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RESEARCH ARTICLE

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Quantification of exhaled propofol is not feasible during single-lung ventilation using double-lumen tubes: A multicenter prospective observational trial

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Abstract

Background: Volatile propofol can be measured in exhaled air and correlates to plasma concentrations with a time delay. However, the effect of single-lung ventilation on exhaled propofol is unclear. Therefore, our goal was to evaluate exhaled propofol concentrations during single-lung compared to double-lung ventilation using double-lumen tubes.

Methods: In a first step, we quantified adhesion of volatile propofol to the inner surface of double-lumen tubes during double- and single-lumen ventilation in vitro. In a second step, we enrolled 30 patients scheduled for lung surgery in two study centers. Anesthesia was provided with propofol and remifentanil. We utilized left-sided double-lumen tubes to separately ventilate each lung. Exhaled propofol concentrations were measured at 1-min intervals and plasma for propofol analyses was sampled every 20 min. To eliminate the influence of dosing on volatile propofol concentration, exhalation rate was normalized to plasma concentration.

Results: In-vitro ventilation of double-lumen tubes resulted in increasing propofol concentrations at the distal end of the tube over time. In vitro clamping the bronchial lumen led to an even more pronounced increase (Δ AUC +62%) in propofol gas concentration over time. Normalized propofol exhalation during lung surgery was 31% higher during single-lung compared to double-lung ventilation.

Conclusion: During single-lung ventilation, propofol concentration in exhaled air, in contrast to our expectations, increased by approximately one third. However, this observation might not be affected by change in perfusion-ventilation during single-lung ventilation but rather arises from reduced propofol absorption on the inner surface area of the double-lumen tube. Thus, it is only possible to utilize exhaled propofol concentration to a limited extent during single-lung ventilation.

Registration of Clinical Trial: DRKS-ID DRKS00014788 (www.drks.de).

KEYWORDS
double-lumen tube, Edmon propofol monitor, exhaled propofol, ion mobility spectrometry, one-lung ventilation, pharmacokinetics, propofol adhesion, single-lung ventilation, total intravenous anesthesia

Editorial Comment

In a two-step 2-center study, the authors quantified the adhesion of volatile propofol to the inner surface of double-lumen tubes during double- and single-lumen ventilation in vitro and then studied 30 patients scheduled for lung surgery in two study centers. Exhaled propofol concentrations were measured at 1-min intervals and plasma for propofol analyses was sampled every 20 min. Surprisingly, the authors found that exhaled propofol concentration increased by approximately one-third. There is speculation that reduced propofol absorption on the inner surface area of the double-lumen tube may be the cause, thus measurement of exhaled propofol concentration has limited clinical value during single-lung ventilation.

1 | INTRODUCTION

Propofol anesthesia is commonly used for bronchoscopy[1] because inhalational anesthetics cannot be scavenged effectively and because inhalational anesthetics may not equilibrate normally during single-lung ventilation.[2] Propofol can be measured in trace range (ppb_v) in exhaled breath[3] and correlates—within a pharmacokinetic model and with a time delay—to plasma concentrations.[4]

It continues to be unclear whether the established relationship between plasma and exhaled propofol remains intact during single-lung ventilation. Reduced pulmonary surface area as well as hypoxic pulmonary vasoconstriction (von Euler–Liljestrand mechanism) during one-lung ventilation are potential opposing factors presumably influencing the amount of exhaled propofol.

However, at such low concentrations in the breath, adhesion of volatile propofol to the inner surface of the tube may be important and could affect the measured concentrations.[5] This circumstance becomes more important, especially in the case of double-lumen tubes with different surfaces during single- and double-lumen ventilation. Therefore, we tested the hypothesis that the measured concentrations of volatile propofol differ when using single- and double-lumen ventilation in-vitro.

