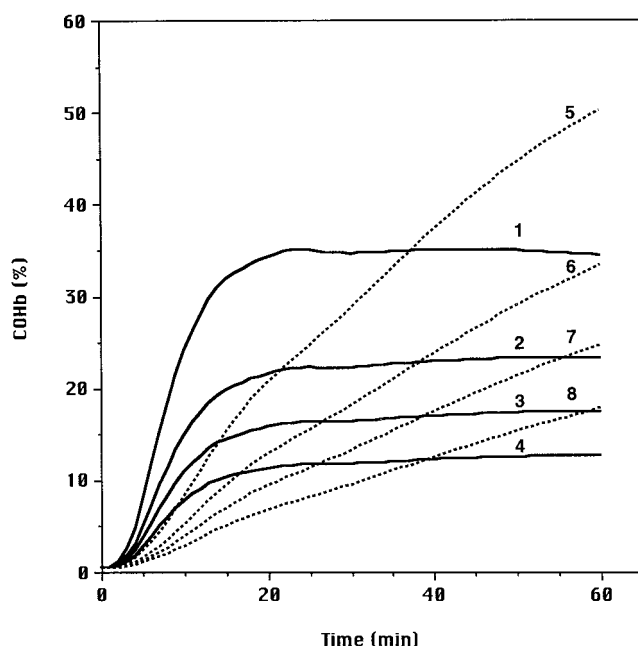
Fig. 3. The predicted effect of patient hematocrit on the carboxyhemoglobin (COHb) saturation in a 70-kg patient receiving an anesthetic at 1,000 ml/min fresh gas flow, tidal volume of 15 ml/kg, respiratory rate of 10 breaths/min, and fraction of inspired oxygen of 40%. Solid lines 1, 2, 3, and 4 represent hematocrits of 18, 30, 42, and 60%, respectively, with a 24-h barium hydroxide lime desiccation time and 7.5% end-tidal desflurane. Dashed lines 5, 6, 7, and 8 represent hematocrits of 18, 30, 42, and 60%, respectively, with a 66-h barium hydroxide lime desiccation time and 1.5% end-tidal isoflurane.

Discussion

Validation of the Model

Existing published data were used to validate this model, which predicts the data of Berry et al.[12] and Frink et al.[5] well. The fit is not as good in comparison to the data of Bonome et al.,[6] where a different anesthesia machine was used with a different circuit configuration, and the assumptions of gas flow patterns used in this model were knowingly incorrect.

Effect of Anesthetic and Degree of Desiccation

The results shown in figure 2 explain clinical observations that the most severe exposures to CO result from desflurane on Monday mornings when 66 h or more of absorbent desiccation have occurred at 10 l/min. An important extrapolation is that, with 24 h or less of absorbent desiccation in a 70-kg subject anesthetized with 1.5% isoflurane, this model predicts carboxyhemoglobin concentrations similar to those seen in smokers. This may not provoke the suspicion of intraoperative CO poisoning solely on the basis of the carboxyhemoglobin concentration, but with ischemic heart disease, even low carboxyhemoglobin concentrations can produce morbidity.[13-16]
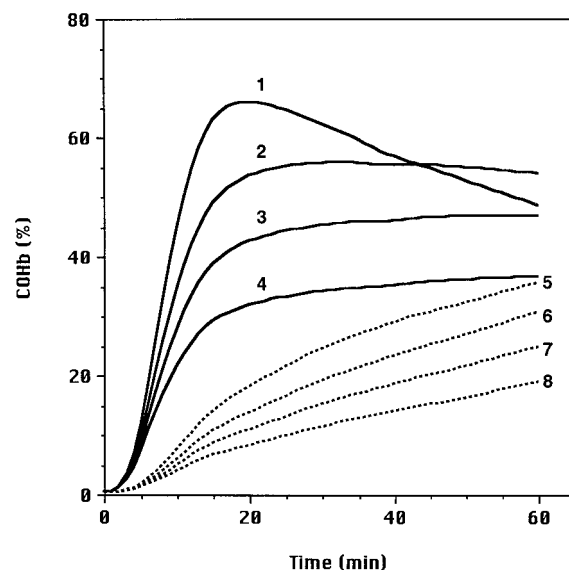
Fig. 4. The predicted effect of patient size on the carboxyhemoglobin (COHb) saturation at 42% hematocrit, 1,000 ml/min fresh gas flow, tidal volume of 15 ml/kg, respiratory rate of 10 breaths/min, and fraction of inspired oxygen of 40%. Solid lines 1, 2, 3, and 4 represent weights of 25, 50, 70, and 100 kg, respectively, with a 48-h barium hydroxide lime desiccation time and 7.5% end-tidal desflurane. Dashed lines 5, 6, 7, and 8 represent weights of 25, 50, 70, and 100 kg, respectively, with a 66-h barium hydroxide lime desiccation time and 1.5% end-tidal isoflurane.

