Anesthesiology
75:230–237, 1991

A System Model for Closed-circuit Inhalation Anesthesia

II. Clinical Validation

Jos G. C. Lerou, M.D., Ph.D.,* Ris Dirksen, M.D., Ph.D.,* Herman H. Beneken Kolmer, M.D., Ph.D.,†
Leo H. D. J. Booij, M.D., Ph.D.,‡ George F. Borm, Ph.D.§

Recently, we described a basic model and its more elaborate variants to predict the uptake and distribution of inhalational anesthetics during closed-circuit anesthesia. As an initial clinical validation of the linear, continuous, 14-compartment basic model, the current study examined its predictive performance in 50 patients by comparing quantitatively the predicted and the measured alveolar concentration–time profiles after bolus injections of liquid isoflurane into the closed system during mechanical ventilation. The two versions of the model studied differed in the size of their peripheral shunt, as 0% (version A) and 16% (version B) of the cardiac output. A total of 15,744 alveolar concentrations of isoflurane (one per 10-s period) were measured by mass spectrometry. For each measured concentration we used computer simulations of version A and version B to calculate a predicted concentration for both versions. For each patient we calculated the bias (indicating over- or underprediction) and the scatter of the prediction errors (indicating the typical error size). The bias and the scatter of the prediction errors, both given as mean (and standard deviation), were 2.25 (13.59) and 12.51 (5.84)% for version A and 12.00 (14.97) and 14.12 (6.54)% for B. Version A performed better than B: both the bias ($P = 0.008$) and the scatter ($P < 0.0001$) were closer to zero for A. Logistic regression analysis showed for version A that scatter, but not bias, increased with age ($P = 0.002$). Gender, body mass index (weight · height^{-2}), and number of injections per hour did not influence scatter or bias. The results indicate that version A is sufficiently accurate to be used for clinical, teaching, research, economic, and ecological purposes. (Key words: Anesthetic techniques: closed-circuit. Anesthetics, volatile: isoflurane. Computer: simulation; models. Pharmacokinetics: uptake; distribution.)

RECENTLY, WE DESCRIBED a basic model and its more elaborate variants to predict the uptake and distribution of inhalational anesthetics during closed-circuit anesthesia.[1] Our basic model is a physiologic multicompartment model that assumes that cardiac output and its distribution to the different body compartments are constant during the uptake of anesthetic agents. Unlike other models for closed-circuit anesthesia,[2,3] our model does not assume a constant arterial concentration or zero circulation time. Circulation times are mimicked by using the concept of blood pools, introduced by Mapleson.[4]

As an initial clinical validation of our basic model, the current study examines its predictive performance in relation to the administration of isoflurane during artificial ventilation. In contrast with the use of a vaporizer outside the circle, the addition of liquid anesthetic to a closed circuit achieves maximal independence of the fresh gas flow rate and vaporizer performance. In addition, no data were available on testing a model's ability to predict the time courses of the alveolar concentrations after bolus injections of liquid anesthetic agent into the closed system. Isoflurane therefore was administered by liquid injection, and the observed alveolar concentration–time profiles were compared quantitatively with those predicted by two versions of the basic model.

Materials and Methods

Patients and Anesthetic Technique

Fifty consenting patients (ASA physical status 1–3) scheduled for elective eye surgical procedures were studied. The study was approved by the Institutional Research Committee. Diazepam 10 mg and droperidol 5 mg were given by mouth 1 h before surgery. An intravenous catheter was inserted, and basic monitoring (ECG, blood pressure, and pulse oximetry) was established. Anesthesia then was induced with intravenous fentanyl 0.1 mg and a dose of thiopental sufficient to obtund the eyelash reflex, followed by vecuronium 0.1 mg · kg^{-1}. After endotracheal intubation with a cuffed tube the lungs were artificially ventilated with a high fresh gas flow of oxygen and nitrous oxide in a 1:2 ratio for 5–10 min. Thereafter the anesthetic system was closed, and closed-circuit anesthesia using the liquid injection method was administered by one of us (JGCL).