Furthermore, propofol concentrations were evaluated in exhaled air and blood plasma in thoracic surgical patients ventilated with both lungs and during single-lung ventilation. Specifically, we evaluated propofol exhalation (propofol exhalation [ng/min] normalized to propofol plasma concentration [µg/mL]) during single-lung compared to double-lung ventilation.

2 | METHODS

2.1 | Adhesion of volatile propofol to double-lumen tubes—in vitro measurements

We quantified the adhesion of volatile propofol to the inner surface of different double-lumen tubes: Rüsch (Teleflex) and Epsa (Medicoplast). For this purpose, the tip of each tube was inserted into a perfluoroalkoxy polymer reservoir (Bola-Planschliff-Reaktionsgefäß PFA 2400 mL, Bohlender), which was flushed with propofol gas (10 ppb_v) using a test gas generator (HovaCAL 4836-VOC, IAS GmbH).[6] The temperature of the gas mixture was maintained at 26°C, the relative humidity at 90%.

Propofol target concentration within the reservoir was verified using multi-capillary column ion-mobility spectrometry (Edmon, B. Braun). The distal ends of the tube (bronchial and tracheal) were connected via a y-piece and the propofol concentration in the gas mixture was determined using multi-capillary column ion-mobility spectrometry as described above. After ventilation of both, tracheal and bronchial lumens for 60 min, the bronchial portion was clamped for a further 60 min. The clamp was then removed and both lumens ventilated again for 60 min. Propofol concentrations were measured in 1-min intervals. These tests were carried out three times for each type of double-lumen tube. Area under the curve (AUC) was calculated for various time-concentration curves during single- and double-lumen ventilation.

2.2 | Subject selection

This prospective observational study was carried out at the Saarland University Medical Center Homburg (Study Center 1) and at the University Hospital in Marburg (Study Center 2), both in Germany. The study was registered with German Clinical Trials (ID 00014788) and adhered to applicable STROBE guidelines. The study was approved by the responsible ethics committees: Identification Numbers 09/18, March 2, 2018, Ärztekammer Saarland, Saarbrücken, Germany and 41/18, May 15, 2018, Ethikkommission Marburg, Germany. Written consent was obtained from 30 patients scheduled for endoscopic or open lung surgery with an expected time of lung separation of more than 60 min at each center. Each was designated American Society of Anesthesiologists physical status I-III, was at least 18 years old, had a body mass index less than 35 kg/m^2, and no significant cardiac, hepatic, renal, or neurological diseases. Exclusion criteria were contraindications for propofol or remifentanil, pregnancy or breastfeeding, renal replacement therapy, drug abuse, and hepatitis.

