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Prediction of expiratory desflurane and sevoflurane concentrations in lung-healthy patients utilizing cardiac output and alveolar ventilation matched pharmacokinetic models

A comparative observational study

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Abstract

The Gas Man simulation software provides an opportunity to teach, understand and examine the pharmacokinetics of volatile anesthetics. The primary aim of this study was to investigate the accuracy of a cardiac output and alveolar ventilation matched Gas Man model and to compare its predictive performance with the standard pharmacokinetic model using patient data.

Therefore, patient data from volatile anesthesia were successively compared to simulated administration of desflurane and sevoflurane for the standard and a parameter-matched simulation model with modified alveolar ventilation and cardiac output. We calculated the root-mean-square deviation (RMSD) between measured and calculated induction, maintenance and elimination and the expiratory decrement times during emergence and recovery for the standard and the parameter-matched model.

During induction, RMSDs for the standard Gas Man simulation model were higher than for the parameter-matched Gas Man simulation model [induction (desflurane), standard: 1.8 (0.4) % Atm, parameter-matched: 0.9 (0.5) % Atm., $P = .001$; induction (sevoflurane), standard: 1.2 (0.9) % Atm, parameter-matched: 0.4 (0.4) % Atm, $P = .029$]. During elimination, RMSDs for the standard Gas Man simulation model were higher than for the parameter-matched Gas Man simulation model [elimination (desflurane), standard: 0.7 (0.6) % Atm, parameter-matched: 0.2 (0.2) % Atm, $P = .001$; elimination (sevoflurane), standard: 0.7 (0.5) % Atm, parameter-matched: 0.2 (0.2) % Atm, $P = .008$]. The RMSDs during the maintenance of anesthesia and the expiratory decrement times during emergence and recovery showed no significant differences between the patient and simulated data for both simulation models.

Gas Man simulation software predicts expiratory concentrations of desflurane and sevoflurane in humans with good accuracy, especially when compared to models for intravenous anesthetics. Enhancing the standard model by ventilation and hemodynamic input variables increases the predictive performance of the simulation model. In most patients and clinical scenarios, the predictive performance of the standard Gas Man simulation model will be high enough to estimate pharmacokinetics of desflurane and sevoflurane with appropriate accuracy.

Abbreviations: ALV = alveolar gas compartment, ASA = American Society of Anesthesiologists, C_{GM} = expiratory anesthetic concentration from the respective Gas Man simulational model, CO = cardiac output, C_P = expiratory anesthetic concentration from the patient data during recovery from volatile anesthesia, FAT = fat compartment, FGF = fresh-gas-flow, MAC = minimal alveolar concentration, MACawake = expiratory anesthetic concentration at first eye opening in response to a verbal command, MDAPE = absolute median performance error, MDPE = median performance error, MUS = muscle compartment, PBPK = physiologically-based pharmacokinetic models, PBWm = predicted body weight in kg for men, PBWw = predicted body weight in kg for women,

1. Introduction

Gas Man is a graphical user interface for interactive simulation of pharmacokinetics, designed to teach and examine the principles of volatile anesthetics uptake, distribution, and elimination.[1,2] It provides modeling of four tissue compartments (alveolar gas, the vessel-rich group, muscle group, and fat group), and further data analyses of pharmacokinetic calculations.[3–6] Multiple physiological variables, such as weight, height, cardiac output (CO), alveolar ventilation (VA) and tissue characteristics (flows and volumes to the different tissue compartments) can be adjusted to modify the underlying pharmacokinetic model individually. There are two studies available that compare clinically measured volatile anesthetics concentrations with data predicted from the Gas Man simulation software.[7,8] However, no study, so far compared expiratory concentrations for desflurane and during induction and emergence of volatile anesthesia on a high temporal resolution base. Also, they did not compare the predictive performance between the standard and modified Gas Man simulation models.

We hypothesized that the patient individual modification of the standard model by VA and CO improves the prediction of desflurane and sevoflurane concentration courses during volatile anesthesia in lung-healthy patients.

To test this hypothesis, we measured expiratory concentrations of desflurane and sevoflurane in patients and simulated the anesthetics concentrations courses during induction, maintenance and emergence of anesthesia with the standard and the parameter-matched simulation model using the Gas Man simulation software.