Throughout anesthesia we did not use any rigid drug regimen to determine the volumes and the timing of the isoflurane injections. The only guideline was to inject one to three boluses of liquid isoflurane 0.01 ml · kg^{-1} (±0.1 ml) after the start of closed-circuit conditions so as to produce rapidly the end-tidal concentration desired in an individual patient. During maintenance we modified the isoflurane administration according to patient response and/or end-tidal concentration measured. The end-tidal carbon dioxide concentration was maintained at 4.0–

* Staff Anesthesiologist.
† Emeritus Professor of Anesthesia.
‡ Professor of Anesthesia; Chairman of the Department of Anesthesiology.
§ Department of Medical Statistics.
Received from the Institute for Anesthesiology, University of Nijmegen. Accepted for publication April 24, 1991. Presented in part at the III International Symposium on Closed Circuit and Low Flow Anesthesia Systems in Washington, DC, May 1988.
Address reprint requests to Dr. Lerou: University of Nijmegen, Institute for Anesthesiology, Geert Grooteplein zuid 10, 6500 HB Nijmegen, The Netherlands.

4.5%. At the end of the procedure the closed system was opened, and a flow of 9 l · min^{-1} oxygen was used to wash out the nitrous oxide and isoflurane.

Instrumentation

The anesthetic equipment consisted of a Modulus II® anesthesia system with an integrated automated anesthesia record-keeper (Ohmeda, Madison, WI). The latter processed the signals provided by the devices used for monitoring a patient's vital signs.[5] Monitors included a respiratory volume monitor (Ohmeda 5400), an oxygen analyzer (Ohmeda 5100), a pulse oximeter (Ohmeda Biox 3700), a noninvasive blood pressure monitor (Ohmeda 2110), an electrocardiograph (Hewlett-Packard 78353B), and a carbon dioxide analyzer equipped with a sample gas return unit (Normocap, Datex, Finland). Finger plethysmography also was applied.

A standing bellows ventilator (Ohmeda 7000) was used. The volume of the anesthetic system including ventilator bellows, absorber and housings was 6.5 l (measured by helium dilution). A gas leak of up to 60 ml · min^{-1} at 3 kPa (30 cmH_2O) was accepted. The fresh gas flows of oxygen and nitrous oxide were adjusted manually so as to maintain the inspiratory oxygen concentration at about 33% and to keep the standing bellows at the same end-expiratory volume. Boluses of isoflurane were injected with the aid of a 1-ml disposable syringe into the expiratory limb of the circuit *via* a homemade injection port. The volume of each bolus injected was entered in the automated anesthesia record keeper.

A respiratory mass spectrometer (Centronic 200 MGA) continuously sampled gas at the lips of the patient through a 30-m nylon catheter with a 10–90% response time of 330 ms for isoflurane.[6] The mass spectrometer sample flow (measured with a bubble flow meter) was 40 ml · min^{-1}. Before using the mass spectrometer, we verified its calibration for isoflurane with a calibration gas mixture containing 1% isoflurane in 30% oxygen, 30% nitrous oxide, and balance nitrogen (AGA Gas, The Netherlands). The coefficient of variation on the mass spectrometer readings is 2%. An eight-channel chart recorder (Gould-Brush 481) running at 6 mm · min^{-1} recorded the mass spectrometer output signals for nitrogen, oxygen, carbon dioxide, nitrous oxide, and isoflurane. The mass spectrometer and the chart recorder were located in a room near the operating theater.

An IBM AT personal computer system (640 kB RAM, 80287 coprocessor, 30 Mb hard disk unit, and Hercules graphics board) and a 12-bit analog-to-digital board (DAS-16, Metrabyte Corporation, Taunton, MA) were used to acquire (from the mass spectrometer) and to display the isoflurane signal in the operating room. This allowed continuous monitoring of the isoflurane waveforms and its actual inspiratory and end-expiratory concentrations. A trend of the inspiratory and end-expiratory concentration of isoflurane of the last 20 min also was displayed. The data acquisition software was developed with the aid of ASYST® Version 2.1 (Asyst Software Technologies, Inc., Rochester, NY).[7] The isoflurane signal from the mass spectrometer was amplified ten-fold, was acquired at a sample rate of 10 Hz, and was saved on the hard disk. We used the same computer system for simulation purposes.

The Model and Its Input

The model we sought to validate was our linear, continuous, 14-compartment basic model,[1] which was developed with a special-purpose simulation language, TUTSIM®¶ Professional Version 6.55 (Meerman Automation, Neede, The Netherlands). Two versions of the basic model were tested: these were version A with 0% and version B with 16% of the cardiac output defined as peripheral shunt. The resulting compartmental distributions of the cardiac output have been described.[1] Part of the model is a gas loss of 100 ml · min^{-1}, *i.e.*, a sample flow of 40 ml · min^{-1} drawn off by the respiratory mass spectrometer plus a leak of 60 ml · min^{-1}.

