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RESEARCH ARTICLE

Isoflurane promotes early spontaneous breathing in ventilated intensive care patients: A post hoc subgroup analysis of a randomized trial

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Abstract

Background: Spontaneous breathing is desirable in most ventilated patients. We therefore studied the influence of isoflurane versus propofol sedation on early spontaneous breathing in ventilated surgical intensive care patients and evaluated potential mediation by opioids and arterial carbon dioxide during the first 20 h of study sedation.

Methods: We included a single-center subgroup of 66 patients, who participated in a large multi-center trial assessing efficacy and safety of isoflurane sedation, with 33 patients each randomized to isoflurane or propofol sedation. Both sedatives were titrated to a sedation depth of −4 to −1 on the Richmond Agitation Sedation Scale. The primary outcome was the fraction of time during which patients breathed spontaneously.

Results: Baseline characteristics of isoflurane and propofol-sedated patients were well balanced. There were no substantive differences in management or treatment aside from sedation, and isoflurane and propofol provided nearly identical sedation depths. The mean fraction of time spent spontaneously breathing was 82% [95% CI: 69, 90] in patients sedated with isoflurane compared to 35% [95% CI: 22, 51] in those assigned to propofol: median difference: 61% [95% CI: 14, 89], $p < .001$. After adjustments for sufentanil dose and arterial carbon dioxide partial pressure, patients sedated with isoflurane were twice as likely to breathe spontaneously than those sedated with propofol: adjusted risk ratio: 2.2 [95%CI: 1.4, 3.3], $p < .001$.

Conclusions: Isoflurane compared to propofol sedation promotes early spontaneous breathing in deeply sedated ventilated intensive care patients. The benefit appears to be a direct effect isoflurane rather than being mediated by opioids or arterial carbon dioxide.

KEYWORDS
anesthesia, inhaled sedation, intensive care, isoflurane, propofol, spontaneous breathing, spontaneous ventilation

Editorial Comment

Spontaneous breathing during mechanical ventilation is preferred for many patients since spontaneous breathing can mitigate atrophy of diaphragmatic musculature and improves gas exchange. This study compared isoflurane or propofol as sedatives for critically ill study participants needing mechanical ventilation (and moderate/deep sedation). At similar sedation depth, opioid dose, and arterial carbon dioxide pressure, participants sedated with isoflurane spent more than twice as much time breathing spontaneously as those given propofol.

1 | INTRODUCTION

Spontaneous breathing in invasively ventilated patients improves respiratory and cardiocirculatory function, decreases ventilation time, and shortens intensive care unit (ICU) stays.[1–4] Disuse atrophy of the diaphragm begins within 24 h.[5] Early return of spontaneous breathing efforts equivalent to those of healthy subjects may thus help to maintain respiratory muscle function required for successful weaning from the ventilator and extubation.[6]

Inhaled sedation is now used in many countries and included in several guidelines as an alternative to intravenous sedation.[7–9] Compromised renal and hepatic function slows elimination of intravenous sedatives in critically ill patients,[10] and exhaled drug monitoring for propofol remains experimental.[11,12] In contrast, volatile anesthetics are eliminated by exhalation, and the end-tidal anesthetic concentration can easily be continuously monitored. Previous observational research suggests that subanesthetic doses of volatile anesthetics allow spontaneous breathing despite deep sedation in critically ill patients[13–15]—an important reason to consider inhaled instead of intravenous sedatives.

Volatile anesthetics reduce opioid requirements,[14,16–19] and increase arterial carbon dioxide partial pressure because volatile anesthetic administration systems increase dead space ventilation[20–22]—both of which are important determinants of respiratory drive. It is thus of considerable interest to assess the relative contributions of opioid dose and arterial carbon dioxide partial pressure on spontaneous breathing during isoflurane sedation, and the extent to which spontaneous breathing with isoflurane might be mediated by either.

Our center participated in a randomized trial comparing the efficacy and safety of sedation with isoflurane and propofol in intensive care patients.[19] Patients sedated with isoflurane breathed spontaneously more often than propofol-sedated patients (50% vs. 37%) with an odds ratio of 1.7 [95% CI: 1.1, 2.6].[19] However, there was considerable heterogeneity across centers as might be expected since spontaneous breathing depends strongly on efforts to achieving it, which were not protocol defined. Our center uses standardized protocols for ventilation, weaning, and analgesia that are designed to promote early spontaneous breathing. An analysis restricted to our patients would therefore provide an estimate of the optimal potential for isoflurane sedation to promote early spontaneous breathing.

Our goal, therefore, was to determine the effects of isoflurane and propofol sedation on early spontaneous breathing in invasively ventilated patients. We conducted a *post hoc* single-center analysis of patients who were enrolled in an international randomized trial. Specifically, we tested the primary hypothesis that surgical intensive care patients sedated with isoflurane spent a greater fraction of their time spontaneously breathing than patients sedated with propofol over the initial 20 h of study sedation. Secondarily, we evaluated the extent to which opioids and arterial carbon dioxide partial pressure mediate the effect of isoflurane sedation on spontaneous breathing.

