A System Model for Halothane Closed-Circuit Anesthesia

Structure Considerations and Performance Evaluation

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Background: Previously, the authors described a physiologic model for closed-circuit inhalational anesthesia. The basic version of this system model was clinically validated for isoflurane. An extended version adopted nonpulmonary elimination causing a constant fraction of anesthetic to be irreversibly lost. This version improved the accuracy of the model for enflurane. The model's performance for other inhalational anesthetics that are not biochemically inert, such as halothane, remained to be evaluated.

Methods: The current study quantified the predictive performance of four versions of the model by comparison of the predicted and measured alveolar halothane concentration-time profiles in 53 patients. Version A did not incorporate nonpulmonary elimination, whereas version D adopted a nonlinear hepatic nonpulmonary elimination following Michaelis-Menten kinetics. A and D used fixed partition coefficients. Their counterparts, A′ and D′, were formulated to examine the impact of age-adjusted partition coefficients on the accuracy of our model. Each concentration measured by mass spectrometry was compared to four predicted concentrations calculated by four computer simulations (one *per* version). For each patient, the authors calculated the root mean squared error (*rmse;* typical error size), bias (systematic component), and scatter of the prediction errors.

Results: Fifty-three patients were anesthetized with 330 ml of liquid halothane *via* 426 bolus injections during more than 61 h; 21,890 alveolar concentrations (average 0.6 vol%) were measured. Version D′ showed the best overall performance with an *rmse* of 19.6 ± 7.2%, a bias of 0.5 ± 15.9%, and a scatter of 13.2 ± 3.5% (mean ± SD).

Conclusions: The model incorporating nonpulmonary elimination and age-adjusted partition coefficients (D′) is sufficiently reliable and accurate to represent halothane closed-circuit anesthesia. This system model, with its various versions, is a valuable tool to predict the dynamics of isoflurane, enflurane, and halothane for clinical, educational, and research purposes. (Key words: Age factors: solubility. Anesthetic techniques: closed-circuit. Anesthetics, volatile: halothane. Biotransformation: drug. Computer, simulation: models. Equipment, circuits: closed. Measurement techniques: mass spectrometry. Pharmacokinetics: distribution; elimination; kinetics; physiologic model; uptake.)

PREVIOUSLY, we defined a physiologic model for closed-circuit inhalation anesthesia to evaluate its predictive performance for the widely used volatile anesthetics.[1] Using isoflurane as the anesthetic, we found close agreement between end-tidal isoflurane concentrations measured in our clinical study and those predicted by our basic system model.[2] For enflurane, we demonstrated that the introduction of a nonpulmonary route of elimination (NPE) into the model improved its clinical accuracy. In the absence of directly applicable data for enflurane, we emulated its NPE by adopting the irreversible loss of a constant fraction of enflurane from the arterial hepatic blood flow.[3]

Many studies reported an even greater NPE for halothane than for enflurane. Moreover, a critical appraisal of the literature showed that (1) the NPE of halothane is better documented than that of enflurane, *e.g.* data are available on the nonlinear kinetics of halothane,[4–7] and (2) there exists an age-dependent variation in the solubility of inhalation anesthetics.[8–10] However, to our current knowledge, there was no validated physiologic model to which all this information was supplied.

The primary objective of the current study was to quantify our model's predictive performance for halothane closed-circuit anesthesia. In addition, we ques-

tioned the impact on the model's accuracy and thus on its clinical relevance of (1) the adoption of a non-linear NPE in this model and (2) the use of age-related *versus* fixed partition coefficients. Therefore, four versions of our system model were formulated. One version (A) does not include NPE; another version (D) accounts for a nonlinear NPE by adopting Michaelis-Menten kinetics in the liver compartment. These two versions use fixed partition coefficients, whereas their counterparts (versions A' and D') use age-related blood-gas and tissue-blood partition coefficients.

The system model is capable of predicting the time courses of the alveolar concentrations of a volatile anesthetic after the addition of increments of a mass of anesthetic into the closed-circuit system. Bolus injections of liquid halothane were administered into the expiratory limb of the closed circuit, and the observed alveolar concentrations were quantitatively compared with those predicted by the different versions of our model.

Materials and Methods

The methods have been described in detail earlier[2,3] and are summarized here with subsequent modifications and elaborations.

Patients and Anesthetic Technique

Fifty-three consenting patients (ASA physical status 1 and 2) scheduled for elective eye surgical procedures were studied after approval of the Institutional Ethical and Research Committee. In the design of our study, we did not include patients with prior halothane anesthesia or middle-aged females (40–60 yr old) who were also very obese (body mass index > 30 kg/m^2), because these epidemiologic features may introduce an increased risk of halothane hepatotoxicity.[11]

Diazepam (5–10 mg) and droperidol (2.5–5 mg) were given orally 1 h before surgery. Anesthesia was induced with 0.1–0.2 mg intravenous fentanyl, a dose of thiopental sufficient to obtund the eyelash reflex, and 0.1 mg/kg vecuronium. After placement of a cuffed endotracheal tube, the lungs of the patient were mechanically ventilated with a high fresh gas flow of oxygen and nitrous oxide in a 1:2 ratio for 5 min or until the end-tidal nitrogen concentration was less than 1 vol%. Subsequently, the anesthetic system was closed, controlled ventilation was instituted (maintaining an end-tidal carbon dioxide concentration of 4.0–4.5

vol%), and anesthesia using the liquid injection method was administered by one of us (P.M.V.). One bolus of liquid halothane 0.015 ml/kg ($\pm$0.1 ml) was injected after the start of closed-circuit conditions to rapidly attain the end-tidal halothane concentration desired in an individual patient. During maintenance, we administered halothane bolus injections of 0.01 ml/kg. We did not use a rigid drug regimen but modified the halothane administration according to the patient's response and/or the end-tidal halothane concentration measured.

Instrumentation

The anesthetic equipment consisted of a Modulus CD anesthesia system (Ohmeda, Madison, WI) with an integrated ARKIVE automated anesthesia record-keeper (Ohmeda, Madison, WI, and DIATEK, San Diego, CA). The latter processed the signals provided by the instruments integrated in the Modulus CD anesthesia system for monitoring patient's vital signs. A standing bellows ventilator (Ohmeda 7850) was used. Leaks in the circuit were detected by plugging the Y-piece, pressurizing the breathing system to 4 kPa (40 cmH$_2$O), and observing the volume and pressure gauge; a gas leak up to 60 ml/min was accepted. A set of corrugated polyethylene tubings (Siemens Elema, Solna, Sweden) was used. Soda-lime was replaced at the beginning of each study day.

The fresh gas flow of oxygen and nitrous oxide was adjusted manually to maintain the inspiratory oxygen concentration between 30% and 40% and to keep the standing bellows at the same end-expiratory volume. We injected boluses of liquid halothane into the expiratory limb of the circuit, using a 2-ml glass syringe and a homemade nickel-plated brass injection port. Immediate contact of the anesthetic agent with plastic tubing was avoided because of the corrosive properties of liquid halothane. Between successive procedures, the ventilator and anesthetic circuit were flushed with a high fresh gas flow of 100% O$_2$ for 5 min.