Each patient's age, body weight, height, and gender were entered into the model, thus allowing the model to derive the following physiologic variables: tissue masses, blood volume, cardiac output, dead space, alveolar space, and tidal volume. The timing of the isoflurane injections and the quantities injected were retrieved from the recordings of the chart recorder and from the automated record, respectively, and subsequently were supplied to the model. The volume of liquid isoflurane was first converted into milliliters of vapor (1 ml liquid isoflurane yields 206 ml vapor at 37° C). This result was then supplied to the model as if the vapor were added to the anesthetic system over a 1-min interval, to mimic the time required for conversion of liquid to vapor. The simulation step size used was 2 s, but only one calculated value per 10-s period was saved on disk. Two simulation runs were performed for each patient: one was for version A and one for version B.

Predictive Performance Measures

We developed an ASYST® application program to: 1) calculate the lowest end-tidal concentration per 10-s period from the patient's isoflurane waveforms that had been saved on hard disk during data acquisition; 2) import the predicted values from TUTSIM®; 3) compare graphically

¶ TUTSIM® is a registered trademark of TUTSIM® Products in the United States and Canada.

the time courses of the measured alveolar concentrations of isoflurane with those predicted; and 4) export the measured and predicted values for further analysis. Figures 1 and 2 illustrate the measures that will serve to determine the predictive performance of our model. These are introduced below.

Prediction Error

For each pair of predicted and measured values the prediction error (pe) expressed as a percentage was given by:

$$pe = \frac{C_{A,p} - C_{A,m}}{C_{A,m}} \times 100 \qquad (1)$$

where $C_{A,p}$ is the predicted alveolar concentration of isoflurane and $C_{A,m}$ is the measured alveolar concentration. Note that pe scales the difference between predicted and measured value to the measured isoflurane value. A negative prediction error indicates that the predicted value is smaller than or underpredicts the measured value, whereas a positive prediction error indicates that the predicted value is greater than or overpredicts the measured value. The prediction errors were calculated for each time period of 10 s for both version A and version B.

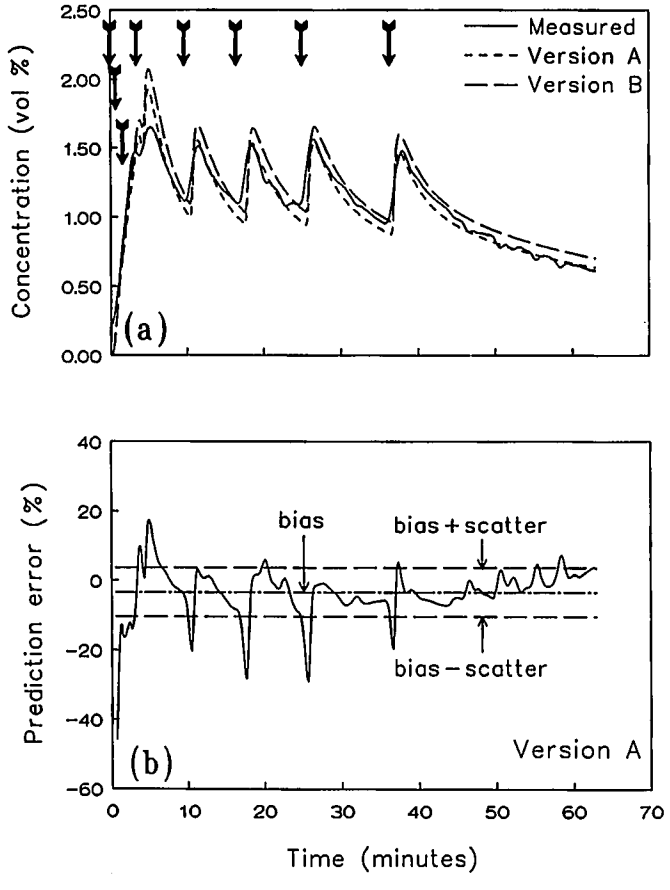

FIG. 1. *A:* Measured and predicted alveolar concentrations of isoflurane obtained in a young patient (19 yr old and 63 kg in body weight). The arrows represent injections of liquid isoflurane 0.7 ml into the closed system. *B:* Time course of the prediction error for version A. Each of the four "curves" in *A* and *B* contains 378 data points. The bias and the scatter for this individual patient were −3.37 and 7.04% (version A), respectively.