2 | METHODS

The underlying trial was approved by our Institutional Review Board (approval date: 18.04.2017, Ethikkommission der Ärztekammer des Saarlandes), and participating patients provided written consent. The current post-hoc analysis was separately approved with waived consent (approval date: 26.01.2021, reference number: 15/21, Ethikkommission der Ärztekammer des Saarlandes).

2.1 | Study design

The underlying "SED001 trial" (EudraCT Number: 2016-004551-67) randomized trial was designed to compare the efficacy and safety of sedation with isoflurane and propofol in invasively ventilated intensive care patients.[19] It was conducted at 21 sites in Germany and 3 in Slovenia and enrolled 301 patients from July 2017 through January 2020.

Patients were randomized 1:1 to either isoflurane or propofol sedation, stratified by study site, in permuted blocks with a centralized electronic randomization system. Treatment allocation was not concealed from clinicians because they needed to evaluate end-tidal isoflurane concentration for safety reasons. The underlying trial's primary endpoint was the fraction of time spent at a target

sedation depth defined by Richmond Agitation and Sedation Scale (RASS) scores between −1 and −4; secondary endpoints were: time to wake-up, opioid requirements, time to extubation, the safety profile of isoflurane (vital parameters, lab values, clinical scores), as well as days free of mechanical ventilation, ICU, delirium, and coma.

Patients were observed under study medication for up to 54 h. If necessary, sedation was continued thereafter according to local standards. Opioids and sedatives were stopped once daily to assess spontaneous awakening and to record wake-up times and to re-assess the need for continuing sedation.

2.2 | Study population

We included all 66 patients who were enrolled in the underlying trial at the Saarland University Medical Center. Patients were admitted to the ICU after elective surgery or on an emergency basis and were expected to require invasive ventilation for at least 24 h. Seventy-four patients consented for the underlying trial at our center. Eight patients were excluded, seven because they did not need further invasive ventilation and one because of hemodynamic instability. The final population therefore contained 66 patients, with 33 each randomized to isoflurane or propofol (Figure 1). Analgesia was provided by intravenous sufentanil. All patients were sedated with propofol prior to inclusion.

2.3 | Inclusion and exclusion criteria

Inclusion criteria for the underlying trial were invasive ventilation and sedation for less than 48 h, expected need for further invasive ventilation and sedation at a RASS target of −1 to −4 for at least 24 additional hours, and sedation with propofol at the time of randomization. We excluded patients predisposed to malignant hyperthermia, and those with acute circulatory failure, hepatic impairment, acute neuropathology, tidal volumes lower than 350 ml, or need for continuous neuromuscular block. No additional criteria were applied for the current analysis.

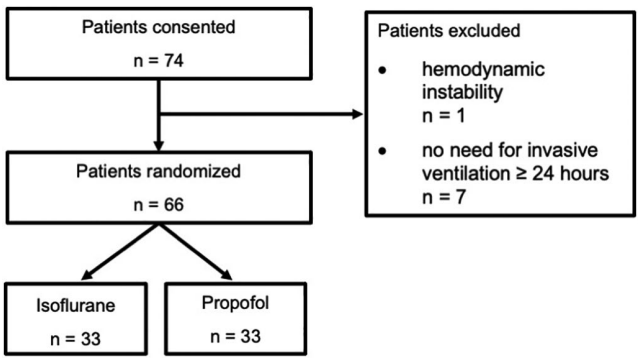

FIGURE 1 Patient flow chart

2.4 | Isoflurane administration

Isoflurane (Isoflurane 100%, Piramal Healthcare) was administered via the Sedaconda Anesthetic Conserving Device (ACD, Sedana Medical AB) as recommended by the manufacturer. Briefly, the ACD was inserted between the endotracheal tube of the patient and the Y-piece of the breathing circuit of a common intensive care ventilator. The ACD was connected to a syringe pump (Perfusor compact, B. Braun) that delivered liquid isoflurane. A gas monitor (Vamos, Dräger Medical Deutschland GmbH) was connected to the ACD to monitor the end-tidal isoflurane concentration. Finally, a charcoal filter (FlurAbsorb, Sedana medical AB) was connected to the expiratory port of the ventilator for gas scavenging.

The original version of the ACD had a dead space of 100 ml (ACD-L) and was used for the first 18 patients. Thereafter, a new version with a dead space of 50 ml (ACD-S) became available and was used in the remaining 15 patients.

After priming the system, the syringe pump was started at an initial rate of 3.0 $ml \cdot h^{-1}$ isoflurane and other sedatives were discontinued. Pump speed was titrated in steps of 0.5–1.0 $ml \cdot h^{-1}$ and sedation depth was assessed at 15-min intervals until stable target sedation was reached (RASS: −4 to −1). Thereafter, sedation depth and end-tidal isoflurane concentration were assessed in 2-h intervals and isoflurane administration was only adjusted as necessary. Isoflurane boluses of 0.3–0.5 ml were allowed up to four times per hour. End-tidal isoflurane concentration was not permitted to exceed 1.5 Vol%.