Data acquisition and part of the instrumentation are illustrated in the upper half of figure 1. A respiratory mass spectrometer (Centronic 200 MGA, CaSE, Biggin Hill, England) continuously sampled gas at the Y-piece *via* a side-stream sampling port through a 30-m nylon catheter with a 10–90% response time of 302 ms for halothane.[12] The mass spectrometer sample flow (measured with a bubble flow meter) was 40 ml/min. Before using the mass spectrometer, we verified its calibration for halothane with a calibration gas mixture containing
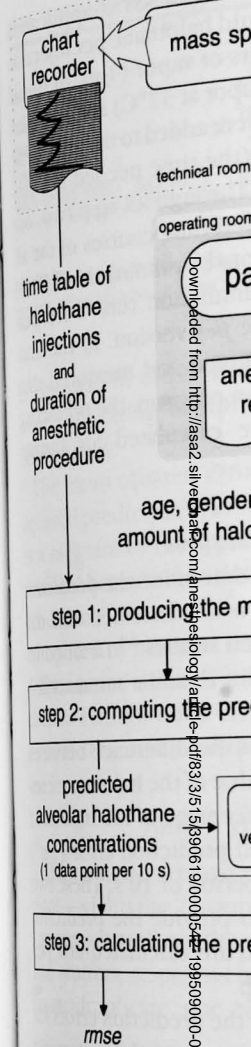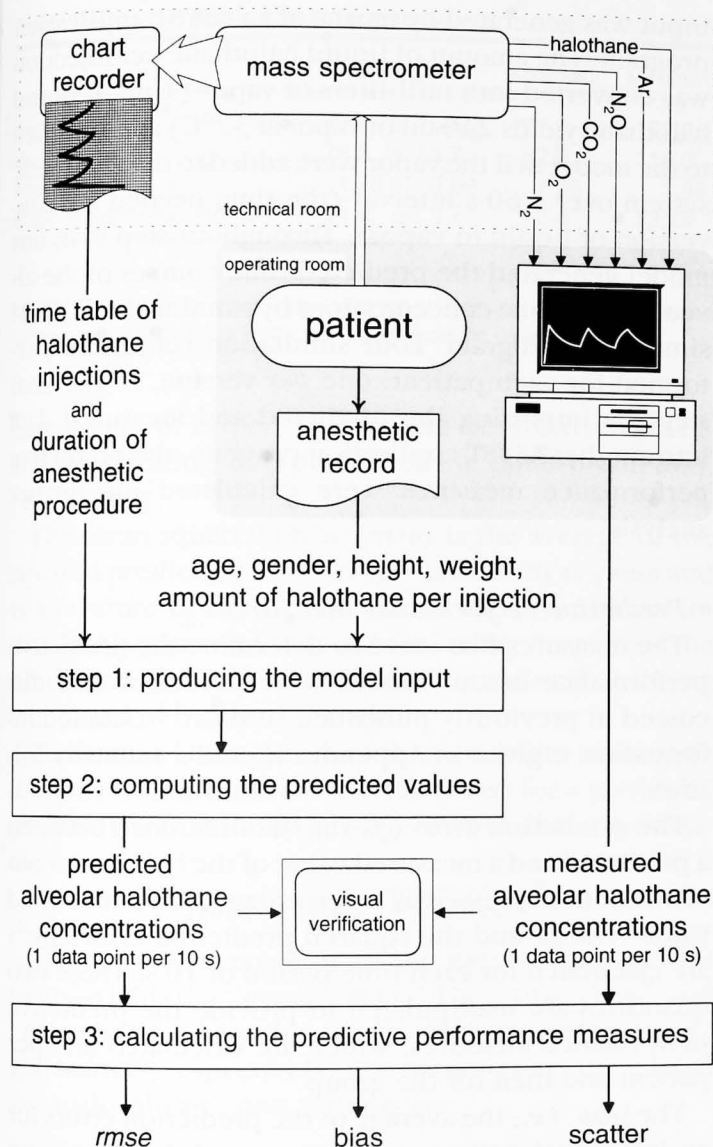
Fig. 1. Flow diagram of data acquisition and data processing. The upper half of the figure depicts the acquisition of data. There was a continuous online analysis and recording of the respiratory waveforms. One alveolar halothane concentration per 10 s was saved on the hard disk of the computer system. The necessary model input data were collected for each individual patient. The lower half of the figure illustrates the three steps of data processing: (1) the anthropometric data and halothane dosage schedule were supplied to the model; (2) computer simulation runs (four, one per model version) generated the predicted values; and (3) the predictive performance measures of the four versions were calculated. *rmse* = root mean squared error.

0.98% halothane in 30.2% oxygen, 6.05% carbon dioxide, 30.1% nitrogen, balance gas nitrous oxide (L'Air Liquide, Antwerpen, Belgium). The coefficient of variation of the mass spectrometer readings is 2%.

‖ A list on paper is available on request.

An eight-channel chart recorder (Gould-Brush 481) running at 6 mm/min recorded the mass spectrometer output signals. The chart recorder and the mass spectrometer were located in a room next to the operating theater.

An AT personal computer system (640 kB RAM, 80287 coprocessor, 30 Mb hard disk unit, and color VGA graphics board, IBM, Portsmouth, United Kingdom) and a 12-bit analog-to-digital board (DAS-16, Keithley Metrabyte, Taunton, MA) processed the signals from the mass spectrometer at a sample rate of 10 Hz. The data acquisition software was developed with the aid of ASYST Version 4.0 (Keithley Metrabyte). Online analysis of the respiratory waveforms allowed the continuous monitoring of the actual inspiratory and end-expiratory concentrations in the operating room of nitrogen, oxygen, carbon dioxide, nitrous oxide, argon, and halothane. The trends of the inspiratory and end-expiratory concentrations of halothane and oxygen of the last 20 min were displayed continuously in the operating room. The last end-tidal halothane concentration *per* 10-s period was saved on the hard disk. We used an Intel 80486-based computer system for simulation purposes and further data processing.

The Model: Its Versions and Input

The model we sought to validate was our physiologic model, which was developed with a special-purpose simulation language (TUTSIM Professional Version 7.0, Meerman Automation, Neede, The Netherlands).‖ Figure 2 schematically depicts the structure of this model, and the inset shows the size and mechanisms of NPE. Version A does not account for a route of NPE, and its structure is identical to the structure of version A in the previous study for isoflurane, which assumed that isoflurane's NPE was zero.[2] In the current study, version D was constructed to define a nonlinear NPE as a result of biotransformation obeying Michaelis-Menten kinetics. To mimic this NPE, we implemented the data of various authors[4-6] who demonstrated a concentration-dependent hepatic halothane metabolism. The equations used to calculate the fractions removed from the liver blood flow are presented in Appendix I.