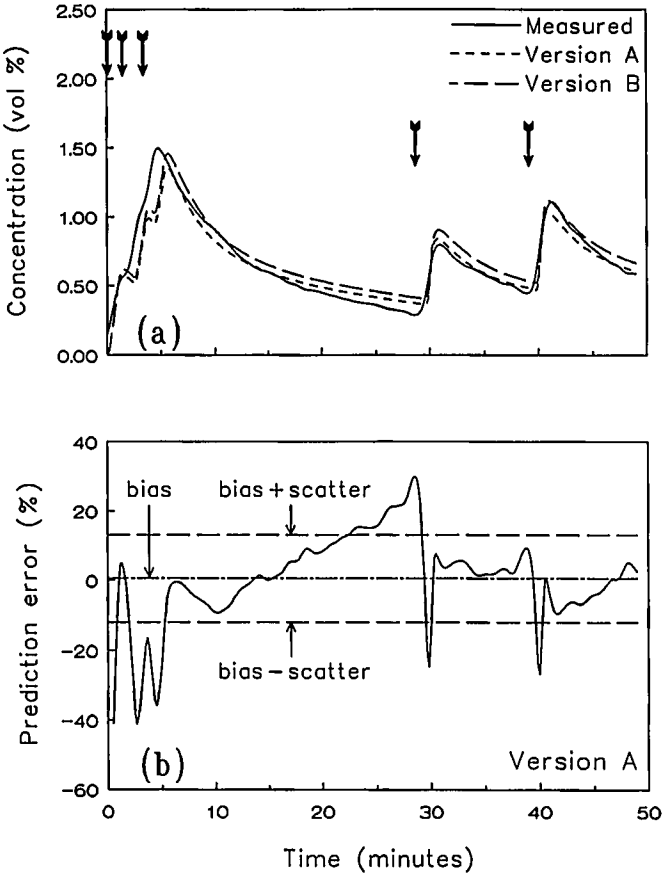

FIG. 2. *A:* Measured and predicted alveolar concentrations of isoflurane obtained in an older patient (65 yr old and 55 kg in body weight). The arrows represent injections of liquid isoflurane 0.6 ml into the closed system; however, the fourth injection was 0.5 ml. *B:* Time course of the prediction error for version A. Each of the four "curves" in *A* and *B* contains 294 data points. The bias and the scatter for this individual patient were 0.61 and 12.54% (version A), respectively.

Mean Prediction Error or Bias

For each patient the mean prediction error (me), or "bias," expressed as a percentage, was calculated as:

$$me = \frac{1}{n - 3} \sum_{i=4}^{n} pe_i \qquad (2)$$

where n is the number of measurements per patient and pe_i is the i-th prediction error. Notice that the bias pos-

TABLE 1. Demographic Characteristics

	Mean (SD)	Minimum	Maximum
Age (yr)	47.6 (16.3)	19.0	76.0
Weight (kg)	72.3 (12.6)	43.0	95.0
Height (m)	1.70 (0.11)	1.44	1.90
Body mass index* ($kg \cdot m^{-2}$)	25.1 (4.2)	18.6	37.9

n = 50.

* Patients with a body mass index ≤ 20 $kg \cdot m^{-2}$ can be considered thin; patients with a body mass index ≥ 26 $kg \cdot m^{-2}$ can be designated obese; and the remaining patients can be assumed to have normal adiposity.

sesses a direction (given by the plus or minus sign) and a magnitude (the value without the sign). A positive or negative bias is a measure of over- or underprediction, respectively. Calculating the numerical average of the 50 biases—one per patient—yields the "group bias."

Typical Error Size (Systematic Component and Scatter)

The bias calculated 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

$$\text{mse} = \frac{1}{n-3}\sum_{i=4}^{n} pe_i^2 \qquad (3)$$

Although the root mean squared prediction error, given by $\sqrt{\text{mse}}$, can be used as a measure of the typical size of the prediction error for each patient, we prefer to use the following relationship (which can be verified easily):

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

to decompose the mean squared prediction error into two terms. The square root of the first term in equation 4 is recognized as the magnitude of the individual bias (me) defined in equation 2. It provides direct information on the magnitude of the systematic component of the prediction error for each patient. Averaging the individual values leads, of course, to the mean magnitude of the systematic component for the entire group.