2.5 | Propofol administration

Propofol 20 $mg \cdot ml^{-1}$ (Propofol Hexal, Hexal AG/Sandoz) was infused by a syringe pump (Perfusor Space, B. Braun). Propofol was initially continued at the existing dose and other sedatives were discontinued. Propofol administration was titrated in steps of 0.5–0.8 $mg \cdot kg^{-1} \cdot h^{-1}$ and sedation depth was assessed at 15-min intervals until stable target sedation was reached (RASS: −4 to −1). Thereafter, sedation depth was assessed in 2-h intervals and the propofol administration adapted as necessary. Propofol boluses of 0.3–0.5 $mg \cdot kg^{-1}$ were allowed up to four times per hour. The maximum allowed dose was 4.0 $mg \cdot kg^{-1} \cdot h^{-1}$.

2.6 | Mechanical ventilation

Patients were ventilated with Evita 4 ventilators (Dräger Medical Deutschland GmbH) in pressure-controlled mode (biphasic positive airway pressure). Inspiratory pressure was adjusted to keep tidal volumes between 6 and 8 $ml \cdot kg^{-1}$ ideal body weight. Patients were under continuous surveillance by intensive care nurses. When spontaneous breathing activity was observed, pressure-controlled ventilation was changed to pressure-support mode. Ventilation mode and parameters were automatically captured by our clinical data management system.

2.7 | Transition to spontaneous breathing

There was no specific protocol that regulated the transition from controlled to spontaneous ventilation. However, the routine at our center is to start spontaneous breathing trials as early as clinically feasible and repeat them every 4–6 h. Specifically, we decreased minute ventilation until end-tidal carbon dioxide partial pressure reached 50–60 mm Hg and gradually reduced opioid administration—all the while checking for spontaneous breathing. If there was still no spontaneous breathing, the sedative was additionally reduced. Each trial ended when patients breathed spontaneously, became agitated, became hemodynamically unstable, or started bucking against the ventilator.

2.8 | Measurements

Data were obtained until the first spontaneous awakening trial which was performed after approximately 20 h of study sedation. All data were digitally extracted from the patient data management system (Copra, Version 5, Copra System). The Simplified Acute Physiology Score II (SAPS II) was calculated according to Le Gall et al.[23] Possible scores range from 0 to 163 points, with higher scores predicting greater mortality; for example, 52 points is associated with 50% mortality. The P/F-ratio was defined as the arterial oxygen partial pressure divided by the inspiratory oxygen fraction. Sufentanil dose and arterial carbon dioxide partial pressure were recorded at 4-h intervals. Spontaneous breathing phases were documented to the nearest 5 min.

2.9 | Primary outcome

The primary outcome was the fraction of time spent spontaneously breathing with pressure support but without mandatory mechanical breaths. We additionally calculated the risk ratio for spontaneous breathing comparing isoflurane and propofol sedation across assessments at 4-h intervals adjusted for sufentanil dose and arterial carbon dioxide partial pressure.

2.10 | Statistical analysis

Data were collected with Excel 2019 (Microsoft). Statistical analyses were carried out with R (*v4.0.2*, R Core Team, 2020) using the packages *readxl* (*v1.3.1*, Wickham & Bryan, 2019), *dplyr* (*v1.0.5*, Wickham, François, Henry & Müller, 2021), *tableone* (*v0.12.0*, Yoshida & Bartel, 2020), *rcompanion* (*v2.4.1*, Mangiafico, 2016), *geepack* (*v1.3-2*; Højsgaard, Halekoh, & Yan, 2006), *parameters* (*v0.14.0*; Lüdecke, Ben-Shachar, Patil & Makowski, 2020), and *ggplot2* (*v3.3.3*; Wickham, 2016).

Normality was assessed by visual assessment of histograms and quantile-quantile plots. Continuous baseline measures are presented as means ± standard deviations (SD) or medians (interquartile ranges [IQR]). Categorical variables are presented as frequencies (percentage). Baseline balance is presented as absolute standardized differences, defined as the absolute difference in means divided by the pooled standard deviation.

Continuous outcome measures are presented as means or medians with the corresponding bias corrected and accelerated 95% confidence intervals (95% CI) were estimated by bootstrapping with 10,000 iterations to account for non-normally distributed data. Intergroup comparisons were performed by independent sample t-tests, Wilcoxon rank-sum tests, or chi-squared tests as appropriate for the type and distribution of data. Repeated-measures data were summarized with a mean for each patient. A two-sided $p < .05$ was considered statistically significant.

The fraction of time spent spontaneously breathing, our primary outcome, was not normally distributed. Because the distribution was bimodal for propofol, medians poorly characterized the data and resulted in an implausibly large difference between the two sedatives. We therefore report the fraction of time spent spontaneously breathing primarily as means (95%CI) and graphically as medians (IQR). The fractions of spontaneous breathing time with each sedative were compared with a Wilcoxon rank-sum test.

The risk ratio for spontaneous breathing at 4-h intervals in isoflurane versus propofol-sedated patients was calculated by Poisson generalized estimating equation regression to account for repeated measurements. A univariable model was used to estimate the crude risk ratio. A multivariable model was used to estimate the direct effects of the sedative on spontaneous breathing activity, adjusted for potential mediation by sufentanil dose and arterial carbon dioxide partial pressure.

We used univariable linear generalized estimating equation regression models to determine whether the relative effects of isoflurane and propofol on spontaneous breathing were mediated by sufentanil dose or arterial carbon dioxide partial pressure. Univariable Poisson generalized estimating equation regression models were used to estimate the risk ratio for spontaneous breathing when sufentanil dose or arterial carbon dioxide partial pressure increase by a single unit. To claim the mediation the sedative must influence sufentanil dose or arterial carbon dioxide partial pressure, which in turn must influence spontaneous breathing.