Versions A and D use fixed partition coefficients according to Lowe and Ernst.[13] Versions A' and D' are the counterparts of versions A and D, respectively. Version A' and D' adopt blood-gas and tissue-blood partition coefficients that are functions of age according to the recent data of Lerman *et al.*[8,9] and Malviya and Lerman.[10] Because they reported values for only five different ages, we had to interpolate for the intervening
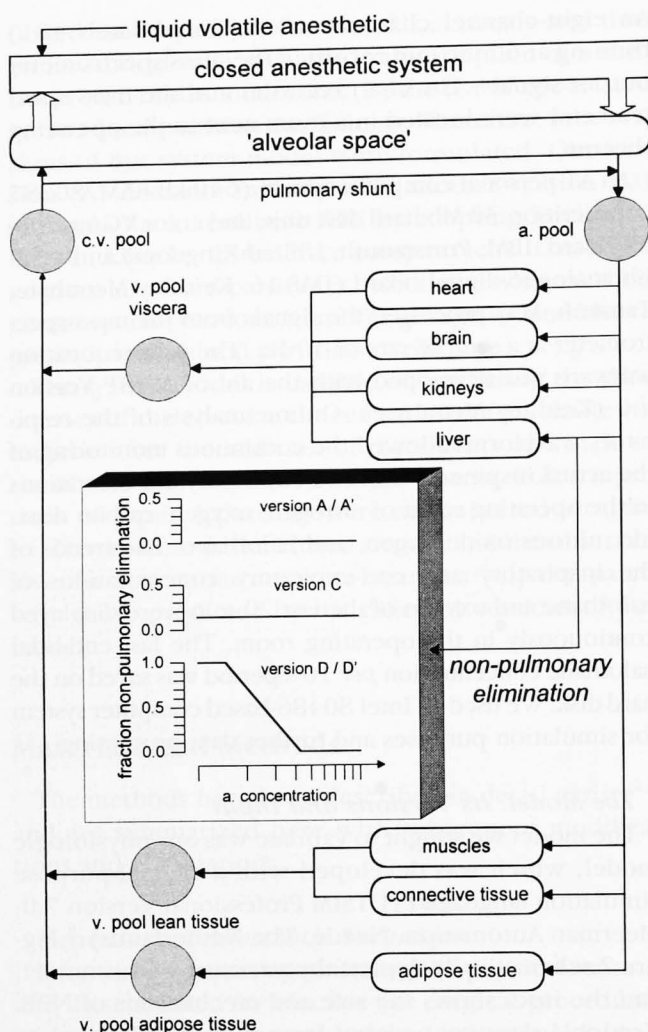
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Fig. 2. Schematic diagram of our 14-compartment physiologic model. (*Inset*) The various versions with special emphasis on nonpulmonary elimination (NPE). The fraction NPE on the ordinate is the fraction of the amount of anesthetic agent irreversibly lost from the hepatic blood flow. The arterial halothane concentration is on the abscissa. Version A has the identical structure of A in the previous validation study for isoflurane and assumes that NPE is zero. Version C has been used only in the enflurane validation study and uses a constant fraction of NPE. Version D incorporates a nonlinear NPE following Michaelis-Menten kinetics. Versions A, C, and D use fixed partition coefficients, whereas A' and D' adopt age-related partition coefficients. (c)v = (central) venous; a = arterial.

ages of individual patients. Where no age-adjusted values were available, the data reported by Lowe and Ernst were used. The drug-specific data for halothane incorporated in the model are listed in table 1.

Data processing was the three-step process shown in the lower half of figure 1. During step one, the model

input was generated by means of an ASYST application program. The amount of liquid halothane per injection was converted into milliliters of vapor (1 ml of liquid halothane yields 240 ml of vapor at 37°C) and supplied to the model as if the vapor were added to the anesthetic system over a 60-s interval (the time needed for conversion of liquid to vapor). Throughout step two, our model generated the predicted time courses of the alveolar halothane concentrations by running the TUTSIM simulation program. Four simulation runs were performed for each patient: one *per* version. In the final step, by importing the predicted and measured data into another ASYST application program, the predictive performance measures were calculated for further analysis.

Predictive Performance Measures

The measures that serve to determine the predictive performance of our model were described and discussed in previously published studies.[2,3] Detailed information is given in Appendix II, and a summary follows.

The prediction error (*pe*) is the difference between a predicted and a measured value of the halothane concentration, expressed as a percentage of the measured value. The *pe* and the squared prediction error (*pe²*) are calculated for each time period of 10 s. These two quantities are manipulated to provide the predictive performance measures, which are calculated first per patient and then for the group.

The bias, *i.e.*, the average of the prediction errors for an individual patient, is a measure of the systematic

Table 1. Halothane Partition Coefficients

	Version* A/D (All Ages)	Version A'/D'† (yr)				
		0	5	35	60	80
Blood–gas	2.4	2.14	2.39	2.65	2.51	2.41
Tissue–blood						
Lung	2.0					
Kidney	1.5					
Heart	2.5	2.06		1.42	2.17	2.06
Brain	2.3	1.54		2.03	1.92	2.02
Liver	2.5	2.12		2.15	2.84	2.80
Muscle	1.3	1.25		1.44	2.31	2.90
Connective	1.2					
Adipose	75.0			60.62	66.56	67.34

* According to Lowe and Ernst.[13]

† According to Lerman et al.[8,9] and Malviya and Lerman[10]; where no age-adjusted values were available, the data reported by Lowe and Ernst were used.

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Table 2. Demographic Characteristics

	Mean ± SD	Minimum	Maximum
Age (yr)	47.4 ± 15.5	21.0	72.0
Weight (kg)	76.8 ± 13.7	52.0	110.0
Height (m)	1.76 ± 0.09	1.55	1.96
Body mass index* (kg · m⁻²)	24.6 ± 3.7	17.8	35.4

N = 53.

* Patients with a body mass index ≤20 kg · m⁻² can be considered slender; patients with a body mass index ≥25 kg · m⁻² can be designated obese.

component of error. The bias can be positive or negative, indicating overprediction or underprediction, respectively.

The mean squared error (*mse*) is the average of the squared prediction errors. *rmse* is defined as $\sqrt{mse}$ and is a measure of the typical size of the error for an individual because it is not influenced by the sign of the prediction errors. *rmse* can be formulated as being composed of bias and scatter.

The scatter is a measure of the variability of the prediction errors around their mean (bias) for a particular patient. The relationship between *rmse,* bias, and scatter is

$$rmse = \sqrt{bias^2 + scatter^2}.$$

The numeric average of all the *rmse*s—one per patient—yields the "group *rmse*." The "group bias" and "group scatter" are the means of the individual biases and scatters, respectively. The measures are calculated in quadruplicate, one *per* version.

Statistical Analysis

The Friedman two-way analysis of variance was used to compare the predictive performances of the four versions. If the Friedman analysis revealed a difference, *post hoc* analysis using sign tests for paired data was done.

We used binary logistic regression to study the potential influence of gender, age, body mass index (weight/height²), duration of closed-circuit anesthesia, and the number of injections per hour on each of two response variables: bias and scatter of the prediction errors.

The criterion for rejection of the null hypothesis was $P < 0.05$ (two-sided).