2. Methods

2.1. Patient data and volatile anesthesia

Patient data used in this study were taken from another study, not published yet. After approval of the Ethics Committee of the University of Freiburg (EK 63/18), registration at the German Register for Clinical Trials (DRKS00014575) and obtaining written informed consent, we studied respiratory mechanics, hemodynamic variables and expiratory volatile anesthetic concentrations in 42 consecutive patients with American Society of Anesthesiologists (ASA) physical status I-III, who underwent orthopedic surgery at the Medical Center of the University of Freiburg, Germany. All participants were eligible for this observational study. Patients were enrolled from May 3, 2018 to October 11, 2018. The exclusion criteria were ASA physical status > III, age < 18 years, pregnancy, emergency procedure, a history of pulmonary disease, or refusal to participate. The volatile anesthesia, either performed with desflurane or sevoflurane, was conducted according to a standardized protocol: All patients received routine monitoring (electrocardiography, SaO_2, noninvasive blood pressure measurement; Infinity Delta XL; Dräger Medical, Lübeck, Germany). After preoxygenation to an expiratory fraction of oxygen of 0.8, anesthesia was induced with 0.3 to 0.5 μ·kg^{-1} iv sufentanil (Janssen-Cilag, Neuss, Germany)

and with a continuous infusion of propofol (Propofol 1%; Fresenius Kabi, Bad Homburg, Germany; target-controlled infusion, effect site target concentration for induction: 6 to 8 μg·mL^{-1}; effect site target concentration for maintenance: 3 to 4 μg·mL^{-1}, Agilia, Schnider Model; Fresenius Kabi). Tracheal intubation was facilitated with 0.15 mg·kg^{-1} predicted body weight iv cisatracurium (Fresenius Kabi). The predicted body weight was calculated according to the Devine Formula,:[9]

$$PBWw = 45.5\,kg + 0.9*(height\ in\ cm - 152)$$

$$PBWm = 45.5\,kg + 0.9*(height\ in\ cm - 152)$$

where $PBWw$ is the predicted body weight for women and $PBWm$ is the predicted body weight for men. Further muscle relaxation was maintained with repeated doses of 0.03 mg kg^{-1} iv cisatracurium. Neuromuscular blockade was monitored with an acceleromyograph (TOFscan; Dräger Medical). Potential hypotension (defined as mean arterial pressure < 65 mmHg) was treated with a continuous norepinephrine infusion (0.03–0.2 μg kg^{-1} min^{-1}). Standard anti-emetic prophylaxis consisted of 4 mg iv dexamethasone, administered early after induction of anesthesia, and 4 mg iv ondansetron, administered 30 minutes before the end of surgery. Volume requirements were addressed individually, according to clinical judgement, with a crystalloid solution (Jonosteril; Fresenius Kabi). For tracheal intubation, tracheal tubes with low pressure cuffs (internal diameter of 7.0 mm for women and 8.0 mm for men; Mallinckrodt Hallo-Contour Rohr; Covidien, Neustadt an der Donau, Germany) were used. After adequate placement of the tracheal tube, the infusion of propofol was reduced to a target concentration of 3–4 μg mL^{-1} and patients were ventilated in the volume-controlled mode (Primus IE; Dräger Medical). The ventilation parameters were adjusted to maintain an end-tidal CO_2 partial pressure between 35 and 38 mmHg, the tidal volume was set to 7 mL kg^{-1} predicted body weight and the inspiration-to-expiration ratio was set to 1:2. After stable ventilation was reached, the continuous intravenous administration of propofol was terminated and volatile anesthesia was induced with an inspiratory concentration of 1.7 age-related minimal alveolar concentration (MAC). During this period, the fresh-gas-flow (FGF) was set to 3 L·min^{-1}.[10] After an expiratory concentration of 1.0 MAC of the respective volatile anesthetic was reached, the FGF was reduced to 0.8 L min^{-1} and the inspiratory concentration of the anesthetic was adjusted to maintain the expiratory fraction of 1.0 MAC during the operative procedure. Emergence from anesthesia was achieved by the termination of anesthetic administration, accompanied by increasing the FGF to 10 L min^{-1}.

2.2. Simulation

To simulate volatile anesthesia for desflurane and sevoflurane, we used the Gas Man software (version 4.2, Med Man Simulations,

Inc., Boston, MA). Gas Man contains a four-compartment mammillary model (ALV, alveolar gas compartment; VRG, the vessel-rich compartment; MUS, muscle compartment; FAT, fat compartment) of tissues, connected with the rebreathing circuit. Depending on the chosen inspiratory concentration, the breathing circuit, the FGF, the VA, the CO and further model parameters (such as fractional tissue flows and volumes), Gas Man simulates the anesthetic model behavior and displays anesthetic partial pressures in the four compartments graphically and numerically (Fig. 1). For each measured data set, two corresponding simulations (standard and parameter-matched Gas Man model) were performed in time steps of 6 seconds. Therefore, we adapted the inspiratory anesthetic concentration during induction (1.7 age-related MAC), chose a semi-closed breathing circuit and simulated the same length of administration of the respective volatile anesthetic for both simulation models. Volatile anesthesia in patients was performed according to the standard of clinical practice in our department (see below). This protocol also includes that the expiratory volatile anesthetics' concentration was held constant at 1.0 MAC. Since the expiratory concentration during the Gas Man simulations was also held constant at 1.0 MAC there is no need to compare data during maintenance. In the parameter-matched model, we also set CO and VA according to the respective patient measures considering the following:

2.3. Cardiac performance

To calculate an estimate of the individual approximate CO for each patient the average stroke volume was multiplied with the heart rate. For further information, please see the Supplemental Digital Content (Appendix), http://links.lww.com/MD/F322.