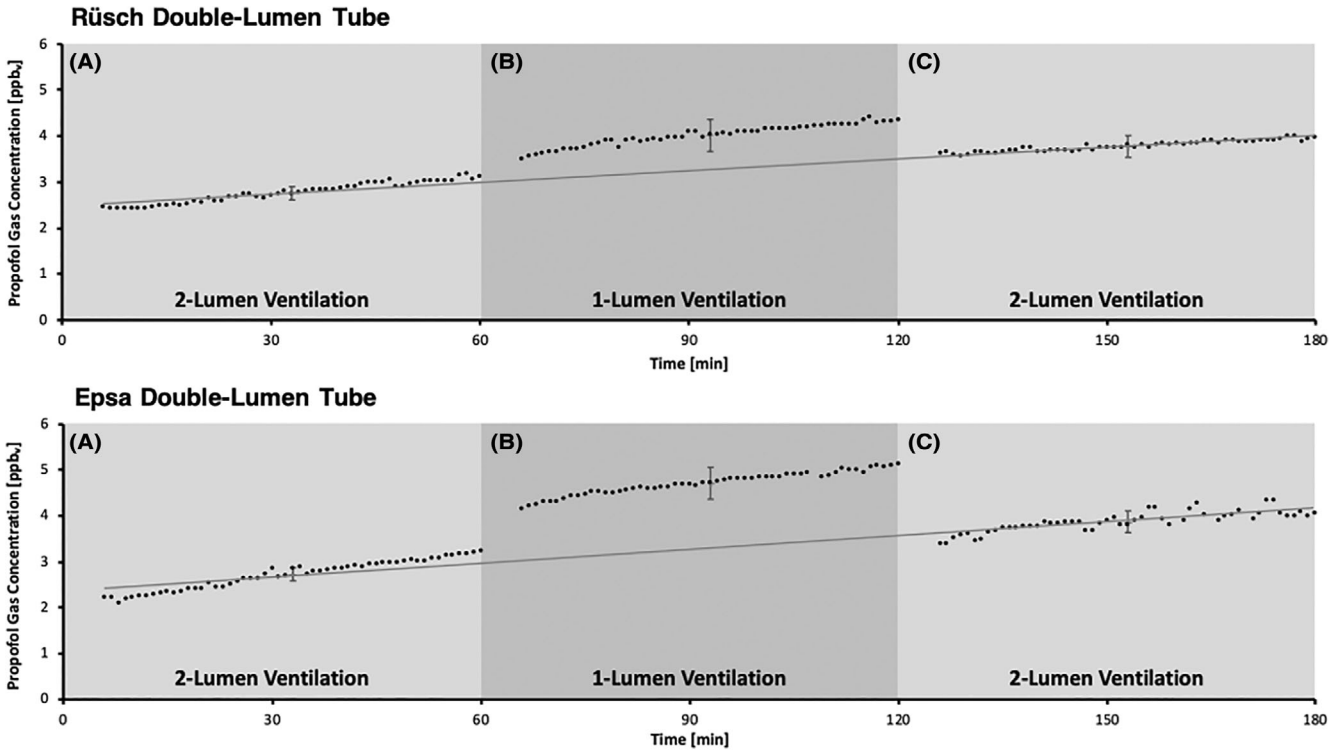

FIGURE 1 In vitro propofol gas concentration [ppb_v] at the distal y-piece of the double lumen tubes (y-axis) used at study center 1 (top) and study center 2 (bottom) over the period of 180 min (x-axis) after maintaining reservoir propofol gas concentration of 10 ppb_v. Measurements were carried out every minute: first 60 min with ventilation of both, tracheal and bronchial lumen (A), subsequent 60 min with ventilation of the tracheal lumen only (B) and again 60 min with ventilation of the tracheal and bronchial lumen (C). The dots show mean values, error bars depict the standard deviations of the respective measurements. The solid line shows the trend (mean) of A and C. The ventilation of the tubes with propofol gas leads to adhesion of volatile propofol at the inner surface of the tubes. This ongoing saturation results in increasing concentrations over time at the distal end of the tubes (AUC 145 for both, Rüsch and Epsa tubes for time period A). Clamping the bronchial lumen interrupts the propofol gas flow and leads to a reduction in the adhesion and thus to an increase in the propofol concentration in the tracheal lumen (AUC 216 for Rüsch and 255 for Epsa tubes for time period B). This increase is more pronounced in the double lumen tubes of the Study Center 2. Opening the clamp again leads to a drop in the propofol gas concentration (AUC 203 for Rüsch and 205 for Epsa tubes for time period C).

2.3 | Protocol

Anesthesia was provided with propofol using Target Controlled Infusion (TCI) Marsh model[7] and remifentanil using TCI Minto model,[8,9] both set to plasma mode (Perfusor Space TCI, B. Braun). Target concentrations (propofol and remifentanil) were chosen by the responsible anesthesiologist, who was not involved in the study. General anesthesia was supplemented, as necessary, with atracurium and epidural analgesia using ropivacaine and sufentanil. Anesthetic drugs were adjusted to maintain Bispectral Index (BIS) between 35 and 50 during lung separation. Two types of left-sided double-lumen tubes were utilized as described above: Rüsch (Teleflex) in Homburg and Epsa (Medicoplast) in Marburg. Patients were ventilated by a respirator (Primus, Dräger) with ventilation parameters and oxygen concentrations adjusted to maintain normoxia and normocarbia. Volume- or pressure-controlled modes were used for artificial respiration. Fresh gas flow was set at 1 L/min. To prevent adsorption of volatile propofol at the sampling point, heat-and-moisture-exchanging filters (Humid-Vent Filter Compact S, Teleflex Medical) were connected to the outlet ports of the anesthesia workstation. Propofol and remifentanil infusion rates, hemodynamic monitoring, BIS values, and ventilation parameters were recorded automatically. Duration of single-lung ventilation was recorded with digital time stamps.