Results

Thirty-four males and 19 females participated in this study; their demographic data are listed in table 2. The

53 patients provided 21,890 samples of intraoperative data. They were anesthetized with 330 ml of liquid halothane during more than 61 h, not including the additional hours after discontinuing closed-circuit conditions; details on the closed-circuit conditions are recorded in table 3.

Figures 3 and 4 illustrate the measured and predicted concentrations as a function of time in two representative patients. Figure 3 provides a visual impression of the quality of the predictions achieved with version D′ for the longest anesthetic procedure. Figure 4 shows the predictions generated by versions A and D′ for the average patient.

Predictive Performance of the Versions

Figures 5 and 6 are two dot diagrams showing the distribution of the individual biases and scatters along with their means and standard deviations for the various versions. Figure 5 shows that version D′ performs better than the other versions as to the number of patients with a negative *versus* positive bias. A positive group bias is a measure of systematic overprediction, whereas a negative group bias indicates a systematic underprediction. Note also the normal distribution of the data for the four versions. Figure 6 illustrates that the range of the individual scatters is smallest for version D′.

Table 4 lists the group *rmse*s, biases, and scatters. The magnitude of the biases of all of the versions was smaller than their scatters. This means that the average, typical size of the prediction error mainly was due to the scatter rather than to the systematic component.

Figure 7 summarizes and displays the results for the four versions. Each patient is represented by one dot on each of the four X-Y plots. The iso-*rmse* lines allow

Table 3. Details on the Duration of Closed-circuit Conditions, the Number of Data Points, and the Administration of Liquid Halothane into the Closed System

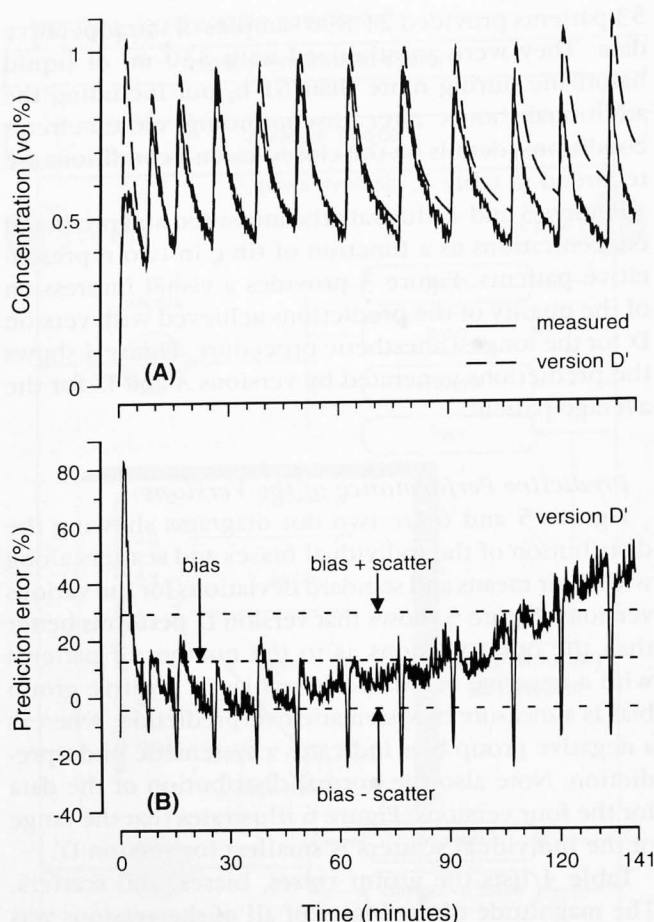|	Mean ± SD	Minimum	Maximum	Total
Duration (min)	69.2 ± 25.7	35.0	141.0	3,666
Number of data points	413 ± 154	208	844	21,890
Number of injections	8 ± 2.5	4	16	426
Number of injections per hour	7.1 ± 1.03	5.1	9.4	
Volume of liquid halothane (ml)	6.2 ± 2.1	2.5	12.2	329.9
Average measured end-tidal halothane concentration (vol%)	0.63 ± 0.11	0.40	0.92	

N = 53.

Fig. 3. (*A*) **Measured and predicted alveolar halothane concentrations obtained in the longest case. A 28-yr-old patient (weight 75 kg, height 1.90 m) was adequately anesthetized with 12 bolus injections of liquid halothane (total 9.55 ml) into the closed-circuit system over 141 min.** (*B*) **Profile of the predictive performance for version D′. The *rmse*, bias, and scatter for this patient were 20.91%, 12.57%, and 16.71%, respectively.**

a visual impression of the overall performance of the model and its versions. A rank order exists for the number of patients having an *rmse* > 30%: A > D > A′ > D′ (13, 10, 7, and 5 out of 53 patients, respectively).

The Friedman analysis revealed that there is a difference between the four versions for the group *rmse*s (*P* < 0.001). The sign tests for paired data showed that version D′ performs better and that version A performs worse than the three other versions. A difference also is found for the group biases: version A differs from A′, D, and D′. The null hypothesis was rejected for the group scatters. Table 4 shows that the group scatter for each of the versions differs from those of the three oth-

ers. This means that the following rank order exists for the scatters: A > D > A′ > D′.

A potential influence of the duration of closed-circuit anesthesia on the bias of versions D and D′ was found. It corroborates the trend toward overprediction during the longer anesthetic procedures, as illustrated in figure 3. The other explanatory variables were not significant.

Discussion

The primary goal of our study was to extend our physiologic model for the anesthetic agent halothane, which is not biochemically inert, and to quantify its predictive performance. We adapted the model's structural features, formulating four versions of this model, by the incorporation of more recent physicochemical data retrieved from the literature. The main point of originality in the design of these new versions lies in the use of age-related partition coefficients and a route of nonlinear hepatic NPE following Michaelis-Menten kinetics. We evaluated the impact of these different inputs of information on the accuracy of our system model without inclining *a priori* to one of these versions.

It is of critical importance to validate a model, because far-reaching conclusions can be drawn from model behavior. Standards to judge the validity of a physiologic model for volatile anesthetics hitherto have not been defined explicitly. Also, in our previous work, we did not substantiate why the reported error size could be qualified as acceptable.[2,3] By analogy with work in other areas of research,[14,15] we need to propose more precise rules to determine whether a physiologic model for inhaled anesthetic agents has acceptable accuracy.

First, a valid operational model should not underpredict or overpredict reality in a systematic way. Although it is reasonable to expect a certain degree of bias for each patient, the group bias should approximate zero. For example, a model that suffers from a systematic underprediction would teach the user in a training environment to administer more drug than the average patient would need to attain a desired endtidal concentration. We propose that the magnitude of the group bias should not exceed 10% because it can be defended that such a degree of bias allows prediction within limits to which inhaled anesthetic agents can be used safely.