2.4. Alveolar ventilation

Alveolar ventilation during mechanical ventilation depends on the tidal volume and the fractional dead space volume. Nunn et al calculated an intrathoracic dead space volume (without the tracheal tube) of 66 mL.[11] For tracheal intubation, we either used tracheal tubes with an inner diameter of 7.0 mm and a length of 31.0 cm (women) or an inner diameter of 8.0 mm and a length of 33.0 cm (men) (Mallinckrodt Hallo-Contour Rohr; Covidien). The approximate volume of the tracheal tube was determined as either 11.9 mL (inner diameter of 7.0 mm) or 16.6 mL (inner diameter of 8.0 mm). Further, the connected heat and moisture exchange filters (Filter SafeStar 55, Dräger Medical) contained an inner volume of 55.0 mL. To calculate the approximate VA during mechanical ventilation, we subtracted the respectively determined dead space volume (132.9 mL for women and 137.6 mL for men) from the individual tidal volumes during the induction and emergence of anesthesia. In the same manner, as the individual CO was calculated to perform parameter-matched simulations for each patient, the individual VA was calculated approximately by using the estimated dead space, the measured tidal volumes and the ventilation frequencies.

For comparisons of induction and emergence curves we calculated the difference in arithmetic mean of the squares '(root-mean-square deviation) (RMSD) as follows:

$$\text{RMSD}\,(\alpha) = \sqrt{\frac{1}{n}\cdot(\alpha_1^2 + \alpha_2^2 + \cdots + \alpha_n^2)} \qquad \text{Equation 1}$$

where α is the difference between the measured expiratory volatile anesthetic concentration of the patient and the calculated expiratory concentration from the Gas Man simulational model for each of n data points. The temporal resolution (sampling frequency) for the measured n data points from the patient data was 1 Hz. As the sampling frequency of the Gas Man simulations was 1/6 Hz only every sixth data point from the patient data was used, for generating data with congruent time intervals.

We further calculated the performance error (PE_{ij}) of the jth datapoint in the ith individual for each measured point to calculate the median performance error (MDPE) and the absolute median performance error (MDAPE) for the whole anesthesia duration as follows[8]:

$$PE_{ij}(\%) = [(C_P - C_{GM})/C_{GM}]\cdot100 \qquad \text{Equation 2}$$

$$MDPE\,(\%) = \text{median}\,PE_{ij}, j = 1,\ldots,N_i \qquad \text{Equation 3}$$

$$MDAPE = \text{median}\,|PE_{ij}|_{ij}, j = 1,\ldots,N_i \qquad \text{Equation 4}$$

where C_P is the expiratory anesthetic concentration from the patient data and C_{GM} is the expiratory anesthetic concentration from the respective Gas Man simulational model.

Decrement times (50%, 60%, 70%, 80% and 90% decrement times) as a fraction of 1.0 MAC expiratory, the respiratory and hemodynamic variables.

2.5. Statistics

Unless stated otherwise, data are presented as mean (SD). If Shapiro-Wilk tests show that data were normally distributed t tests were used. If the data were not normally distributed, we performed Mann-Whitney U tests. Therefore, we used R based software [jamovi project (2018), jamovi (Version 0.9.2.3), retrieved from https://www.jamovi.org)]. $P < .05$ was considered statistically significant.

There was no a priori sample size calculation to this observational study as we used already existing data. Therefore, we performed a post-hoc power calculation. Regarding the primary endpoint RMSD, based on a double-sided t test, the statistical test power was >0.99.

3. Results

We randomly collected 10 data sets from volatile anesthesia with desflurane and 10 data sets from volatile anesthesia with sevoflurane. Patient characteristics are given in Table 1.