2.4 | Measurements

Two milliliters of arterial blood were sampled from an arterial catheter 5 min after anesthesia induction and subsequently every 20 min or 5–10 min after changing propofol TCI target concentration. During single-lung ventilation the sampling interval was reduced to 15 min.

A volume of 0.6 mL blood plasma was used for the sample preparation by solid phase extraction. For each patient a calibration curve with nine blank plasma samples (lyophilized drug-free serum, Bio-Rad) spiked with propofol to concentrations of 8, 6, 5, 4, 3, 2, 1, 0.5, and 0.25 μg/mL was prepared with a certified reference standard (Sigma-Aldrich). To create the calibration curve, the peak area was plotted against the concentration using a linear fit. Separation was carried out on an Agilent 1260 Infinity series liquid chromatography system (Agilent). Detection was performed on an atmospheric pressure ionization-electrospray coupled mass selective detector model G6130BA

TABLE 1 Ventilation parameters and concentrations.

	Study Center 1			Study Center 2		
Parameter	**2-Lung-ventilation**	**1-Lung-ventilation**	***p*-Value**	**2-Lung-ventilation**	**1-Lung-ventilation**	***p*-Value**
MV [L/min]	5.6 (±1.6)	5.9 (±1)	.005	4.8 (±1.6)	5 (±1.4)	<.001
PEEP [mbar]	4 (±1.9)	4.4 (±0.9)	n.s.	5.6 (±2)	5.2 (±1.5)	<.001
P_{peak} [mbar]	16 (±4)	19 (±3)	<.001	18 (±4)	20 (±4)	<.001
P_{plat} [mbar]	15 (±3)	18 (±3)	<.001	17 (±4)	19 (±4)	<.001
P_{mean} [mbar]	7 (±3)	9 (±1)	<.001	10 (±3)	11 (±2)	<.001
$etCO_2$ [mmHg]	32.6 (±5.6)	32.2 (±4)	<.001	36.3 (±5.2)	35.8 (±4.3)	<.001
SpO_2 [%]	100 (±2)	99 (±2)	n.s.	99 (±2)	97 (±4)	<.001
HR [bpm]	73 (±16)	77 (±13)	<.001	69 (±19)	67 (±18)	n.s.
MAP [mmHg]	78 (±15)	78 (±13)	n.s.	86 (±23)	86 (±17)	n.s.
BIS	39 (±17)	37 (±8)	n.s.	43 (±16)	37 (±9)	<.001
Propofol target concentration [μg/mL]	3.8 (±0.3)	3.9 (±0.3)	n.s.	3.1 (±0.5)	3.2 (±0.5)	<.001
Remifentanil target concentration [ng/mL]	10.0 (±2.5)	11.5 (±2.6)	<.001	8.7 (±2.7)	9.6 (±2.6)	<.001
Propofol plasma concentration [μg/mL]	3.1 (±1.2)	3.2 (±1.2)	n.s.	3.0 (±1.2)	3.0 (±1.1)	n.s.
Propofol breath concentration [ppb_v]	4.6 (±1.1)	5.4 (±1.2)	<.001	2.6 (±0.8)	3.1 (±1.1)	<.001
Propofol elimination [ng/min]	182 (±62)	224 (±62)	<.001	82 (±44)	110 (±59)	<.001

Note: Ventilation and cardiovascular parameters, propofol and remifentanil target concentrations as well as propofol concentrations (plasma, breath) and elimination in exhaled air expressed as means (±SD); *p*-value for comparison between groups using unpaired *t*-Test or Mann–Whitney Rank Sum Test, respectively.