2.11 | Power considerations

Based on previous data we estimated that patients sedated with propofol would breathe spontaneously 20% of the time.[14] A power analysis revealed that we would be able to detect a difference when the spontaneous breathing time fraction equals 53% or more in patients sedated with isoflurane, based on the given total sample size of 66 patients randomized 1:1 to either propofol or isoflurane sedation with an alpha of .05 and a power of 80%. This analysis was performed with the web-based version of the Power and Sample Size Calculation program by Dupont and Plummer.[24]

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics were similar in patients sedated with isoflurane and propofol. The average simplified acute physiology score II was slightly lower in isoflurane sedated patients: isoflurane: 34 ± 14 [range: 13–76], propofol: 42 ± 20 [range: 13–82], absolute standardized difference: 0.42. Approximately half of the patients in each sedation group were ventilated for pulmonary reasons; however, none suffered from severe acute respiratory distress syndrome (ARDS) or had P/F-ratios below 100 mm Hg. Ventilation time prior to study inclusion did not differ between the groups (Table 1).

3.2 | Clinical treatment measures

Physiological characteristics did not differ significantly except for mean core temperature which was slightly higher in patients sedated with isoflurane than propofol: 37.4°C [95% CI: 37.1, 37.6] versus 37.0°C [95% CI: 36.7, 37.2], $p = .023$. Sufentanil dose, arterial carbon dioxide partial pressure, sedation depth, and ventilator settings were similar in each sedation group. During spontaneous breathing, tidal volumes and respiratory rates were slightly higher but inspiratory pressure was lower than during controlled mechanical ventilation. Observation times until the first spontaneous awakening trial averaged 20 h in each sedation group (Table 2). Most patients needed further sedation and ventilation, only 6 patients in each sedation group were extubated during the first spontaneous awakening trial.

3.3 | Primary outcome — spontaneous breathing

Patients sedated with isoflurane spent a substantially higher mean fraction of time spontaneously breathing than those randomized to propofol: 82% [95% CI: 69, 90] versus 35% [95% CI: 22, 52], median difference: 61% [95% CI: 14, 89], $p < .001$ (Table 2, Figure 2). The crude risk for spontaneous breathing was 2.4-times higher with isoflurane compared to propofol sedation: risk ratio: 2.4 [95% CI: 1.5, 3.7], $p < .001$. After adjustments for sufentanil dose and arterial carbon dioxide partial pressure, patients sedated with isoflurane still breathed spontaneously about twice as much as patients sedated with propofol: adjusted risk ratio: 2.2 [95% CI: 1.4, 3.3], $p < .001$ (Figure 3).

3.4 | Spontaneous breathing – opioid dose and arterial carbon dioxide

The sedation method had no significant effect on sufentanil dose or arterial carbon dioxide partial pressure, excluding strong mediation of the effect of the sedative on spontaneous breathing (relative effect of isoflurane versus propofol sedation on sufentanil dose: regression coefficient: −0.6 [95% CI: −1.3, 1.5], $p = .123$; relative effect of isoflurane versus propofol sedation on arterial carbon dioxide: regression coefficient: 1.6 [95% CI: −1.4, 4.7], $p = 0.292$).

While an increase in sufentanil dose by 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ reduced the risk for spontaneous breathing by 13%, arterial carbon dioxide partial pressure did not significantly affect spontaneous breathing (relative risk for spontaneous breathing associated with an increase in sufentanil dose by 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$, risk ratio: 0.87 [95% CI: 0.76, 0.99], $p = .034$; relative risk for spontaneous breathing associated

TABLE 1 Baseline characteristics

Parameter	Isoflurane	Propofol	Absolute standardized difference
n	33	33	—
Sex [male]	21 (64)	22 (67)	0.064
Age [years]	64 ± 12	65 ± 14	0.049
Weight [kg]	83 ± 21	89 ± 26	0.253
Height [cm]	173 ± 9	173 ± 8	0.004
SAPS II	34 ± 14	42 ± 20	0.418
Emergency admissions [*n*]	17 (52)	18 (55)	0.061
Pulmonary reason for ventilation [*n*]	16 (49)	19 (58)	0.183
Ventilation time before study inclusion [h]	21 (1–37)	20 (2–31)	0.010
P/F-ratio [mm Hg]	269 ± 94	263 ± 89	0.066
Sedation depth [RASS]	−4 (−4 – (−3))	−4 (−5 – (−4))	0.277
Spontaneously breathing patients [*n*]	14 (42)	10 (30)	0.254

Note: Data are reported as means ± standard deviations, medians (interquartile ranges), or number (percentage). The absolute standardized difference is presented as a measure of baseline balance.

Abbreviations: P/F-ratio, ratio of arterial oxygen partial pressure and inspiratory oxygen fraction; RASS, Richmond Agitation Sedation Scale; SAPS II, Simplified Acute Physiology Score II.