Second, if the group bias approximates zero, the typical error size should be acceptable for a majority of
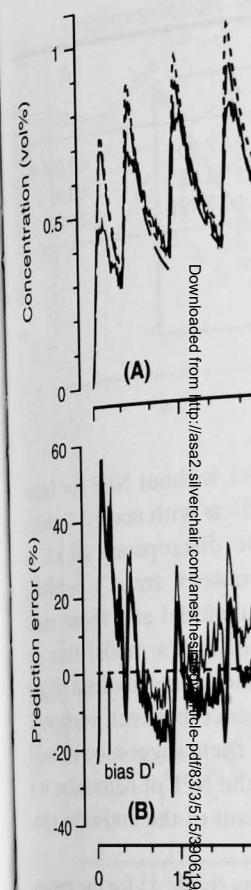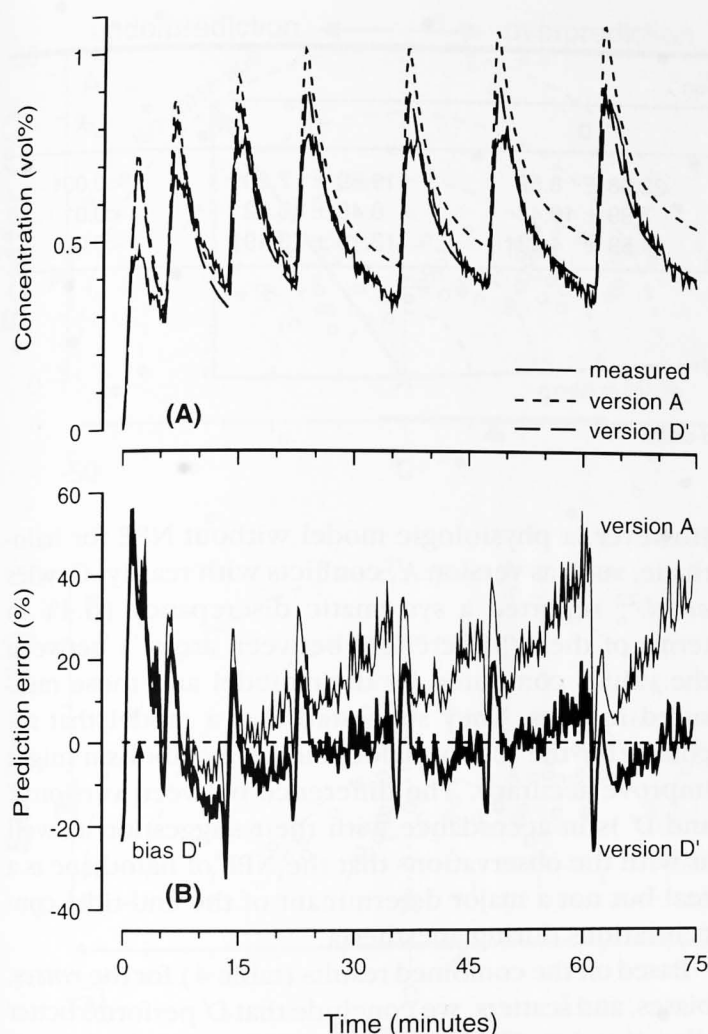
Fig. 4. (A) Measured and predicted alveolar halothane concentrations obtained in the average patient. A 52-yr-old patient (weight 74 kg, height 1.67 m) was adequately anesthetized with seven bolus injections (total 5.50 ml) of liquid halothane into the closed-circuit system over 75 min. (B) Time course of the prediction errors for version A without nonpulmonary elimination (NPE) and fixed partition coefficients and version D′ with a nonlinear NPE and age-adjusted partition coefficients. The *rmse*, bias, and scatter for this patient were 11.37%, 0.24%, and 11.37%, respectively for version D′. As a comparison, the *rmse*, bias, and scatter were 22.42, 17.64, and 13.83%, respectively for version A.

the patients. An acceptable error size must be defined on the basis of the biologic variability found in a general human population. The variability in uptake of inhaled anesthetics ranges from 10% to 33% (coefficient of variation, *i.e.,* one standard deviation divided by the mean times 100).[16–21] On these grounds, we propose that the typical error size of a physiologic model with zero group bias is acceptable if the *rmse* of at least 68% of the subjects studied is <30%. From the point of view of the user of a model, one would wish that
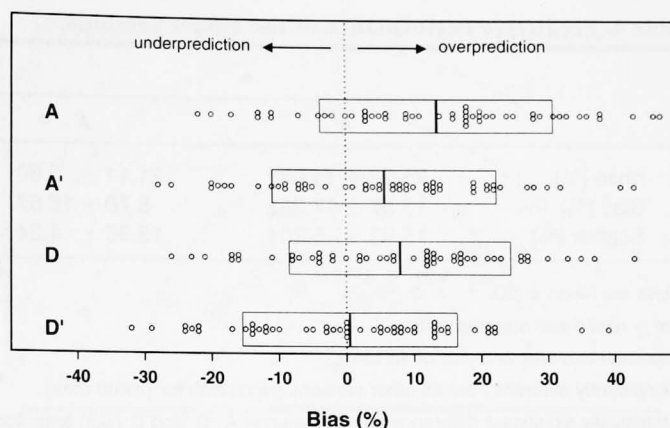

Fig. 5. Dot diagram showing the distribution of the individual biases (n = 53) and the group biases with their standard deviations for the four versions. Version A shows a systematic overprediction (group bias 13.57%). Version D′ has a more equal distribution of the number of negative *versus* positive biases and produces a clinically negligible group bias (0.48%). The values for the individual biases were rounded to whole numbers to avoid superposition of dots. Note that the dots represent four times 53 paired observations. | = group bias.

the *rmse* is less than 30% for an even greater proportion of the subjects (preferably 90% or more). This may only prove possible if some knowledge on an individual patient can be supplied to the model.

Although a physiologic model can be designated valid on the basis of the two quantitative requirements given above, some discussion remains when its structure fails to reflect some well established data from the literature.
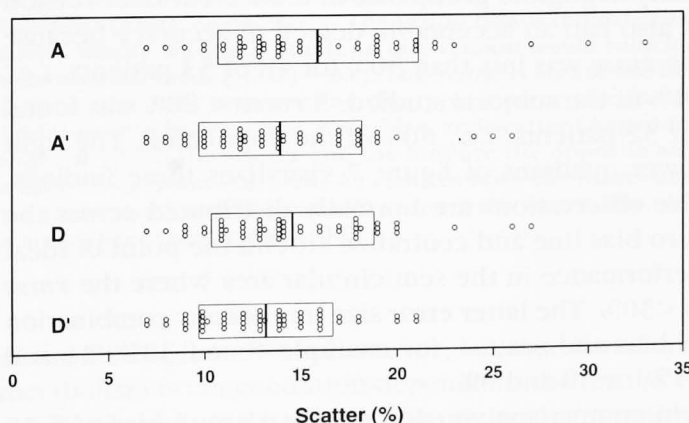

Fig. 6. Distribution of the individual scatters (n = 53) for the four versions as well as the group scatters and their standard deviations. Statistical significant difference between the versions results in the rank order A > D > A′ > D′. The incorporation of age-adjusted partition coefficients (versions A′ and D′) lowers the scatters, *i.e.* improves the accuracy of the model. The values for the individual scatters were rounded to whole numbers to avoid superposition of dots. Dots represent four times 53 paired observations. | = group scatter.