Abbreviations: BIS, Bispectral Index; HR, heart rate; MAP, mean arterial pressure; MV, minute ventilation; n.s., not significant.

(Agilent). All calibrators, the patient samples, as well as two quality control (QC) standards with a known concentration of 1, 4, and 6 μg/mL propofol were measured in triplicates.[10]

The calibration's linearity was verified at three different days during the validation of the method with $R^2 = .98$. The criterion of acceptance for a measurement run was a coefficient of determination of at least $R^2 = .98$ for the calibration curve. The standard deviation (SD) of the regression lines' y-intercepts as well as the slope of the calibration curve were utilized to calculate the lower limit of detection at 0.0016 μg/mL and the lower limit of quantification at 0.048 μg/mL. The intra-day precision of the method was calculated as relative standard deviation (RSD) from two QC samples at 1 (±0.3% RSD), 4 (±0.1% RSD), and 6 (±0.5% RSD) μg/mL, each measured in triplicate. For the inter-day imprecision, the measurement was repeated once after 14 days with 7.1, 3.6, and 1.0% RSD.

Breath samples were collected via a t-piece, directly connected to the active endotracheal tube lumen, through a 1.8 m polytetrafluoroethylene sample tube (Bohlender). Exhaled propofol (ppb_v) was quantified by multi-capillary column ion-mobility spectrometry (Edmon, B. Braun).[4] Baseline samples were obtained before induction of anesthesia, and thereafter at 1-min intervals until extubation.

2.5 | Data analysis

Propofol exhalation rate (ng/min) was calculated using propofol concentration in expired air (ppb_v) and the minute ventilation (L/min) analogous to the general gas equation:

$$\text{Exhalation rate}\left[\frac{\text{ng}}{\text{min}}\right] = \text{Concentration}\left[ppb_v\right] \times \frac{178.29\left[\frac{\text{g}}{\text{mol}}\right]}{25.4564\left[\frac{\text{L}}{\text{mol}}\right]} \times \text{minute ventilation}\left[\frac{\text{L}}{\text{min}}\right].$$

2.6 | Statistical analysis

Statistical evaluation was carried out using SigmaPlot (Version 12.5, Systat Software). Data were tested for normal distribution (Shapiro–Wilk) and expressed as means (±SD) or median (25%–75%). Comparison between groups was performed via two-sided unpaired *t*-Test or Mann–Whitney Rank Sum Test, when indicated, each with a significance level of <.05. Propofol exhalation was defined as the ratio of exhaled propofol (ng/min) to propofol plasma concentration (μg/mL).

2.7 | Sample size calculation

Sample size was estimated based on two-tailed *t*-tests detecting the difference between two dependent means (matched pairs) with given alpha error of 0.05, power of 0.95, standard deviation of difference of 0.5, and an effect size of 0.3 (G*Power 3.1, University of Düsseldorf). With an expected difference of 15% for propofol exhalation between double- and single-lung group, sample sizes were calculated to 147 propofol blood/air samples in each group. Thus, each patient's