3.1. Root-mean-square deviation, decrement times, MDPE and MDAPE

During induction and elimination of volatile anesthesia from desflurane and sevoflurane, the RMSDs between the patient data and the standard Gas Man simulation model [RMS (Patient) – RMS (standard model)] were higher compared to the RMSDs between the patient data and the parameter-matched Gas Man simulation model [RMS (Patient) – RMS (parameter-matched
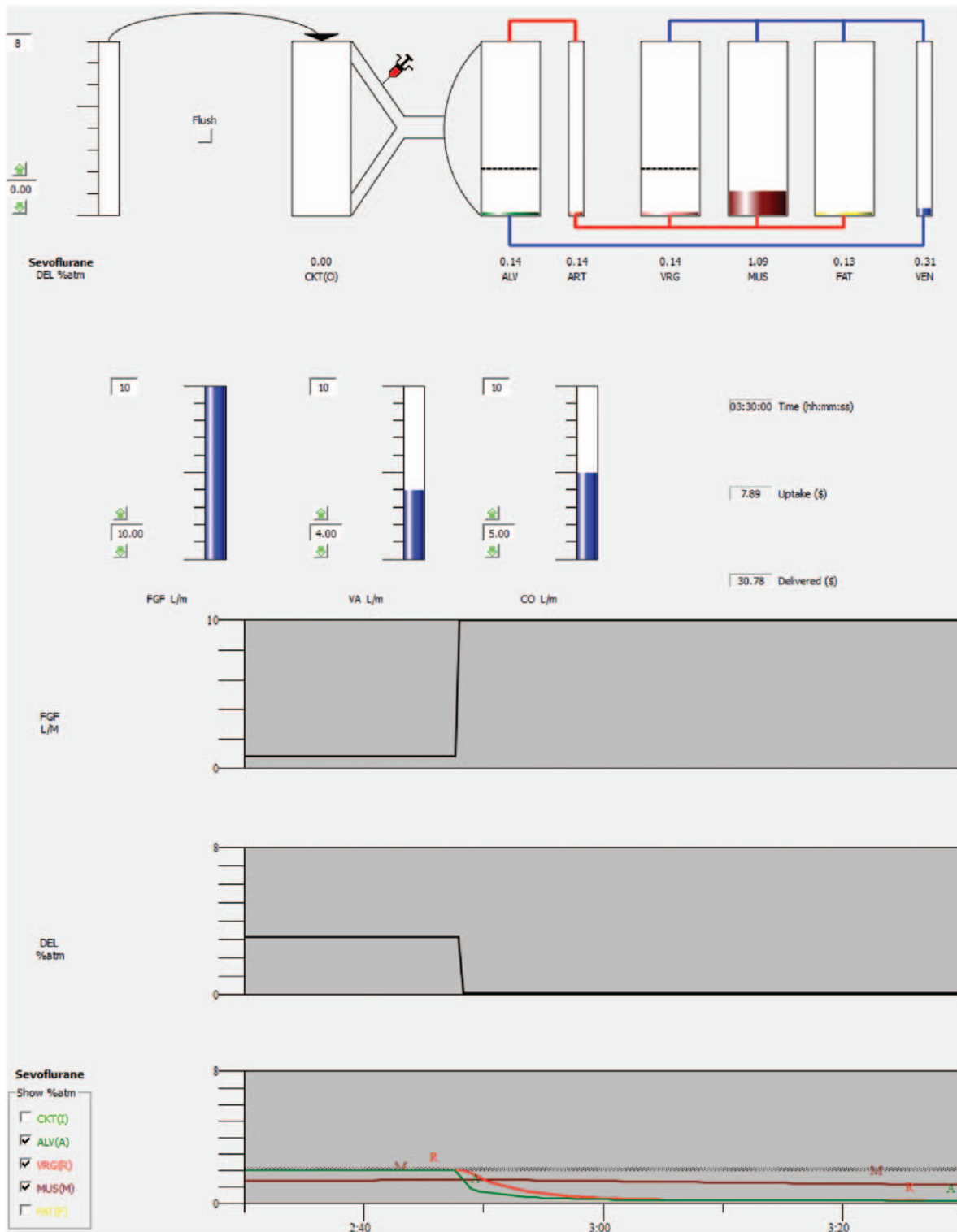
Figure 1. Gas Man Picture (top) and Graph (bottom) after 2 hours and 47 minutes of sevoflurane administration of 1.0 MAC expiratory. DEL, delivered sevoflurane concentration (% of 1 Atm); CKT, circuit; ALV, alveolar; ART, arterial blood; VRG, vessel-rich-group; MUS, muscular; FAT, fat; VEN, venous blood; FGF, fresh gas flow; VA, alveolar ventilation; CO, cardiac output. After 2 hours and 47 minutes, the administration of sevoflurane was stopped, the circuit was opened (non rebreathing) and the FGF was increased to 10 L/min. The Gas Man Graph (bottom) indicates the FGF, the DEL and the course of anesthetic tension in the chosen compartments over time. The predictive performance of this simulation (performed with the standard Gas Man simulation model) was compared to the parameter-matched Gas Man model (including individually adapted hemodynamic and respiratory variables). The minimum alveolar concentration (MAC) in this exemplary simulation used in this study was 2.1% of 1 Atm, indicated by the dotted line in the bottom part of the figure. In every simulation that was performed for this study, we used the same age-adjusted MAC as displayed by the anesthesia machine (Dräger Perseus A500, Dräger Medical).[10].

Table 1

Patient characteristics.

	Desflurane (n = 10)	Sevoflurane (n = 10)
Age (yr)	51.2 (16.4)	52.9 (19.3)
Gender (n), female/male	3/6	6/4
ABW (kg)	79.7 (20.9)	71.9 (10.9)
PBW (kg)	69.0 (8.3)	65.2 (9.6)
BMI (kg m^{-2})	21.2 (9.3)	22.7 (9.9)

ABW = actual body weight, BMI = body mass index, PBW = predicted body weight.

model)] (Fig. 2). During maintenance of anesthesia, the RMSDs between the patient data and the standard Gas Man simulation model and the parameter-matched Gas Man model showed no significant difference (Table 2). To allow a higher temporal resolution, we did not show RMSDs during maintenance of anesthesia in Figure 2. The calculated expiratory decrement times

for desflurane and sevoflurane showed no significant differences between both simulation models and the patient data (Fig. 3).

