Negative Drift of Sedation Depth In Critically Ill Patients Receiving Constant Minimum Alveolar Concentration of Isoflurane, Sevoflurane, or Desflurane: A Randomized Controlled Trial

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Research

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Abstract

Background: Intensive care unit (ICU) physicians have extended the minimum alveolar concentration (MAC) to deliver and monitor long-term volatile sedation in critically ill patients. There is limited evidence of MAC's reliability in controlling sedation depth in this setting. We hypothesized that sedation depth, measured by the electroencephalography (EEG)-derived Narcotrend-Index (burst-suppression N_Index 0 – awake N_Index 100), might drift downward over time despite constant MAC values.

Methods: This prospective single-centre randomized clinical study was conducted at a University Hospital Surgical Intensive Care Unit and included consecutive, postoperative ICU patients fulfilling the inclusion criteria. Patients were randomly assigned to receive uninterrupted inhalational sedation with isoflurane, sevoflurane, or desflurane. The end-expiratory concentration of the anaesthetics and the EEG-derived index were measured continuously in time-stamped pairs. Sedation depth was also monitored using Richmond-Agitation-Sedation-Scale (RASS). The paired t-test and linear models (bootstrapped or multilevel) have been employed to analyze MAC, N_Index and RASS across the three groups.

Results: Thirty patients were recruited (female/male: 10/20, age 64±11, Simplified Acute Physiology Score II 30±10). In the first 24 hours, 21.208 pairs of data points (N_Index and MAC) were recorded. The median MAC of 0.58±0.06 remained stable over the sedation time in all three groups. The t-test indicated in the isoflurane and sevoflurane groups a significant drop in RASS and EEG-derived N_Index in the first versus last two sedation hours. We applied a multilevel linear model on the entire longitudinal data, nested per patient, which produced the formula N_Index=43–0.7·hours (R^2=0.76), showing a strong negative correlation between sedation's duration and the N_Index. Bootstrapped linear models applied for each sedation group produced: N_Index of 43–0.9, 45–0.8, and 43–0.4·hours for isoflurane, sevoflurane, and desflurane, respectively. The regression coefficient for desflurane was almost half of those for isoflurane and sevoflurane, indicating a less pronounced time-effect in this group.

Conclusions: Maintaining constant MAC does not guarantee stable sedation depth. Thus, the patients necessitate frequent clinical assessments or, when unfeasible, continuous EEG monitoring. The differences across different volatile anaesthetics regarding their time-dependent negative drift requires further exploration.

Trial registration: NCT03860129.

Background

In the past decades, the use of inhalational anaesthetics, such as isoflurane, sevoflurane, or desflurane, has been extended from the operating room to long-term sedation of critically ill patients. It has been documented that volatile sedation offers cardio-protection, minimal metabolism, and shorter emergence times than classic intravenous sedation (1).

Another advantage is seamless monitoring at the bedside: the end-expiratory minimal alveolar concentration (MAC) reflects, at steady-state, the gas concentration in the brain (2). The MAC at which half of the patients do not respond to verbal commands is known as MAC_{awake}. For isoflurane, sevoflurane, or desflurane, the reported MAC_{awake} values are 0.38, 0.34, and 0.34, respectively (2, 3).

Although the recent analgosedation guidelines advocate for minimal sedation and sufficient analgesia to mitigate long-term deep sedation's detrimental effects, the indications for more profound sedation still vary across clinics (4). The task of optimizing sedation depth to simultaneously avoid the complications of excessive sedation and prevent traumatic awareness is a challenging one, especially given the heterogeneity of ICU patients.

Regarding the ICU, most authors chose to deliver variable MAC values around 0.5, above the MAC_{awake} threshold (5–8). Nonetheless, we found no study related to our primary hypothesis: despite stable age-adjusted MAC, the sedation depth deepens over time. Secondary, we investigate this downdrift trend across the three subgroups (receiving isoflurane, sevoflurane, and desflurane).

Methods

Ethics statement

The Institutional Review Board of the Ruhr University Bochum (No. 4780-13, Chair Prof. M. Zenz), approved the study, registered at ClinicalTrials.gov (NCT03860129, on Sep 24 2018). This study was conducted in complete compliance with the Declaration of Helsinki (2013), and all patients provided written informed consent before study participation.

Inclusion and exclusion criteria

Inclusion criteria: adult patients below 80 years of age, non-pregnant, with an American Society of Anaesthesiologists classification I–III, without a language barrier, scheduled for major abdominal, vascular, or orthopaedic interventions, requiring postoperative invasive ventilation due to surgical indications or cardiopulmonary impairment. The exclusion criteria were contraindications to volatile anaesthetics such as brain injuries, increased intracranial pressure, neuromuscular diseases, and malignant hyperthermia.

Randomization

After ICU admission, the primary investigator randomized patients using the closed-envelope method, ten envelopes for each volatile anaesthetic: isoflurane, sevoflurane (both AbbVie, Ludwigshafen, Germany), or desflurane (Baxter, Unterschleissheim, Germany).