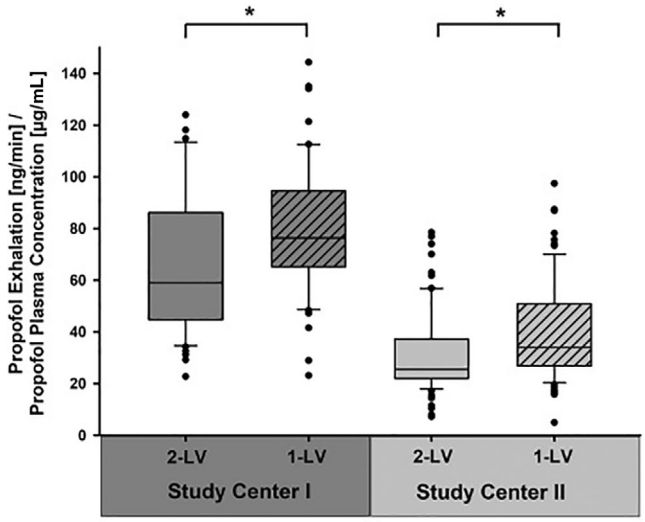

FIGURE 2 Ratio of propofol exhalation [ng/min] normalized to propofol plasma concentration [µg/mL] in patients with double- (58; 25–75th, 44–86) and single-lung-ventilation (76; 25–75th, 65–95) at study center I, respectively. The ratios at study center II were 26 (25–75th, 22–37) for double- and 34 (25–75th, 27–51) for single-lung-ventilation. The middle, upper, and lower edges of the boxplots indicate the 50, 75, and 25th percentiles, respectively. *$p < .05$ significant different ratios between double- and single-lung ventilation (Mann–Whitney Rank Sum Test). 1-LV, single-lung ventilation; 2-LV, double-lung ventilation.

blood had to be sampled at least five times during single-lung and two-lung ventilation, respectively.

3 | RESULTS

In-vitro ventilation of double-lumen tubes resulted in increasing propofol concentrations at the distal end of the tube over time. Clamping the bronchial lumen (single-lumen ventilation) led to an even more pronounced increase in propofol gas concentration. This difference between single- and double-lumen gas exposure was more noticeable in tubes used in Study Center I (Figure 1).

The 30 participating patients had a mean age of 59 (±18) years, weight of 72 (±16) kg, and height of 172 (±10) cm; 11 were women. Target propofol concentration (Marsh model) was marginally increased during single-lung (3.6 ± 0.5 µg/mL) compared to double-lung ventilation (3.5 ± 0.5 µg/mL, $p < .001$). Target remifentanil concentration (Minto model) was elevated during single-lung (10.6 ± 2.7 ng/mL) compared to double-lung ventilation (9.3 ± 2.7 ng/mL, $p < .001$). Bispectral Index (BIS) values were comparable between single-lung (37 ± 8) and double-lung ventilation (37 ± 11).

A total of 361 arterial blood samples were analyzed, 195 during double-lung and 166 during single-lung ventilation. Propofol plasma concentrations were comparable between double-lung (3.0 ± 1.2 µg/mL) and single-lung ventilation (3.1 ± 1.2 µg/mL, $p = .895$).

We quantified propofol in 6693 samples of exhaled air, 4002 during double-lung and 2691 during single-lung ventilation. Exhaled propofol concentration was significantly higher by about a third during single-lung (4.3 ± 1.6 ppb_v) compared to double-lung ventilation (3.5 ± 1.4 ppb_v, $p < 0.001$). Single-lung ventilation increased propofol elimination: 167 (±82) ng/min versus 126 (±69) ng/min ($p < 0.001$). Ventilation and cardiovascular assessments, propofol and remifentanil target concentrations, as well as observed propofol concentrations in plasma and exhaled air are shown in Table 1. Propofol exhalation, normalized to propofol plasma concentration, was 31% greater during single-lung than during double-lung ventilation (Figure 2).

4 | DISCUSSION

Propofol concentrations can only be measured in blood plasma with great effort. Therefore, it is only possible to estimate the pharmacokinetics by clinical patient assessment. However, within a pharmacokinetic model and with a time delay, propofol breath concentration correlates with plasma concentration. Thoracic surgical interventions are frequently performed using single-lung ventilation with total intravenous anesthesia to avoid room air contamination from volatile anesthetics during bronchoscopy. It is unknown whether volatile propofol concentration decreases during single-lung ventilation and whether this correlation between volatile and plasma concentration persists.