MDPE and MDAPE showed no significant differences between the standard and the parameter-matched Gas Man simulation model for both volatile agents, desflurane and sevoflurane (Table 2).

3.2. Respiratory and hemodynamic variables

No significant differences in respiratory and hemodynamic variables were found between the two groups (Table 3).

4. Discussion

In this study, we investigated the performance of the standard and a parameter-matched Gas Man simulation model on the prediction of expiratory desflurane and sevoflurane concentrations during induction, maintenance and elimination of
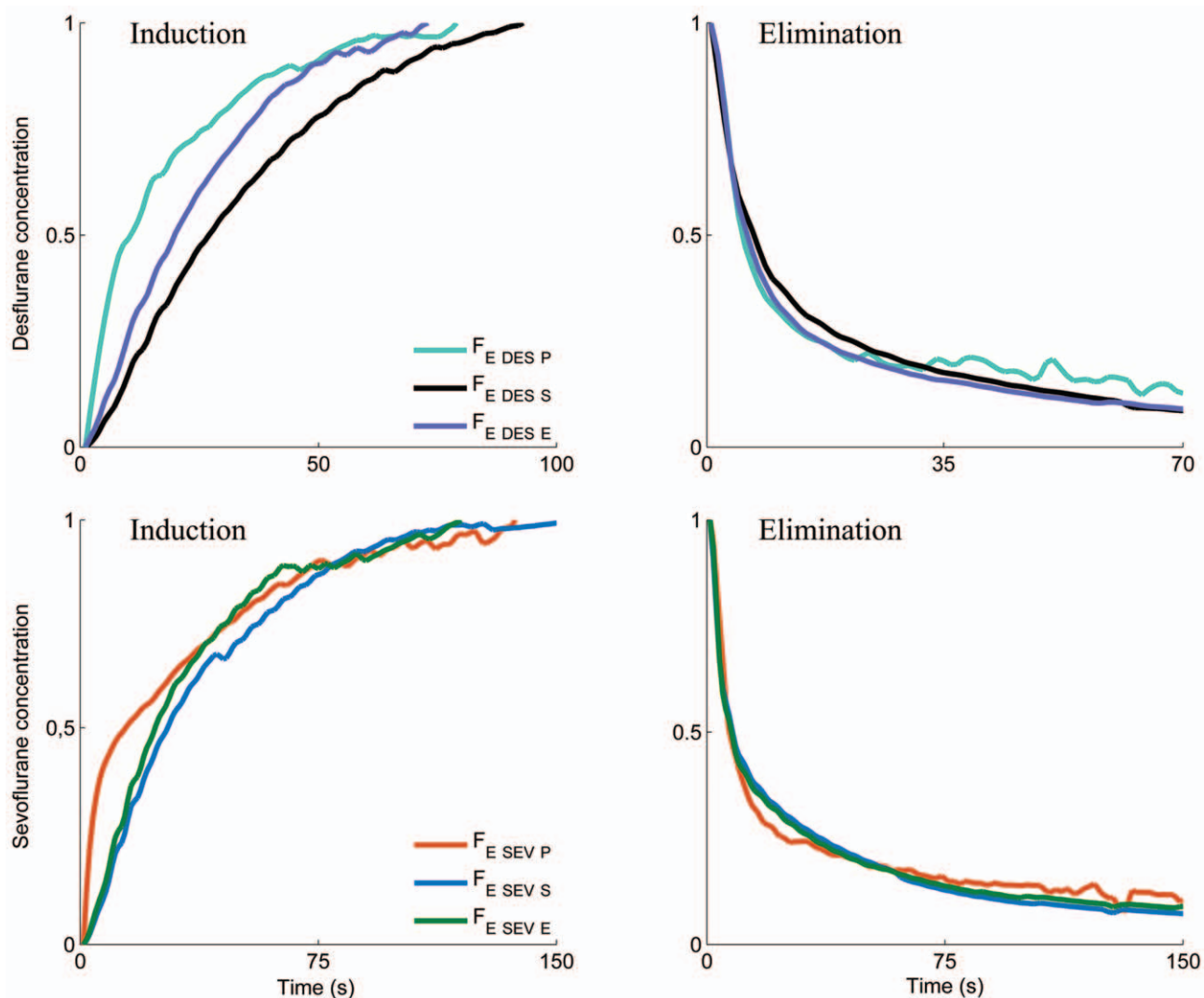
Figure 2. Mean expiratory concentrations of desflurane and sevoflurane during induction and elimination, normalized to 1.0 age-related MAC.[10] $F_{E\_DES\_P}$ = mean expiratory fraction of desflurane for patients, $F_{E\_DES\_S}$ = mean expiratory fraction of desflurane for the standard Gas Man model, $F_{E\_DES\_E}$ = mean expiratory fraction of desflurane for the parameter-matched Gas Man model. $F_{E\_SEV\_P}$ = mean expiratory fraction of desflurane for patients, $F_{E\_SEV\_S}$ = mean expiratory fraction of desflurane for the standard Gas Man model, $F_{E\_SEV\_E}$ = mean expiratory fraction of desflurane for the parameter-matched Gas Man model.