TABLE 2 Clinical treatment measures

Parameter	Isoflurane	Propofol	*p*
n	33	33	—
Core temperature [°C] *	37.4 [37.1, 37.6]	37.0 [36.7, 37.2]	**.023**
Heart rate [bpm]*	85 [79, 91]	84 [80, 89]	.968
Mean arterial blood pressure [mmHg]*	74 [72, 77]	76 [74, 79]	.384
SpO_2 [%]*	98 [97, 98]	98 [98, 99]	.271
pH*	7.37 [7.35, 7.39]	7.38 [7.37, 7.39]	.514
P_aCO_2 [mm Hg]*	46 [44, 48]	44 [42, 46]	.304
Sedation and analgesia			
Observed sedation time [h]	20 [18, 21]	20 [19, 21]	.796
End-tidal isoflurane concentration [Vol%]	0.4 [0.3, 0.5]	—	—
Propofol dose [$mg \cdot kg^{-1} \cdot h^{-1}$]	—	1.9 [1.5, 2.3]	—
Sufentanil dose [$\mu g \cdot kg^{-1} \cdot h^{-1}$]	0.20 [0.16, 0.24]	0.23 [0.18, 0.28]	.235
Sedation depth [RASS]	−4.0 [−4.0, (−3.8)]	−4.0 [−4.0, (−3.4)]	.514
Spontaneous breathing and ventilation			
Primary outcome:			
Spontaneous breathing time [%]*	82 [69, 90]	35 [22, 52]	**<.001**
Median difference [%]	61 [14, 89]		
Spontaneous breathing at any time [*n*]	31 (94)	19 (58)	**.002**
Inspiratory pressure support [cmH_2O]	9 [7, 9]	11 [6, 11]	.312
PEEP [cmH_2O]	10 [8, 10]	8 [8, 11]	.990
Tidal volume [ml]	623 [543, 689]	589 [496, 621]	.605
Respiratory rate [bpm]	14 [10, 18]	13 [11, 13]	.577
Mechanical ventilation at any time [*n*]	21 (64)	27 (82)	.167
Inspiratory pressure [cmH_2O]	20 [15, 21]	22 [19, 25]	.123
PEEP [cmH_2O]	7 [5, 8]	8 [7, 12]	**.049**
Tidal volume [ml]	517 [474, 560]	567 [530, 591]	.265
Respiratory rate [bpm]	12 [12, 15]	14 [13, 18]	.071

Note: Summary statistic of repeated measures of the first 20 h of study sedation. Repeated measures were summarized with a mean for each patient.

Data are reported as means (*) or medians [95% confidence intervals], or number (percentage).

P-values < .05 are written in bold letters to highlight statistically significant differences.

Abbreviations: P_aCO_2, arterial carbon dioxide partial pressure; PEEP, positive end-expiratory pressure; RASS, Richmond Agitation Sedation Scale; SpO_2, oxygen saturation by pulse oximetry.

with an increase in arterial carbon dioxide partial pressure by 1 mm Hg, risk ratio: 1.01 [95% CI: 1.00, 1.02], $p = .095$; Figure 4, Figure S1).

4 | DISCUSSION

Ventilated patients sedated with isoflurane breathed spontaneously more than twice as much as those sedated with propofol, even after adjusting for opioid dose and arterial carbon dioxide partial pressure. Our findings are generally consistent with the underlying trial that included 301 patients.[19] However, we observed a substantially greater effect of isoflurane sedation on spontaneous breathing, probably because our center makes substantial efforts to promote spontaneous breathing. Our current results thus represent the optimal effect of isoflurane sedation on spontaneous breathing.

Our results are consistent with previous observational studies in intensive care settings. For example, isoflurane sedation was associated with more spontaneous breathing than propofol or midazolam in a retrospective study of 38 patients who had continuous lateral rotational therapy.[14] Similarly, 62 patients with moderate to severe acute respiratory distress syndrome who were deeply sedated with sevoflurane breathed spontaneously during 91% of their prone position time.[15] In contrast to previous studies, we analyzed a subgroup