The second term in equation 4 is a measure of the scatter of the prediction errors (pe_i) around their mean (me). To allow easier interpretation, the square root of the second term is used to express the scatter of the prediction errors for an individual patient. The numerical average of these 50 terms—one per patient—represents the "group scatter."

Equations 2–4 show that we do not include the three first data points, *i.e.*, the first 30 s of observations, for each patient in the statistical analysis. Reasons for this are given in the Discussion section.

STATISTICAL ANALYSIS

The sign test was used to compare the predictive performance of version A with that of version B. We therefore tested the hypothesis of whether the bias for version A or version B was closer to zero. The same hypothesis was tested for the scatter. For version A, we used binary logistic regression[8] to study the potential influence of gender, age, body mass index (= weight · height^{-2}), and the number of injections per hour of closed-circuit anesthesia on each of two response variables: 1) the bias; and 2) the scatter of the prediction errors.

Differences yielding $P < 0.05$ were considered significant.

Results

Twenty-eight women and twenty-two men were studied; their characteristics are listed in table 1. Details on the duration of closed-circuit conditions, the number of data points, and the administration of the liquid isoflurane are given in table 2. Figures 1A and 2A show the measured and predicted concentration–time profiles in two representative patients—a younger and an older pa-

TABLE 2. Details on the Duration of Closed-circuit Conditions, the Number of Data Points, and the Administration of Liquid Isoflurane into the Closed System

	Mean (SD)	Minimum	Maximum	Total
Duration (min)	53.0 (18.8)	16.0	113.0	2,649
Number of data points	315 (113)	93	675	15,744
Number of injections	7.4 (2.6)	3	15	370
Number of injections per hour	9.0 (3.2)	4.2	17.6	
Volume of liquid isoflurane (ml)	4.2 (1.4)	1.2	7.6	207
Average measured end-tidal isoflurane concentration (vol %)	0.83 (0.22)	0.35	1.15	

n = 50.

tient—thus providing a visual impression of the quality of the predictions achieved with version A and version B.

The scatterplot in figure 3, which summarizes the results for the biases, shows a linear relationship between the individual biases for version A *versus* version B. For version A, the number of patients with a positive bias (26 patients) was almost equal to the number with a negative bias (24 patients). A linear relationship between the individual scatters of the prediction errors for version A *versus* version B is recognized in figure 4. Version A performed better than version B because both the bias and the scatter were smaller for version A (table 3). Figures 1B and 2B therefore document the time course of the prediction error for version A rather than for version B. Table 3 shows that the magnitude of the bias of version A was less important than its scatter. This means that, *on average,* the typical size of the prediction error was due mainly to the scatter rather than to the systematic component. This was found for 32 of the 50 patients.

Table 4 presents a binary logistic regression analysis performed for version A, the best of the two versions. This analysis shows that age was associated with the scatter, *i.e.*, the scatter of the prediction errors was greater for older patients ($P = 0.002$). The three other explanatory variables—gender, body mass index and number of injections per hour—were not significant. Table 4 also shows that none of the explanatory variables had a significant effect on the bias.

Discussion

Although numerous mathematical models of anesthetic uptake and distribution have been proposed, few investigations have directly compared calculated and experimental results. Close agreement between theory and experiment is, however, mandatory to validate a model. We constructed our model on the basis of physiologic and physicochemical knowledge. There is little reason, *a priori,* to expect such a model actually to predict the alveolar concentrations. This points out the importance of combining computer simulation[1] and clinical validation.

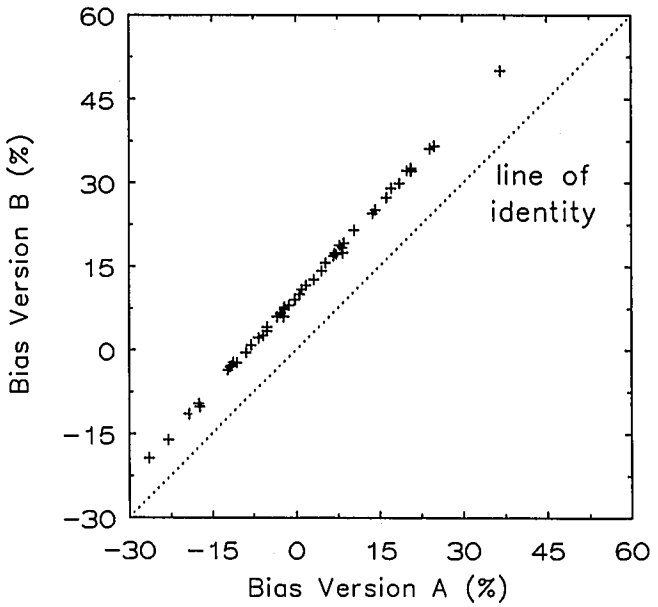

FIG. 3. A scatterplot of the bias for version B *versus* the bias for version A (n = 50).