Table 4. Predictive Performance of the Model Versions

	Version				
	A	A′	D	D′	*P**
rmse (%)	25.28 ± 11.08†	21.11 ± 8.60	22.08 ± 8.59	19.59 ± 7.20†	<0.001
Bias (%)	13.57 ± 17.35‡	5.70 ± 16.67	7.99 ± 16.44	0.48 ± 15.92	<0.01
Scatter (%)	15.92 ± 5.20†	13.96 ± 4.24†	14.59 ± 4.23†	13.18 ± 3.49†	<0.001

Values are mean ± SD.

rmse = root mean squared error.

* Friedman two-way analysis of variance.

† Significantly different from all other versions (sign tests for paired data).

‡ Statistically significant difference *versus* versions A′, D, and D′ (sign tests for paired data).

The goal of physiologic modelling is to put into overt form the *a priori* knowledge about a system. In a teaching situation, a model for the uptake, distribution, and elimination of halothane without NPE would clash with the information on halothane biotransformation. In the case of model versions with similar accuracies but different structures, we therefore propose to select the model version with the structure incorporating the greatest part of available data.

Major Findings

The principal finding of this study is that only versions A′, D, and D′ match our quantitative criteria outlined above and are considered valid (fig. 7 and table 4). The results indicate that these three versions only slightly overpredict reality. Version D′ produced a clinically negligible group bias of 0.48 ± 15.92%. Version D′ also had an acceptable degree of accuracy because the *rmse* was less than 30% for 48 of 53 patients, *i.e.*, 91% of the subjects studied. A *rmse* < 20% was found for 32 patients, *i.e.*, 60% of the population. The right lower quadrant of figure 7 visualizes these findings. The observations are normally distributed across the zero bias line and centralize around the point of ideal performance in the semicircular area where the *rmse* is <30%. The latter error size implies any combination of bias and scatter, for example 0 and 30%, 21 and 21%, or 30 and 0%.

In comparison, version A′ gave a group bias of 5.70 ± 16.67%. The distribution of patients with a negative *versus* positive bias as shown in figures 5 and 7 represents the slight systematic overprediction of this version. A *rmse* less than 30% or 20% was found for 46 or 31 patients, respectively, *i.e.*, 87% or 58% of the population. These figures are little less than for D′ and thus suggest that our basic system model is robust.

However, a physiologic model without NPE for halothane, such as version A′, conflicts with reality. Cowles *et al.*[22] reported a systematic discrepancy (6.4% in terms of their "differences between areas") between the values computed by their model and those measured in dogs. They suggested that a model that accounts for the loss of halothane by metabolism might improve accuracy. The difference between version A′ and D′ is in accordance with their suggestion as well as with the observations that the NPE of halothane is a real but not a major determinant of the end-tidal concentrations during anesthesia.

Based on the combined results (table 4) for the *rmse*s, biases, and scatters, we conclude that D′ performs better than A′ and D. The structure of D′ also reflects the well documented NPE of halothane. Therefore, we prefer to use version D′ for further work with halothane.

Nonpulmonary Elimination

Although version D′ closely predicts the alveolar concentration of halothane, our results do not prove that its structure is absolutely correct. One of the difficulties with physiologic models lies in obtaining the necessary quantification data,[23] especially if a model for humans is to be conceived and completed.

All hydrocarbon inhalation anesthetics undergo biotransformation, and small quantities leave the body unchanged *via* nonpulmonary excretory pathways[24-30] or the ventilator or closed-circuit system during anesthesia.[31-35] Mass balance studies do not discriminate between the sources of anesthetic loss: They measure the total irreversible anesthetic loss. As such, these studies seemed useful for an all-embracing formulation of NPE with only one parameter, *e.g.*, a fixed extraction ratio. Unfortunately, there is a large variability in the experimental results: a range of "anesthetic loss" as
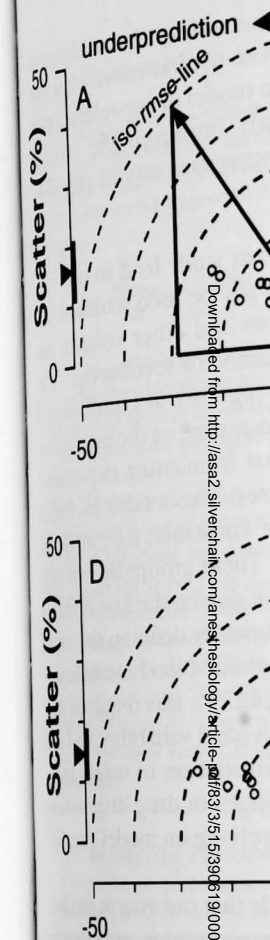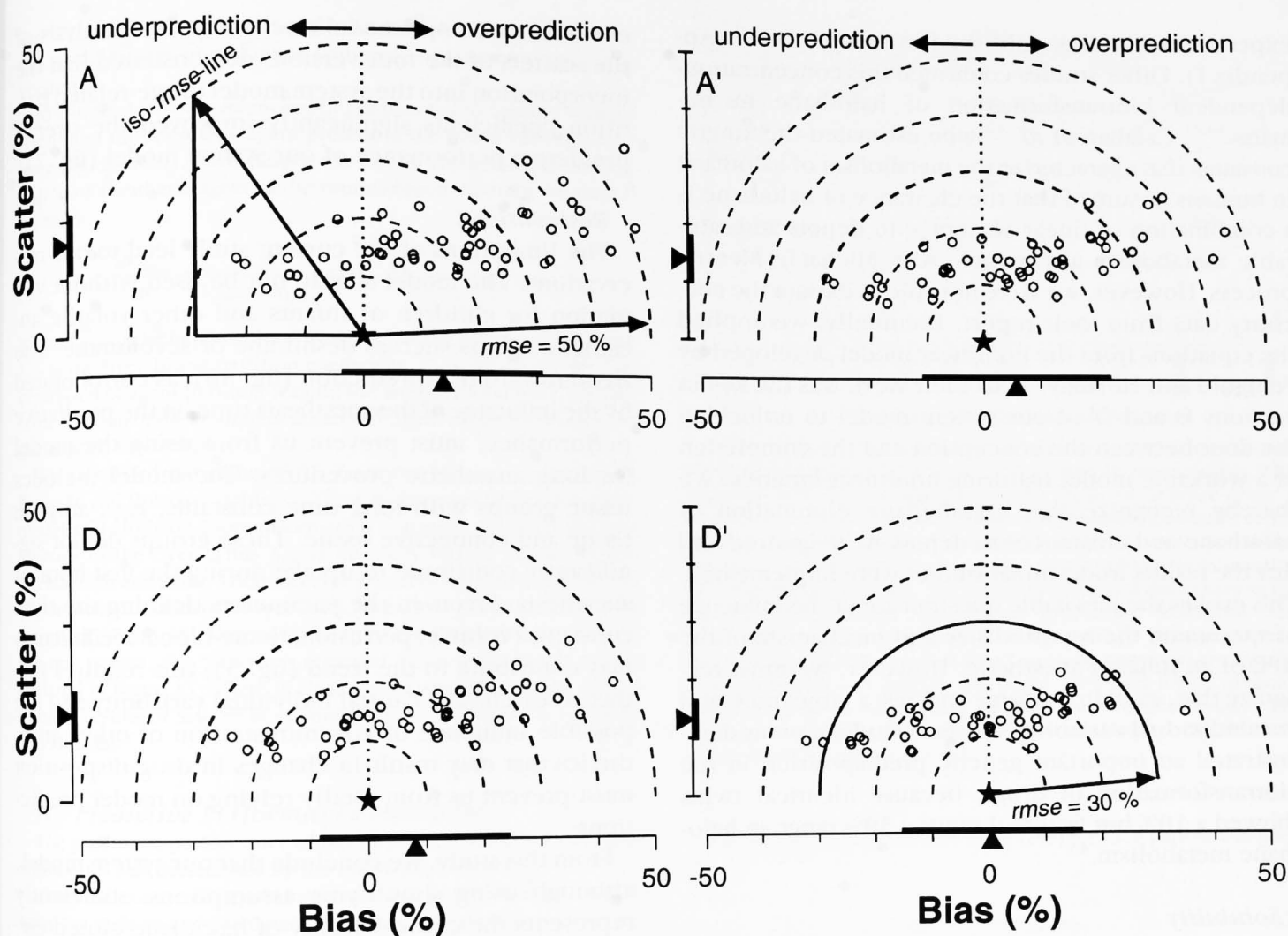
Fig. 7. Comparison of predictive performance measures obtained for model versions A, A′, D, and D′ in 53 patients. The individual scatters of the patients are plotted *versus* their individual biases for the four versions. The triangles and the thick lines on the abscissas and the ordinates represent the group biases (±SD) and scatters (±SD), respectively. The group biases indicate that all versions suffer from overprediction, with A taking the worst position. Ideally, all observations on one version would coincide with the star representing the point of ideal performance (root mean squared error (*rmse*) = 0%). The semicircles are the iso-*rmse*-lines from 10% to 50%. The distance between the star and a dot is the *rmse* representing the typical error size for an individual patient. The left upper plot visualizes the mathematical relationship between the *rmse*, bias, and scatter (Appendix II, equation A5). The *rmse* is the hypotenuse of a right-angled triangle of which the scatter and the bias are the opposite and the adjacent, respectively. The adoption of a nonlinear nonpulmonary elimination (D *versus* A) reduces both the biases and the scatters. The incorporation of age-adjusted partition coefficients (A′ *versus* A and D′ *versus* D) reduces the *rmse*s. The plot for D′ shows that 91% of the patients are found in the semicircular area where the *rmse* is <30%.