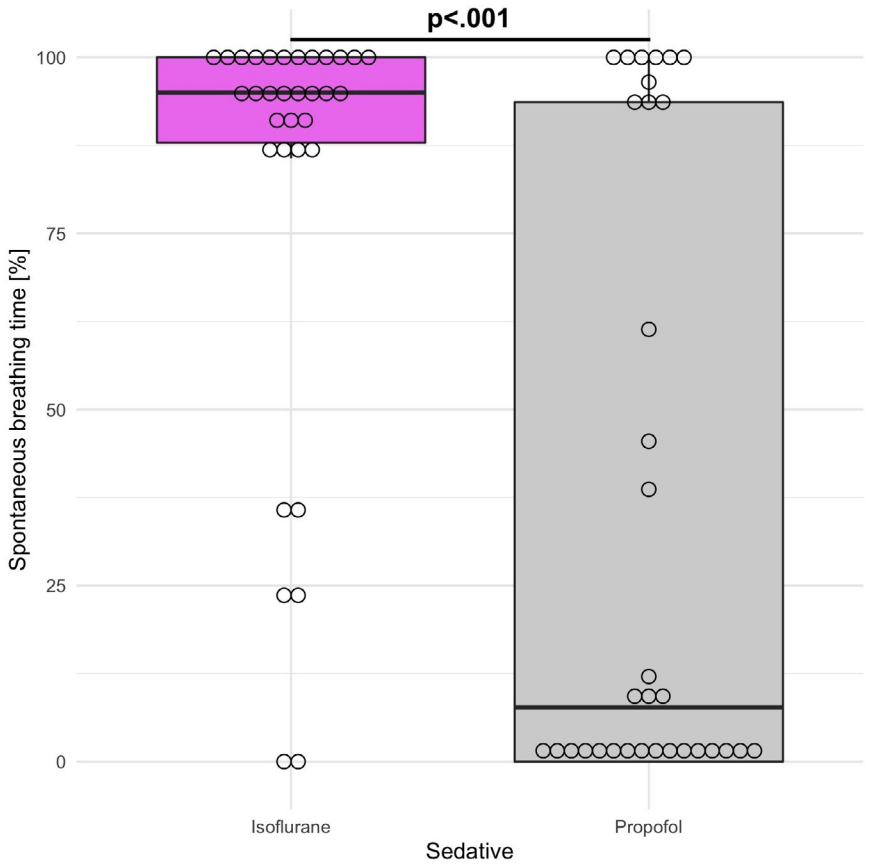

FIGURE 2 Fraction of time spent spontaneously breathing. The fraction of time spent spontaneously breathing was calculated for each patient, expressed in percent of the total observation time, and compared between sedation groups by a Wilcoxon rank-sum test. Dots present the distribution of raw data for the fraction of time spent spontaneously breathing

of a randomized controlled trial, thus avoiding selection bias and minimizing confounding. Our results add to increasing evidence that spontaneous breathing is better preserved with inhaled than intravenous sedation.

Inhaled sedation reduces opioid consumption.[14,16–19] Inhaled sedation systems also increase dead space ventilation and consequently arterial carbon dioxide partial pressure.[20–22] We therefore expected both opioids and carbon dioxide partial pressure to at least partially mediate isoflurane's effect on spontaneous breathing. However, both effects were trivial, suggesting that sufentanil dose and arterial carbon dioxide are more likely to be covariates of spontaneous breathing rather than mediators of isoflurane's effect on spontaneous breathing. Isoflurane compared to propofol sedation therefore appears to directly improve respiratory drive, rather than the benefit being mediated by opioids or arterial carbon dioxide.

In the central nervous system, activity of (Phox2b-expressing) chemosensitive neurons of the retrotrapezoid nucleus is crucial for maintaining spontaneous breathing under general anesthesia.[25] Whereas isoflurane increases the excitability of Phox2b neurons, propofol does not.[26,27] Isoflurane therefore consistently causes less respiratory depression than equipotent doses of propofol,[28–30] and subanesthetic doses of isoflurane such as 0.5 minimum alveolar concentration (MAC) even increase respiratory frequency and tidal volume in animals.[29] In fact, the end-tidal isoflurane concentrations in our patients were about 0.5 MAC. Our results are therefore consistent with the preclinical finding that subanesthetic doses of isoflurane promote spontaneous breathing.

Of note, both anesthetics were titrated to a comparably deep sedation level. Many of the included patients were severely ill, as evident from high SAPS II scores. Several were admitted to the ICU on an emergency basis, had sepsis and/or moderate ARDS, and were included within 24 h after intubation—consistent with the clinical need for a relatively deep sedation. Our results therefore should be interpreted in the context of moderate-to-deep sedation. It remains unclear whether the observed difference in spontaneous breathing during isoflurane and propofol sedation would be maintained at lighter sedation depths.

The results of the underlying trial showed that sedation with isoflurane is effective and well tolerated in invasively ventilated ICU patients.[19] Based on these results, isoflurane has now been approved for this indication by most European countries. Secondary results of the study were reduced opioid dose, more frequent spontaneous breathing on day 1 and faster wake-up times on day 2 after prolonged sedation with isoflurane compared to propofol. Other outcome parameters did not significantly differ, such as extubation times (isoflurane vs. propofol, median [IQR]: 30 [10–136] vs. 40 [18–125] min), ventilator-, coma-, delirium-, and ICU-free days (17 vs. 13 days), as well as mortality (23% vs. 20%).

Volatile anesthetics are much criticized for their global warming potential.[31] However, the Sedaconda ACD consumes even less volatile anesthetic than a conventional circle-system under low fresh gas flow.[32] Furthermore, about 80% of the environmental impact of volatile anesthetics is caused by desflurane, with a 5 times higher global warming potential than isoflurane.[33] And finally, the development