We demonstrated in-vitro that ventilation with propofol gas leads to adhesion of volatile propofol to the inner surface of the tubes. This ongoing saturation results in increasing concentrations over time at the distal end of the tube. Clamping the bronchial lumen interrupts the propofol gas flow and might lead to a reduction in adhesion and thus to an increase in propofol concentration in the tracheal lumen. This increase depends on the material of the endotracheal tube. Lorenz et al. demonstrated that propofol reversibly binds to plastic tubes and breathing circuits, exhibiting saturation kinetics. Moreover, propofol concentration sampled directly from the endotracheal tube was substantially higher than at the expiratory end of the breathing circuit.[11] Additionally, propofol absorption depends on the material itself: silicone, polyurethane and tygon absorb virtually the entirety of volatile propofol, while, in contrast, perfluoralkoxy and polytetrafluorethylene only absorb a negligible amount.[5] Therefore, the larger inner surface area using both lumens during double-lung ventilation possibly explains lower volatile propofol concentrations. The larger the inner surface of the endotracheal tube, the greater the adhesion and the lower the measurable concentration. For this reason, the size, the material and consequently the side of single-lung ventilation potentially exerts a significant influence on the volatile propofol concentration: using a left-sided double-lumen tube, the inner surface area is considerably larger when the left lung is ventilated compared to the right lung.

Interestingly, the AUC of both double-lumen-tubes (part A and part C of the in-vitro experiment) and thus the propofol adhesion is relatively similar, although the in-vivo results differ significantly between the two study centers. A reason for this could be different

ventilation parameters and propofol concentrations between the study centers.

We expected that increased shunt volume and smaller pulmonary exchange area during single-lung ventilation would decrease propofol exhalation, although hypoxic pulmonary vasoconstriction could possibly diminish the effect. However in fact, single-lung ventilation actually increased propofol exhalation by approximately a third. The increase was statistically significant and similar in each study center. Exhaled concentrations were normalized to plasma concentration, thus eliminating the influence of dosing on exhaled air concentration. In any case, the plasma concentrations remained nearly identical during double-lung and single-lung ventilation. Thus, our primary hypothesis that single-lung ventilation reduces propofol exhalation must be rejected.

Two factors contribute to propofol pulmonary elimination: propofol concentration in expired air (ppb_v) and minute ventilation (L/min). Although minute ventilation was 5% higher during single-lung ventilation, that hardly accounts for the 30% increase in propofol exhalation. A more likely reason for increased propofol exhalation is loss of adhesion in the bronchial (or tracheal) lumen of the tube after bronchial (or tracheal) clamping.

Before volatile propofol concentration can be put into clinical practice, exhalation kinetics need to be determined in detail, considering how numerous hemodynamic and pulmonary parameters influence exhalation. For example, anesthetic side effects along with mechanical ventilation alter cardiac output and induce changes in the ventilation-perfusion ratio. Yet, the latter is one factor the propofol blood-breath correlation coefficient is dependent upon.[12]

Single-lung ventilation causes a decrease in cardiac output.[13] However, reduced cardiac output and pulmonary blood flow do not meaningfully affect the relationship between propofol breath and plasma concentration.[14] Additionally, as shown by multiple inert gas elimination theories, increased dead space ventilation by reduced cardiac output does not exert any relevant effect on propofol breath-blood ratios.[14] Conversely, increasing cardiac output distributes propofol between different compartments,[15] even within the lung. This results in decreasing plasma concentration,[16] while leaving propofol concentration in expired air unaffected.[14] Increased first-pass dilution and clearance of propofol are further mechanisms decreasing its plasma concentration.[17] Again, higher cardiac output leads to lower propofol plasma concentrations,[17] unpredictable correlation between propofol blood and breath concentrations,[14] as well as even higher BIS values.[18]

Single-lung ventilation decreases arterial desflurane and sevoflurane concentration due to ventilation-perfusion mismatch.[19] Interestingly, the decline appears independent of the blood-gas partition coefficient. However, no study has evaluated the influence of single-lung ventilation on the elimination of both inhalational anesthetics and propofol.