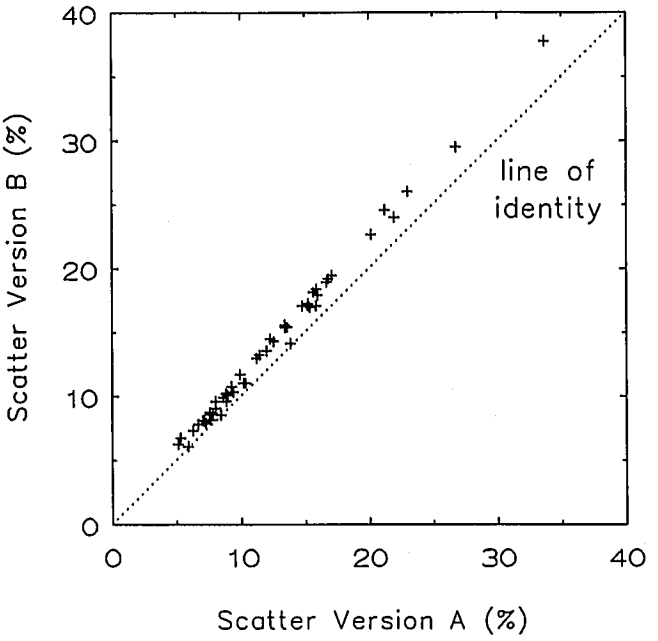

FIG. 4. A scatterplot of the scatter of the prediction errors for version B *versus* that for version A (n = 50).

A model can be considered valid if: 1) its predictions do not result in a systematic over- or underprediction; and 2) the accuracy of the model given by the typical error size is acceptable for a majority (preferably 90% or more) of the patients studied. After its validation in a specific context, a model is suitable for clinical, teaching, and research uses in comparable circumstances. Our approach was to obtain the measured values under clinical conditions and thus ensure the clinical relevance of our results.

Major Findings

The principal finding of this study is that version A 1) performs better than version B; and 2) must be considered

TABLE 3. Predictive Performance of Version A *versus* Version B

	Version A Mean (SD)	Version B Mean (SD)	*P*
Bias (%)	2.25 (13.59)	12.00 (14.97)	0.008
Scatter of prediction errors (%)	12.51 (5.84)	14.12 (6.54)	<0.0001

n = 50.

TABLE 4. Binary Logistic Regression Analysis of Factors Associated with the Scatter and Bias of the Prediction Errors for Version A

Factor	Scatter		Bias	
	Logistic coefficient	P	Logistic coefficient	P
Gender	0.15	0.84	1.4010	0.08
Age	0.0985	0.002	0.0249	0.37
Body mass index	−0.0447	0.61	0.0439	0.61
Number of injections per hour	0.1908	0.14	−0.1400	0.29

n = 50.

a valid model if judged by the criteria outlined above. Version B overpredicted reality (table 3), whereas version A produced an insignificant group bias with a 95% confidence interval of −1.61% to +6.12% and a nearly even 24:26 distribution of patients with negative *versus* positive bias (fig. 3). Version A had a moderate but acceptable degree of accuracy for most of the 50 patients: for 48 the magnitude of the bias was less than 25%, and for 47 the scatter of the prediction errors was less than 22%.

The accuracy of version A can be appreciated further by considering an alternative approach to analyzing the differences between the model and reality. We elected to analyze the scaled prediction error as defined in equation 1, but the whole data analysis also can be performed on the unscaled difference between predicted and measured alveolar concentration. This difference is then expressed in volume percent (vol %). Such an analysis on the 50 patients reveals that for 46 the magnitude of the bias was less than 0.17 vol %, and for 45 the scatter was less than 0.13 vol %. These figures reflect the intersubject variability in anesthetic uptake[9,10] but also suggest that version A is sufficiently accurate to be accepted as a valid model.