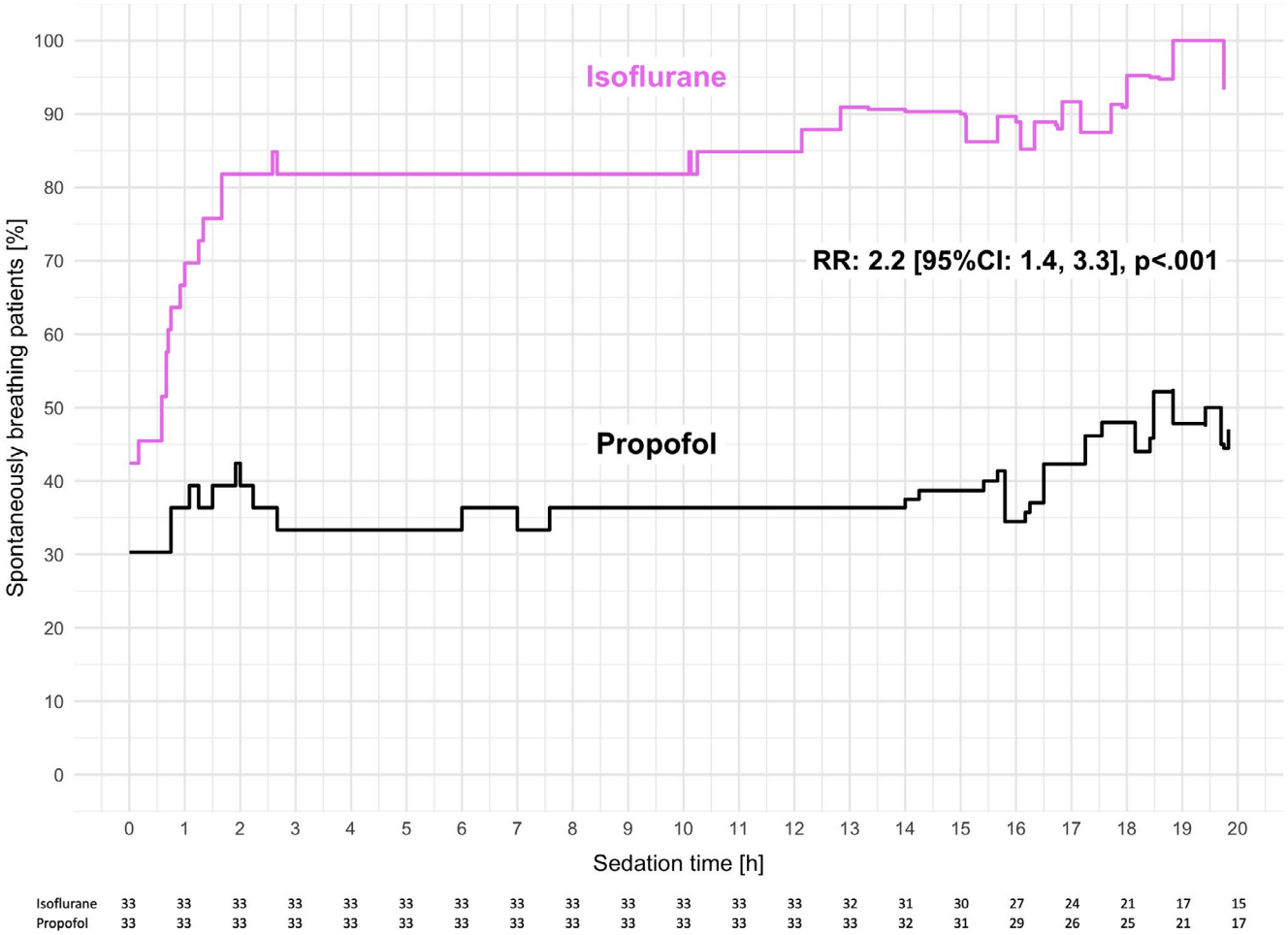

FIGURE 3 Percentage of spontaneously breathing patients over time. Numbers at the bottom of the figure represent the total patients included at the respective time point of the x-axis. The given risk ratio (RR) describes the effect of isoflurane versus propofol sedation on spontaneous breathing and is adjusted for sufentanil dose and arterial carbon dioxide partial pressure. 95%CI, 95% confidence interval

of even more efficient application systems as well as systems for elimination or recycling of volatile anesthetics may soon diminish ecological concerns.[34]

Controlled mechanical ventilation with complete diaphragmatic inactivity for as little as 18–69 h results in marked atrophy of the diaphragm,[5] which impacts clinical outcomes.[6] In contrast, spontaneous breathing reduces dorso-caudal atelectasis and improves cardiac output.[35–37] Consequently, spontaneous breathing improves respiratory physiology, renal perfusion,[38] and hepatic blood flow.[39] Spontaneous breathing is thus favorable in invasively ventilated patients[40,41]—and our results indicate that early return of spontaneous breathing is more than twice as common with isoflurane than propofol sedation.

A limitation of our analysis is that the transition process to spontaneous breathing was not strictly controlled. However, sedation depth, opioid dose, and arterial carbon dioxide pressure were similar with each sedative which suggests that there were comparable efforts for achieving spontaneous breathing with each drug. An additional limitation is that investigators were not blinded to treatment in the underlying trial, as many procedures reveal the use of isoflurane (e.g., suctioning or replacing certain parts of the ACD, monitoring, or scavenging setup). Furthermore, continuous isoflurane monitoring was necessary to safely titrate the drug and avoid sedation progressing to general anesthesia. Patients sedated with propofol had slightly higher SAPS II scores, but the difference seems unlikely to explain our results. And finally, while we clearly show improved spontaneous breathing with inhaled isoflurane, our population was far too small to evaluate clinically meaningful outcomes.