The most obvious limitation of our study is sampling at the proximal end of the endotracheal tube rather than bronchially. A different approach might have clarified the influence of single-lung ventilation on volatile propofol concentration more reliably. Yet measuring exhaled propofol during bronchoscopy is even less meaningful, since the breathing system is open at that moment, which would result in a considerable dilution of propofol in the exhaled air. Second, which side of the lung was ventilated has not been taken into account. This probably exerts a considerable influence on propofol concentration in exhaled breath, as the inner surface area differs between left and right single-lung ventilation. These shortcomings could be addressed within a further study, where, instead of a double-lumen tube, a bronchial blocker could be used in combination with a normal tube. Third, to date, there is no gold standard for measuring exhaled propofol concentrations and ion mobility spectrometry is only one possible approach. For this reason, the results of this study can only be interpreted using this technique and may differ with other detection methods. And finally, epidural anesthesia might affect cardiac output, which in turn could alter volatile propofol concentration. We did not adjust volatile propofol for this influence. Further studies should treat the patients uniformly, to rule out such an influence of the epidural anesthesia on volatile propofol. However, there was no significant difference in mean arterial pressure between patients with (79 mmHg; 25–75th, 72–89) and without epidural anesthesia (79 mmHg; 25–75th, 70–95; $p = .59$). This influence is therefore possibly negligible.

Our study design makes it clear that any potential reduction in propofol exhalation by single-lung ventilation is offset and overcome, respectively, by the substantial adhesion in the tube.

Measurement of propofol (breath) concentration is of great relevance for estimating pharmacokinetics of propofol, because validation of numerous pharmacokinetic models displays a mean prediction error of approximately 25%. This error cannot be reduced below 20% even by adding further covariates in larger patient collectives.[20] For this reason, measurement of propofol concentration is an important element in estimating the pharmacokinetics of propofol with high interindividual variability. Even though the correlation between volatile and plasma propofol concentration has not yet been validated on larger patient numbers, the results of this study are of great relevance.

Consequently, employing this study design, the effect of single-lung ventilation on exhaled propofol concentration cannot be conclusively determined. In clinical practice, interpreting the propofol concentration in exhaled air during single-lunge ventilation proves to be more difficult than anticipated. Additional potentially influencing factors—besides propofol plasma concentration and minute ventilation—are tube size and internal surface area, side of ventilation, material, and ventilation-perfusion mismatch. Until these questions have been systematically addressed, the use of volatile propofol concentration for estimating plasma concentration remains uncertain.

5 | CONCLUSION

During single-lung ventilation, propofol concentration in exhaled air, in contrast to our expectations, increased by approximately one third. However, this observation might not be affected by change in perfusion-ventilation during single-lung ventilation but rather arises

from reduced propofol absorption on the inner surface area of the double-lumen tube. Thus, it is only possible to utilize exhaled propofol concentration to a limited extent during single-lung ventilation.

AUTHOR CONTRIBUTIONS

Tobias Hüppe: Clinical measurement, manuscript preparation; **Sascha Kreuer**: Conceptualization, statistical analysis, manuscript preparation; **Hinnerk Wulf**: Conceptualization, clinical measurement, manuscript preparation; **Dennik Freitag**: Clinical measurement; **Martin Seidel**: Clinical measurement; **Tobias Teucke**: In-vitro measurements; **Felix Maurer**: Measurement propofol blood concentration, quality management measurement blood concentration; **Andreas Kirschbaum**: Surgery, clinical measurement; **Tilo Koch**: Clinical measurement, quality management; **Frank Langer**: Surgery, clinical measurement; **Thomas Volk**: Conceptualization, manuscript preparation; **Carsten Feldmann**: Clinical measurement.

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