Choosing a measure to quantify the typical size of the prediction errors is an important step in evaluating the predictive power of a model. Our measure is based on the squared prediction errors (equations 3 and 4) and thus gives much weight to the differences between the predicted and observed values. Other measures have been suggested[11] and used to examine typical error size. For example, the mean absolute prediction error[12] and the median absolute prediction error[13] have been used to measure the predictive performances of pharmacokinetic models for alfentanil. These two measures are based on the absolute values of the prediction errors. As a consequence, they yield a smaller typical error size when compared with a measure based on the squared errors. The mean absolute prediction error uses all data points, whereas the median absolute prediction error is insensitive to possibly marked prediction errors in 49 of 100 data points.

We believe that because of the narrow therapeutic range of the volatile anesthetics, it is crucial to choose a measure based on 1) squared prediction errors and 2) all data points; *i.e.*, the measure is calculated first for the individual and then for the entire group. This approach protects against too-favorable estimations of the typical error sizes, which may mislead the clinical anesthesiologist. Its drawback is that the brief and clinically unimportant differences between the model and reality during the first 30 s of the comparison are also given much weight. We believe that omitting the first three data points for each patient (150 of 15,894 data points) did not violate but rather augmented the value of the comparison between prediction and reality for clinical purposes.

FACTORS ASSOCIATED WITH BIAS OR SCATTER

Elderly patients had biases (which are influenced by the signs of the prediction errors) similar to those of young patients. This is not totally surprising, since at least one possible source of bias was prevented by the model's calculation of the functional residual capacity for each individual patient. The functional residual capacity decreases with age and is an important factor in determining the total volume of the closed system[1] and thus the end-tidal concentrations of isoflurane. Neglecting this age-dependency of the functional residual capacity would have led to systematic over- or underpredictions for patients younger or older than the "model patient." Age was associated, however, with the second component of the typical size of the prediction errors (table 4). This means that the scatter was greater for older patients (figs. 1B and 2B). This finding may be explained by assuming that elderly patients suffered from greater alterations in the cardiac output throughout anesthesia and surgery. These may have been responsible for overshoots and undershoots of the expected alveolar concentrations, which were predicted by a model that assumes a constant cardiac output.

Because Saraiva and co-workers reported a positive correlation between the halothane uptake rate and adiposity[14] and because our model assumes a fixed ratio of fatty tissue mass to body size, we had reason to expect that the agreement between model and experiment would

be worse for obese patients. However, the body mass index was associated neither with the magnitude of the bias nor with the scatter (table 4). Besides isoflurane's lower fat–gas partition coefficient (94.5 *vs.* 185.0 for halothane), the combined effects of the body-weight-dependent model variables on the predicted concentrations might be responsible for the finding that the predictive performance was equally good for all individuals in our patient sample, regardless of body composition.

Although we had the visual impression that the number of injections per unit of time (figs. 1 and 2) could augment the typical size of the prediction errors, statistical analysis showed that this number was not a primary explanatory variable (table 4).

Alveolar ventilation is known to influence the pharmacokinetics of inhalation anesthetics; however, we did not have to consider its influence on our results. Goldberg and co-workers actually reported that even large variations in the dead space–tidal volume ratio (V_D/V_T) have only very small effects during closed-circuit anesthesia.[2] Our model confirms this finding, which is easily explained by the increase in inspiratory concentration after an increase of V_D/V_T in a closed system. The anesthetic returning from the dead space is totally rebreathed, since it is not vented to the atmosphere as in semi-open systems; the rebreathing thus compensates for an increased dead space.

Reservations

The reservations one must make while using the model originate from the obvious limitations of the current study: only adult patients anesthetized with isoflurane were studied, and the average anesthetic duration was only 53 min. The model should therefore not be used without validation for children or infants because of their age-dependent characteristics, which change the pharmacokinetics of inhaled anesthetics.[15] In addition, one should be aware that the model still must validated for other volatile anesthetic agents such as halothane or enflurane and for long anesthetic procedures. A general reservation is that patient-to-patient variability must prevent us from relying totally on model predictions.

Although version A closely predicts the alveolar concentrations of isoflurane, our results do not prove that the structure of version A is completely correct. For example, it is very unlikely that the cardiac output of the patients was, as our basic model assumes, constant throughout the anesthetic procedure. Similarly, although version A performs better than version B, our results do not indicate that a peripheral shunt is an unnecessary part of a physiologic model. Our results only lend credence to the assumptions upon which version A is based and do not demonstrate that our model is unique. Variants of the model's structure that would yield results similar to ours are possible; even variants including a peripheral shunt are possible. This reflects a weakness of a complex physiologic model that tries to emulate reality by incorporating as much knowledge as possible through the use of many compartments. Indeed, the importance of the individual structural elements and compartments could be substantiated only by direct measurements that may present insuperable difficulties.