5 | CONCLUSION

Isoflurane sedation promotes early spontaneous breathing better than propofol in invasively ventilated surgical ICU patients under moderate-to-deep sedation. The benefit appears to be a direct drug effect rather than being mediated by opioid dose or arterial carbon dioxide partial pressure. Isoflurane sedation is thus a reasonable approach when early return of spontaneous breathing is desired in ventilated patients.

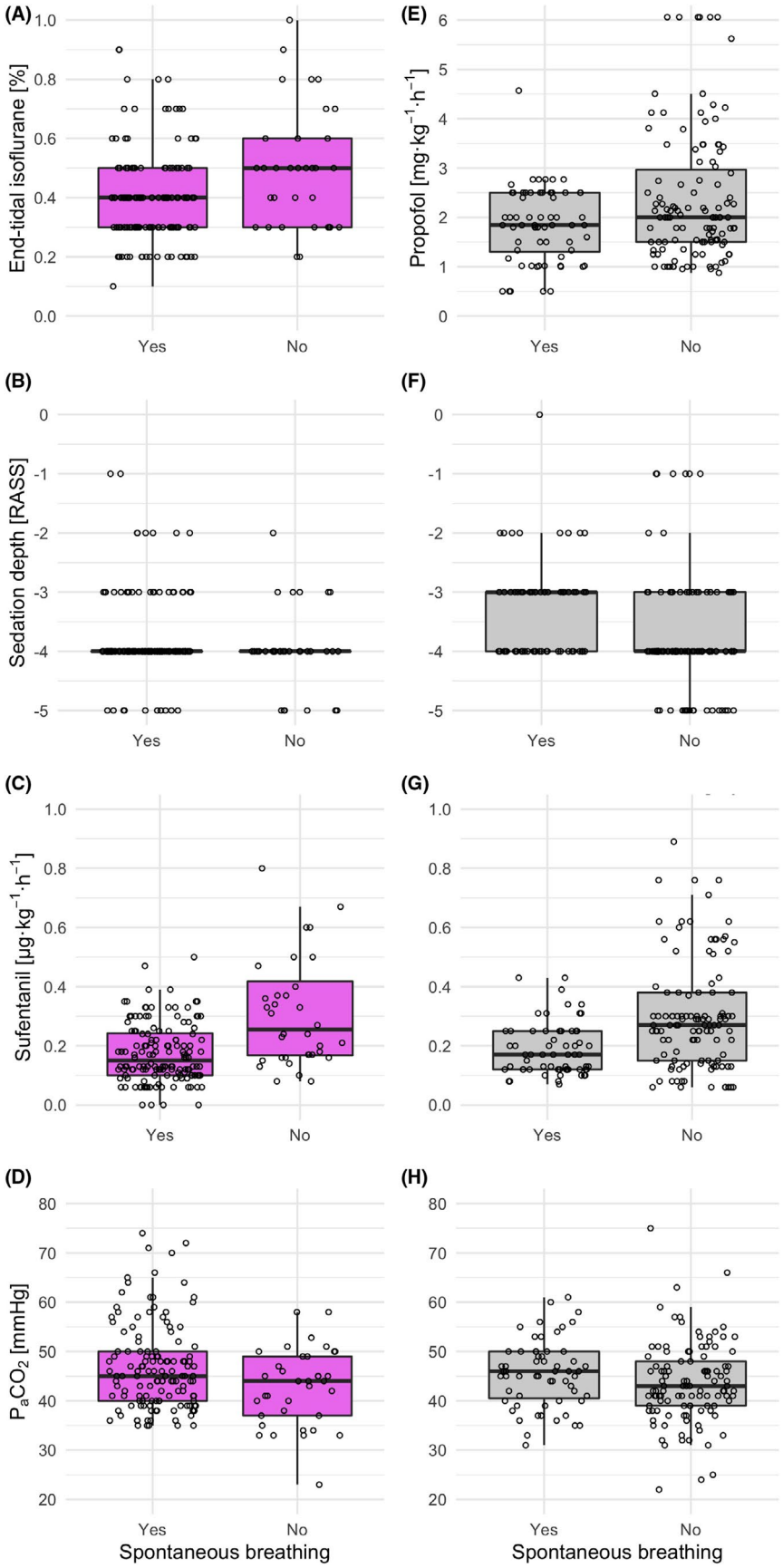

FIGURE 4 Influences on spontaneous breathing. (A–D, violet) Isoflurane-sedated patients; (E–H, gray) Propofol-sedated patients. Data are presented as medians and interquartile ranges. Dots present raw data. RASS, Richmond Agitation Sedation Scale; P_aCO_2, arterial carbon dioxide partial pressure

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Lukas M. Müller-Wirtz: This author helped with conception and design, performed data analysis, interpreted results, and wrote the first draft of the manuscript. **Florian Behne**: This author performed data collection and helped with data analysis. **Azzeddine Kermad**: This author helped with interpretation and discussion of the results. **Gudrun Wagenpfeil**: This author helped with data analysis. **Matthias Schröder**: This author helped with interpretation and discussion of the results. **Daniel I. Sessler**: This author helped with interpretation of the results and manuscript preparation. **Thomas Volk**: This author helped with interpretation and discussion of the results. **Andreas Meiser**: This author was the driving force in conception and design, helped with data analysis, interpreted results, and helped to write the first draft of the manuscript. All authors critically revised and approved the manuscript for submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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