Comparison of the root-mean-square deviation (RMSD), the median performance error (MDPE) and absolute median performance error (MDAPE) for expiratory concentrations between measured data from volatile anesthesia in patients and calculated data from simulations.

		Patient vs. standard Gas Man model	Patient vs. parameter-matched Gas Man model	*P* value
RMSD (Desflurane) (% Atm.)	Induction	1.8 (0.4)	0.9 (0.5)	.001
	Maintenance	0.07 (0.02)	0.07 (0.02)	.100
	Elimination	0.7 (0.6)	0.2 (0.2)	.014
RMSD (Sevoflurane) (% Atm.)	Induction	1.2 (0.9)	0.4 (0.4)	.029
	Maintenance	0.06 (0.01)	0.06 (0.01)	.100
	Elimination	0.7 (0.5)	0.2 (0.2)	.008
MDPE (%)	Desflurane	4.7 (3.6)	5.0 (4.0)	.859
	Sevoflurane	*4.7 (3.3–6.8)	4.2 (0.5)	.694
MDAPE (%)	Desflurane	5.8 (2.2)	6.0 (2.5)	.817
	Sevoflurane	*9.5 (5.6–10.2)	*7.6 (4.2–9.0)	.563

IQR = interquartile range, MDAPE = absolute median performance error, MDPE = median performance error, RMSD = root mean square deviation. For data that were not normally distributed (*), values are given in median (IQR).

volatile anesthesia. Therefore, we compared expiratory concentrations of patient data and simulation data from the Gas Man simulation software. The main findings of our study confirm our hypothesis that the Gas Man simulation software is able to predict expiratory concentrations of desflurane and sevoflurane in lung-healthy patients during volatile anesthesia with good accuracy. Further, modification of the model by individual VA and CO improved the accuracy of the prediction during anesthesia induction and elimination. The overall predictive performance of both, the standard and the parameter-matched, Gas Man simulation models were higher during elimination than during induction. During the maintenance of volatile anesthesia, the expiratory concentration of the respective volatile anesthetic was held constant at 1.0 MAC. Hence it is expected that, during the maintenance phase of volatile anesthesia, there is no significant difference in RMSDs between the measured patient data and calculated data from both simulation models.

The application of physiologically-based pharmacokinetic (PBPK) models has become a very important factor for the predictability of pharmacokinetic behavior for many anesthetic drugs. For intravenous anesthetics, target-controlled infusion systems implement PBPK algorithms to support patient-individual drug dosage and titration.[12] Usually, the performance of these target-controlled infusion systems is evaluated by the estimation of anesthetic concentrations in blood samples.[13,14] Compared to these investigations, our pharmacokinetic model showed a clearly better predictive performance for the temporal courses of desflurane and sevoflurane concentrations. However, while target-controlled infusion systems generally provide calculated information about predicted recovery times, systems utilizing volatile anesthesia lack of algorithms to predict individual recovery profiles. Our study demonstrates that the implication of individual ventilatory and hemodynamic input variables that can be estimated during general anesthesia without additional risks for patients improves the predictive performance of the Gas Man simulation model. However, the differences in RMSDs between the standard and the parameter-matched Gas Man model only were small and thus might not be helpful for clinicians or investigators. Based on the observed good accuracy of the standard Gas Man model, an implementation of this model might help to refine pharmacokinetic models used by anesthesia decision support tools like SmartPilot (Dräger Medical, Lübeck, Germany) and Navigator (GE Healthcare, Helsinki, Finland).

Regardless of the duration of anesthesia, induction and elimination in patients and both simulation models were faster

with desflurane than with sevoflurane. This is in accordance with the physicochemical properties of these volatile anesthetics, and clinical, and theoretical investigations.[15–18] There are two studies available that compare the predictive performance of the standard Gas Man model: Bouillon and Shafer compared expiratory concentrations of desflurane, isoflurane, and sevoflurane during the elimination of volatile anesthesia in patients with the standard Gas Man model.[7] Since those authors did not export simulation data, their analysis did not evaluate their data with high temporal resolution and they did not conduct a point-by-point performance error calculation. Athiraman et al conducted performance error calculations during the whole course of volatile anesthesia with isoflurane in 34 patients using the standard Gas Man simulation model. Since their monitor used to measure anesthetic concentrations approximated the value to the nearest 0.05 decimal, the accuracy of their investigation was limited. It should be noted that the anesthetic monitor used in this study approximates the concentration value to the nearest .01 decimal. Despite this minor limitation, they showed that the standard Gas Man simulation model is able to predict the expiratory concentration of isoflurane with good accuracy.[8]