broad as 50–80% has been reported.[30,36–39] Therefore, we refrained from using a fixed extraction ratio. In addition, adopting a fixed extraction ratio would have patently conflicted with the studies confirming nonlinear kinetics.[4–7,28] Many studies in humans, including the numerous toxicity investigations and case reports on halothane hepatitis, have shown halothane biotransformation. Most of these studies focused on the formation and measurement of metabolites, and all reports agree on the fact that the liver is the primary site

of the NPE of halothane. However, because halothane metabolism is concentration-dependent, the results of metabolic and uptake studies at a single concentration may not apply at another.

Sawyer *et al.*[4] demonstrated in miniature swine that a greater fraction of the halothane delivered to the liver disappeared at lower concentration. They defined the fraction removed as equal with halothane metabolism. Feingold and Holaday[6] formulated a mathematical model for this nonlinear kinetics, approximating the

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experimental results published by Sawyer *et al.* (Appendix I). Other studies confirmed this concentration-dependent biotransformation of halothane in humans.[40,41] Calahan *et al.,*[42] who estimated the kinetic constants that characterize the metabolism of halothane in humans, assumed that the clearance of halothane is a combination of linear clearance to depots and saturable metabolism attributable to a Michaelis-Menten process. However, we were not able to extract the necessary data from their report. Eventually, we applied the equations from the nonlinear model developed by Feingold and Holaday. Thus their work was the key in versions D and D′ of our system model to unlocking the door between the conception and the completion of a workable model featuring nonlinear kinetics. We thereby recognize that extrahepatic elimination of halothane and clearances to depots were ignored and that the results from animal studies were implemented. This evokes the inevitable question about the influence of species on the reported size and mechanism of the NPE of an inhaled anesthetic. However, we must recognize that, even in the same species, a large inter- and intraindividual variability exists. A study in twins demonstrated an important genetic predisposition in the biotransformation of drugs, because identical twins showed a 10% but fraternal twins a 30% range in halothane metabolism.[43]

Solubility

The quality of the predictions of a physiologic model relies on the validity of the data used. A reliable simulation of the pharmacokinetics of inhalational anesthetics therefore depends, *inter alia,* on well chosen values for the partition coefficients. This becomes especially important at the higher anesthetic concentrations used in clinical practice, when metabolism plays a smaller role in the rate at which elimination occurs, thereby permitting solubility to play a more important role.[41] In versions A and D, we used the data of Lowe and Ernst,[13] who applied fixed partition coefficients in agreement with those mentioned by Steward *et al.*[44] in their review, to be "the most likely values." However, age-related changes occur in the constituents (water, protein, and lipid concentration) of human tissues, and the partition coefficients thus may differ with aging. Because Lerman *et al.*[8,9] and Malviya and Lerman[10] reported such an effect of age on both the blood-gas and tissue-blood partition coefficients of inhalation anesthetics, two different versions A′ and D′ were created to evaluate the impact of the use of age-related partition

coefficients on our model's accuracy. The analysis of the scatters of the four versions demonstrated that the incorporation into the system model of age-related partition coefficients significantly improved the overall predictive performance of our system model (fig. 7).

Reservations

The limitations of the current study lead to our reservations. The model should not be used without validation for children or infants and other volatile anesthetic agents such as desflurane or sevoflurane. The trend toward overprediction (fig. 3B), as corroborated by the influence of the anesthesia time on the predictive performance, must prevent us from using the model for long anesthetic procedures. The model includes tissue groups with long time constants, *e.g.,* adipose tissue and connective tissue. These groups do not significantly contribute to uptake during the first hour of anesthesia. Errors in the parameters defining the time constants (volume, perfusion, tissue-blood coefficients) may contribute to the trend (fig. 3); this requires further research. The natural individual variability and the possible influence of coadministration of other anesthetics that may result in changes in drug disposition must prevent us from totally relying on model predictions.

From this study, we conclude that our system model, although using simplifying assumptions, sufficiently represents the clinical reality of halothane closed-circuit anesthesia. The choice to apply version D′ is in accordance with the many reports on halothane biotransformation, suggesting that a nonlinear NPE is an indispensable part of a physiologic model for the uptake, distribution, and elimination of halothane. The new version, D′, of this system model combines the following features: It does not assume a zero circulation time, and it uses age-related partition coefficients, incorporates nonlinear NPE, and is capable of predicting the alveolar concentration of anesthetic after bolus injection of halothane into the closed circuit. This validated physiologic model provides a valuable tool to be used for a variety of so called "what happens if" scenarios—with the necessary reservations—for clinical, teaching, economical, ecologic, and research purposes.