Effect of Size and Hematocrit

These two factors are related because both determine the quantity of hemoglobin, which determines both carboxyhemoglobin concentrations and the quantity of CO removed from the breathing circuit. The effect of size is
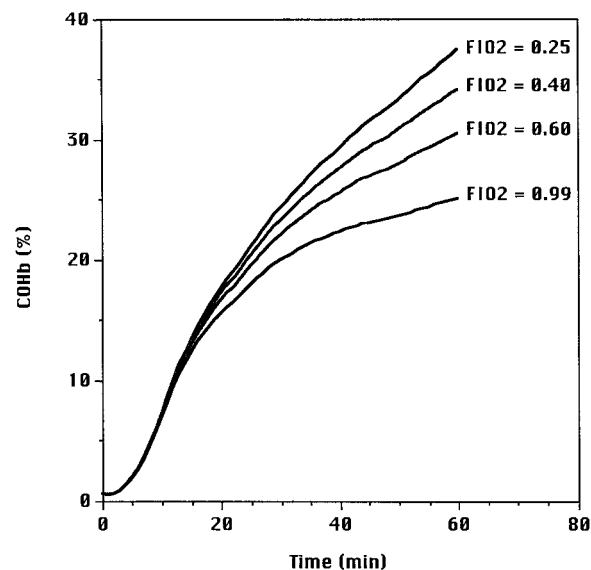

Fig. 5. The predicted effect of fraction of inspired oxygen (F_{IO_2}) on the carboxyhemoglobin (COHb) saturation in a patients receiving an anesthetic with 1.5% end-tidal isoflurane at 1,000 ml/min fresh gas flow. Other parameters are a 48-h barium hydroxide lime desiccation time, tidal volume of 15 ml/kg, respiratory rate of 10 breaths/min, hematocrit of 42%, and size of 25 kg.

more complex than the effect of hematocrit because smaller patients have proportionately smaller lungs and a lower diffusing capacity of CO.

Effect of Fraction of Inspired Oxygen

It is important to note that greater F_{IO_2} was less effective at preventing a rapid increase in carboxyhemoglobin concentrations than that predicted in a prior study using the CFK equation unmodified for uptake by the patient.[10] CO exposures in an anesthesia machine are unique in that a small quantity of CO is produced compared with environmental exposures. CO absorbed by the subject is removed from the breathing circuit, and this reduces the partial pressure, driving it to bind with hemoglobin. In a physically large patient with a relatively small CO exposure, equilibrium is never achieved. A high F_{IO_2} has minimal benefit because the CFK equation predicts that the uptake of CO is rate limited. Fortunately, physically large nonanemic patients are predicted to rarely experience a potentially lethal exposure to CO unless desflurane reacts with extremely dry absorbents. Conversely, a small patient with a low hematocrit will more rapidly attain equilibrium concentrations of carboxyhemoglobin, and a large protective effect of high F_{IO_2} is predicted.

Limitations of the Model

Conditions that result in hemoglobin desaturation in arterial blood cannot be modeled because the CFK equation requires that hemoglobin be saturated with either or both CO or oxygen. This model also requires that breathing circuit configuration to be the same as that postulated in Methods because only then will the fraction of gas rebreathed and eliminated from the circuit be adequately modeled. Validation of this model was performed against historical data where assumptions were required for the missing or unpublished data. Nevertheless, this model can be used to provide reasonable predictions of carboxyhemoglobin concentrations in a variety of situations likely to be encountered clinically.

The physiologic effects of CO poisoning cannot be predicted by this model. The physical status of an actual patient during anesthesia may mitigate or exacerbate any physiologic effect of CO. Patients with coronary artery disease may be injured by relatively small CO exposures that do not appear severe by carboxyhemoglobin concentrations.

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