Because of their clinical importance, common pharmacokinetic investigations focus on the characterization of context-sensitive decrement times. None of the previous comparative studies compared measured decrement times of patients with those of the Gas Man simulation model. Especially the expiratory volatile anesthetic concentration at first eye opening in response to a verbal command during recovery from volatile anesthesia (MACawake) is of clinical importance. In case of an anesthetic drug induced MAC reduction (e.g. caused by the administration of opioids or sedative-hypnotics), the threshold of cerebral concentration of volatile anesthesia leading to a measurable cognitive impairment may be decreased.[19] It follows that higher decrement times (i.e., 80%- and 90%-decrement times) may be of higher clinical importance. In this regard, it is even more interesting that both the standard and the parameter-matched Gas Man simulation model, predict these higher decrement times with comparable high accuracy. Further, it should be stated that the MACawake is only helpful in steady state situations during volatile anesthesia. During emergence from volatile anesthesia, awakening occurs when the concentration of the volatile anesthetic reaches a distinct and individually different threshold in the central nervous system. It follows that the MACawake (measured by the expiratory concentration of the respective
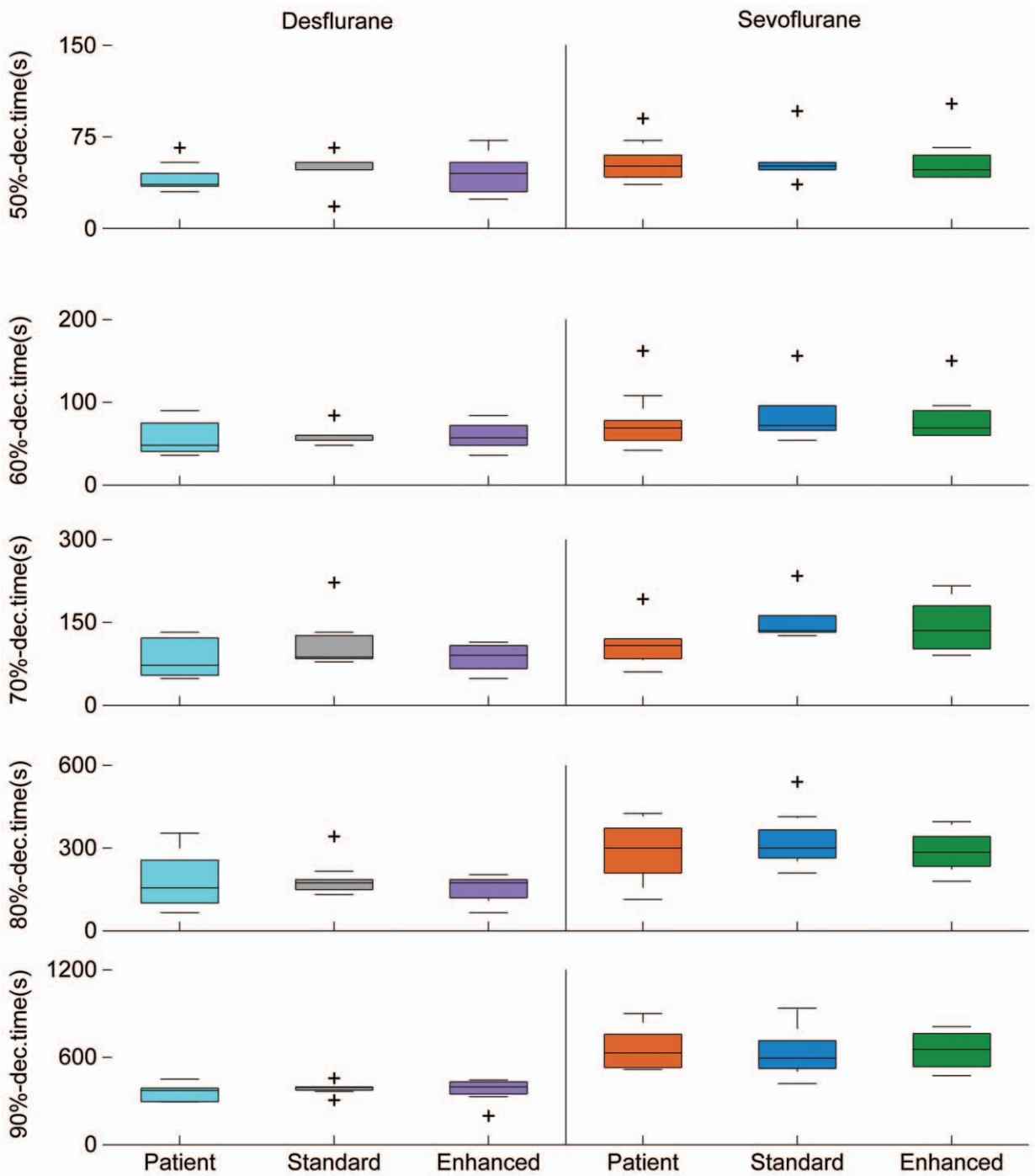
Figure 3. Comparison of decrement times (dec.time) for desflurane and sevoflurane between the measured patient data ('Patient') and simulation data from the standard ('Standard') and the parameter-matched ('Enhanced') Gas Man simulation model. All decrement times are displayed in the percentage of expiratory concentration of 1.0 MAC. There was no statistically significant difference between the decrement times of the patient and the simulation data Mann-Whitney U test). On each box, the central mark indicates the second quartile, the bottom, and top edges indicate quartiles (25th percentile and 75th percentile). On each box, the whiskers indicate the range of data points. Outliers are plotted individually ('+').