Appendixes

I: Nonlinear Nonpulmonary Elimination

We refer to our previous study[1] for a complete mathematical formulation of the original system model, which does not account

for NPE and is designated version A. In this Appendix, we describe the modifications of version A that were necessary to construct version D.

NPE in version D was mimicked by the irreversible loss of a variable fraction of the anesthetic agent present in the blood flowing to the liver (fig. 2, inset). Accordingly, the rate of change of the concentration of anesthetic agent in the venous blood draining the liver is given by

$$\frac{dC_{V_{liver}}}{dt} = \frac{\dot{Q}_{liver}}{V_{liver} \times \lambda_{T/B}} (C_a(1 - f_{NPE}) - C_{V_{liver}}),$$

where $\dot{Q}_{liver}$ is the hepatic blood flow, V_{liver} is the volume of the liver, $\lambda_{T/B}$ is the liver/blood partition coefficient, C_a is the fractional concentration of agent in blood leaving the arterial blood pool, and f_{NPE} is the fraction of the amount of anesthetic agent irreversibly lost from the hepatic blood flow.

We calculated the value of f_{NPE} from the equations reported by Feingold and Holaday[6] (table 5). These authors described a nonlinear model of halothane biotransformation featuring Michaelis-Menten kinetics in the liver. Thus f_{NPE} is inversely related to the hepatic arterial concentration. Therefore, they used an approximation of the experimental results of Sawyer et al.,[4] who studied miniature swine weighing 35–45 kg. After conversion of the different units used in the two papers, the "fractions removed" from both papers are visualized in figure A1. There is close agreement between the experimental results of Sawyer et al. and the approximation by Feingold and Holaday.

II: Predictive Performance Measures

The predictive performance of our physiologic model for volatile anesthetics was determined by the following measures.

The prediction error (pe), expressed as a percentage, was calculated for each pair of predicted and measured values as

$$pe = \frac{C_{A,p} - C_{A,m}}{C_{A,m}} \times 100, \tag{A1}$$

where $C_{A,p}$ is the predicted alveolar concentration of halothane, and $C_{A,m}$ is the measured alveolar concentration. A negative pe implies that the predicted value underpredicts the measured value, whereas a positive pe indicates that the predicted value overpredicts the measured value. The prediction errors were calculated for each period of 10 s for the separate versions.

Table 5. Equations for f_{NPE}*

$C_a^{\#}$	f_{NPE}
>10	0
10 to 10^{-1}	$-0.010 \log C_a^{\#} + 0.010$
10^{-1} to 10^{-5}	$-0.195 \log C_a^{\#} - 0.175$
10^{-5} to 10^{-9}	$-0.050 \log C_a^{\#} + 0.550$
$<10^{-9}$	1.0

* According to Feingold and Holaday.[6]

f_{NPE} = the fraction of the amount of anesthetic agent that is irreversibly lost from the hepatic blood flow; $C_a^{\#}$ the arterial concentration of anesthetic agent expressed as mmol/100 ml.
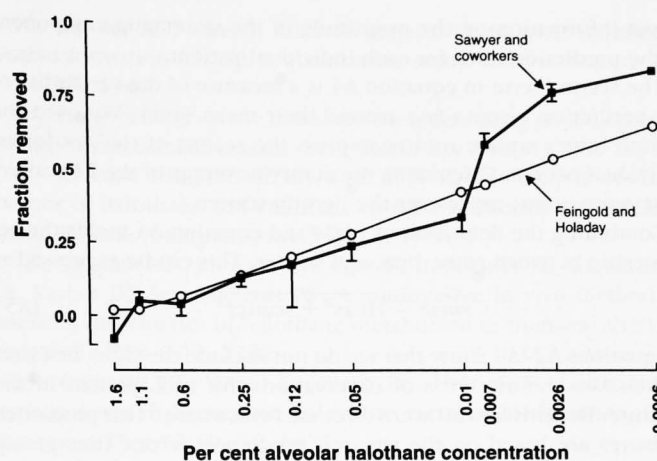
Fig. A1. Comparison of the fractions of halothane removed from the hepatic blood flow as reported in two studies. This figure is based on a figure from the study of Sawyer et al.[4] It shows their experimental results obtained in miniature swine (data expressed as mean and SEM). Alveolar concentrations below 0.0026% result in a nearly complete hepatic extraction of halothane. However, the fraction removed decreases as the percentage alveolar halothane increases. Feingold and Holaday[6] used the equations listed in table 5 to approximate the findings of Sawyer et al. The fractions removed are similar in both studies, especially between 1.6% and 0.01% alveolar halothane. This range was used in our clinical study. The equations of Feingold and Holaday were incorporated in versions D and D' of our model.

The bias or mean prediction error (me) for each patient was given by

$$me = \frac{1}{n-3} \sum_{i=4}^{n} pe_i, \tag{A2}$$

where n is the number of measurements per patient, and pe_i is the ith prediction error. The numeric average of all the biases—one per patient—yields the "group bias." The bias possesses a direction (given by the plus or minus sign) and a magnitude (the value without the sign). The bias for each patient is influenced by the negative or positive sign of the prediction error, and thus does not provide information about the typical size of the prediction error if there are both under- and overpredictions in an individual patient. The influence of the sign can be avoided by defining a measure based on squared errors. Therefore, we first consider the mean squared prediction error (mse), given by

$$mse = \frac{1}{n-3} \sum_{i=4}^{n} pe_i^2. \tag{A3}$$

The root mean squared prediction error (rmse), given by $\sqrt{mse}$, is a measure of the typical size of the prediction error for each individual patient. The numeric average of all the rmses yields the group rmse. The mse can be decomposed into two terms:

$$mse = me^2 + \frac{1}{n-3} \sum_{i=4}^{n} (pe_i - me)^2 \tag{A4}$$

The square root of the first term in equation A4 is recognized as the magnitude of the individual bias defined in equation A2, providing

direct information on the magnitude of the systematic component of the prediction error for each individual patient.

The second term in equation A4 is a measure of the variability of the prediction errors (pe_i) around their mean (me). We used the second term's square root to express the scatter of the pes for an individual patient. Calculating the numeric average of the 53 scatters (one *per* patient) represents the "group scatter."

Combining the definition of *rmse* and equation A4 yields the relationship between *rmse*, bias, and scatter. This can be expressed as

$$rmse = \sqrt{bias^2 + scatter^2}. \qquad (A5)$$

Equations A2–A4 show that we do not include the three first data points, *i.e.*, the first 30 s of observations, for each patient in the measure. Reasons for this were discussed elsewhere.[2] Our predictive measures are based on the squared prediction errors, thus giving much weight to the differences between the predicted and observed values. The drawback of this approach (squaring the differences) is that the brief and clinically unimportant differences between model and reality during the first 30 s of the comparisons are also given much weight. Omitting the first three data points for each patient, *i.e.*, 159 of 21,890 data points, does not violate but rather augments the value of comparison between prediction and reality for clinical purposes.

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