Closed-circuit Anesthesia with Liquid Injection

From table 2 one can deduct that closed system anesthesia is economical and minimally polluting. With regard to the use of isoflurane, 50 patients were adequately anesthetized with only 207 ml liquid isoflurane during more than 44 h, not including the additional hours after discontinuing closed-circuit conditions. As previously reported by Nunn,[16] the manual addition of increments of mass of anesthetic has inherent simplicity and, in contrast with the use of a vaporizer outside the circle, achieves maximal independence of the fresh gas flow rate during artificial ventilation. However, the frequent interventions while injecting the liquid boluses add to the array of tasks of the anesthesiologist. A feedback-controlled infusion system therefore may represent a more suitable means of administration. Designing such a system will benefit from the use of a valid model.[1]

Based on our results, we conclude that the basic model version A is an adequate representation of the clinical reality of closed-circuit anesthesia using isoflurane and thus provides a valuable tool to be used, with the necessary reservations, for clinical, teaching, research, economic, and ecological purposes. Consequently, we suggest several possible applications of the model: calculating and testing drug regimens, enhancing our understanding of anesthetic uptake and distribution, fine-tuning feedback-controlled delivery systems, calculating costs of anesthesia, and calculating operating room pollution.

References

1. Lerou JGC, Dirksen R, Beneken Kolmer HH, Booij LHDJ: A system model for closed-circuit inhalation anesthesia: I. Computer Study. ANESTHESIOLOGY 75:345–355, 1991
2. Goldberg IS, Mostert JW, Lanzl EF, Lowe HJ: A pharmacokinetic model of closed-circuit inhalation anesthesia. Ann Biomed Eng 6:231–249, 1978
3. Lowe HJ, Ernst EA: The Quantitative Practice of Anesthesia. Baltimore, Williams & Wilkins, 1981
4. Mapleson WW: Circulation-time models of the uptake of inhaled anaesthetics and data for quantifying them. Br J Anaesth 45: 319–334, 1973
5. Lerou JGC, Dirksen R, van Daele M, Nijhuis GMM, Crul JF: Automated charting of physiological variables: A quantitative

comparison of automated versus handwritten anesthesia records. J Clin Monit 4:37–47, 1988
6. Lerou JGC, van Egmond J, Beneken Kolmer HH: Evaluation of long sampling tubes for remote monitoring by mass spectrometry. J Clin Monit 6:39–52, 1990
7. Hary D, Oshio K, Flanagan SD: The ASYST software for scientific computing. Science 236:1128–1132, 1987
8. Matthews DE, Farewell VT: Binary logistic regression, Using and Understanding Medical Statistics. 2nd Edition. Basel, S. Karger, 1988, pp 141–144
9. Westenskow DR, Jordan WS, Hayes JK: Uptake of enflurane: A study of the variability between patients. Br J Anaesth 55:595–601, 1983
10. Eger EI II, Guadagni NP: Halothane uptake in man at constant alveolar concentration. ANESTHESIOLOGY 24:299–304, 1963
11. Sheiner LB, Beal SL: Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 9:503–514, 1981
12. Maitre PO, Stanski DR: Bayesian forecasting improves the prediction of intraoperative plasma concentrations of alfentanil. ANESTHESIOLOGY 69:652–659, 1988
13. Raemer DB, Buschman A, Varvel JR, Philip BK, Johnson MD, Stein DA, Shafer SL: The prospective use of population pharmacokinetics in a computer-driven infusion system for alfentanil. ANESTHESIOLOGY 73:66–72, 1990
14. Saraiva RA, Lunn JN, Mapleson WW, Willis BA, France JM: Adiposity and the pharmacokinetics of halothane: The effect of adiposity on the maintenance of and recovery from halothane anaesthesia. Anaesthesia 32:240–246, 1977
15. Brandom BW, Brandom RB, Cook DR: Uptake and distribution of halothane in infants: In vivo measurements and computer simulations. Anesth Analg 62:404–410, 1983
16. Nunn JF: Closed-circuit anaesthesia (editorial). Br J Anaesth 50: 733–734, 1978