Table 3

Respiratory and hemodynamic variables.

Variable	Desflurane	Sevoflurane	P value
V_T (mL)	459 (62)	487 (46)	.260
V_T PBW (ml kg^{-1})	6.9 (1.5)	7.4 (1.3)	.445
VF (min^{-1})	13.2 (4.5)	10.3 (3.2)	.116
PetCO$_2$ (mmHg)	36.4 (1.3)	36.1 (1.1)	.602
PIP (cmH$_2$O)	21.4 (5.9)	21.3 (3.7)	.964
PEEP (cmH$_2$O)	7.2 (1.5)	5.9 (1.4)	.056
C$_{RS}$ (ml cmH$_2$O^{-1})	42.5 (15.9)	46.5 (12.9)	.545
Heart rate (min^{-1})	63.0 (8.7)	61.1 (9.2)	.642
SAP (mmHg)	109.9 (6.8)	108.5 (11.1)	.718
DAP (mmHg)	57.6 (4.5)	57.3 (7.1)	.903
MAP (mmHg)	77.3 (4.0)	79.3 (7.5)	.478
CO (L min^{-1})	4.9 (0.7)	4.8 (0.7)	.642
Duration of anesthesia (min)	101.0 (25.5)	*85.7 (71.0–91.2)	.277

Values are stated as mean (SD). V_T, tidal volume; V_T PBW, tidal volume per predicted body weight;[9] C$_{RS}$ = respiratory system compliance, DAP = mean diastolic arterial blood pressure, MAP = mean arterial pressure, PEEP = positive end-expiratory pressure, PetCO$_2$ = end-tidal carbon dioxide partial pressure, PIP = peak inspiratory pressure, SAP = mean systolic arterial blood pressure, VF = ventilation frequency; CO, cardiac output (calculated by the multiplication of the stroke volume of the comparative literature analysis [supplemental content; http://links.lww.com/MD/F645] and the respective individual heart rate). IQR, interquartile range. For data that were not normally distributed (*), values are given in median (IQR).

volatile anesthetic) cannot reflect the exact concentration of the volatile anesthetic in the central nervous system.

5. Limitations

In many diseases and physiological changes (e.g., age-related), tissue volumes and tissue flows can deviate from those in the standard Gas Man simulation model. For example, obesity, muscularity, and cachexia alter body composition and tissue flows. These changes can be addressed individually in the Gas Man simulation software. However, since the aim of this study was to investigate the accuracy of a cardiac output and alveolar ventilation matched Gas Man model and to compare its predictive performance with the standard pharmacokinetic model, we did not change the tissue volumes and flows of the model. A further limitation of this study is that we did not measure CO during anesthesia in the chosen patient collective. Since the most common practice method to measure CO with high accuracy is the pulmonary artery catheterization. This technique is associated with various potential risks. It follows that the potential risk of such an invasive cannot be applied in the chosen patient collective. It also should be noted that the dead space calculation might underestimate dead space during mechanical ventilation. [11]

6. Conclusion

This is the first study to conduct performance analysis of the Gas Man simulation software for volatile anesthesia with desflurane and sevoflurane and to compare the predictive performance of the standard and parameter-matched Gas Man simulation models. Utilizing data from volatile anesthesia in lung-healthy patients, the standard and a parameter-matched Gas Man simulation model, we could demonstrate that the Gas Man software offers a tool to predict expiratory concentrations of desflurane and sevoflurane during volatile anesthesia in lung-healthy patients. The improvement of the parameter-matched Gas Man model only was small and thus might not be useful for clinicians and investigators.

Author contributions

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Investigation: Jonas Weber, Claudia Mißbach.
Methodology: Jonas Weber, James H. Philip, Steffen Wirth.
Software: Jonas Weber, Johannes Schmidt, James H. Philip.
Supervision: Jonas Weber, Johannes Schmidt, Steffen Wirth.
Validation: Jonas Weber, Johannes Schmidt, Stefan Schumann.
Visualization: Jonas Weber.
Writing – original draft: Jonas Weber.
Writing – review & editing: Jonas Weber, Claudia Mißbach, Johannes Schmidt, Christin Wenzel, Stefan Schumann, James H. Philip, Steffen Wirth.

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