Sedation delivery, clinical and EEG-based depth assessment

MIRUS™ (TIM, Koblenz, Germany) delivered inhalational sedation by employing an inhalational anaesthetic reflector, which features a controller to maintain the age-adjusted MAC pre-set target, regardless of changes in flow and minute-ventilation (9, 10). The device continuously recorded the concentration of isoflurane, sevoflurane, or desflurane. Age-adjusted MAC was kept constant around 0.55.

Richmond-Agitation-Sedation-Scale (RASS) was documented by nurses every 2–4 hours; a physician assessed the first and last RASS values. The analgesia was frequently titrated to achieve a Behavioural Pain Scale (BPS) < 3 in all patients.

The EEG monitor, Narcotrend-Compact M ICU Version 3.2 (Hannover, Germany), logged the sedation depth every minute with a dimensionless number (N_Index) between 0 (flat line) and 100 (full electrical activity, awake) (11, 12).

Sample size estimation and statistical analysis

We used G*Power (Heinrich-Heine-University, Dusseldorf, Germany; version 3.1.9.4) to compute the power sample of a paired *t*-test with α 0.05 and effect size 0.6 on two dependent means: N_Index of the same patients, the mean value in the first and last 2 hours of sedation. For a sample size of 30 patients, the test had a power of 0.89. We used the open-source R programming language 3.6.1 for data pre-processing, visualizations, and statistical analyses.

The Kolmogorov–Smirnov test was applied to test the normality of distribution of all continuous variables. Continuous variables with normal distribution are presented as mean ± standard deviation; non-normal variables are reported as median ± interquartile range.

For the analysis of the MAC, RASS and N_Index values in the first versus last two sedation hours, the one-tailed paired (per patient) *t*-test was applied. The Kruskal–Wallis and Dunn's tests were used to compare two or three groups of variables that were not normally distributed. The frequencies of categorical variables (like gender) were compared using Pearson $\chi 2$. A value of $p < 0.05$ was considered significant.

Since the sedation duration is not always foreseeable, the number of measurements varies across patients and groups. Therefore, we employed two approaches to address this heterogeneity and analyze all longitudinal data: equal bootstrapping per patient and multilevel regressions.

Bootstrapping refers to random sampling with replacement and allows accuracy measures, such as variance, bias, and confidence intervals. This method serves us to assign each patient the same importance in the model (13).

The multilevel models split the observed effects into fixed (e.g., MAC and time under sedation) and random (group/patient) types. In the case of non-normal distribution, the convergence was obtained using the penalized quasi-likelihood (14). Compared to ANOVA, multilevel models do not require the homogeneity of regression slopes. The Shatterwaite degrees of freedom approximation were used to extract the p-values from the hierarchical models.

Results

Number of measurements

After processing the MIRUS™ and Narcotrend logs and excluding incomplete measurements, a total of 21.208 time-stamped pair observations (N_Index and MAC) were obtained. The number of observations per patient was 1019 ± 430, 852 ± 797, and 1158 ± 436 for the isoflurane, sevoflurane, and desflurane groups. The duration of sedation per group in rounded hours was comparable across groups: 18 [16 to 21]; 17 [10 to 37], and 18 [15 to 22] for isoflurane, sevoflurane, and desflurane, respectively (p = 0.71).

Demographics and secondary variables

Seventy-eight patients underwent major surgeries with an expected longer ICU stay and met the inclusion criteria of eligibility. Of these, 30 patients required postoperative mechanical ventilation. The included patients required postoperative invasive ventilation because they met at least one of the following criteria: surgical indication for strict immobility (after extensive aortic or spinal surgery), increased opioid requirements (> 0.15 µg/kg/h sufentanil), reduced oxygenation (PaO_2/FiO_2 < 200), or haemodynamic instability. Table 1 and Fig. 1 present the patient's demographics, common diseases, surgeries, clinical scores, and laboratory values. The variables do not vary significantly across groups and show no linear correlation with the N_Index. Norepinephrine was the only administered vasopressor: 0.139 ± 0.004 µg/kg/min, N = 10 in the isoflurane subgroup; 0.095 ± 0.003, N = 7 in sevoflurane; 0.164 ± 0.004, N = 8 in the desflurane group; p = 0.32.

Table 1
Patients demographics along with frequent diseases and surgeries

	isoflurane	sevoflurane	desflurane	p-value
Gender [male : female]	8 : 2	7 : 3	5 : 5	0.5
Age [years]	65 ± 10	68 ± 10	60 ± 13	0.23
Weight [kg]	85 ± 10	83 ± 21	69 ± 16	0.06
SAPS	29 ± 10	34 ± 10	26 ± 10	0.23
Arterial hypertension [N]	4	7	7	0.45
Smoking [N]	4	4	2	0.69
Renal insufficiency [N]	1	1	0	1
Coronary disease [N]	2	3	0	0.32
Surgical interventions [N]	5	4	2	0.32
Esophagectomy	0	1	0	1
Necrotizing fasciitis	1	1	3	0.57
Aortic surgery	2	0	3	0.32
Pancreatic surgery	1	2	1	1
Peritoneal debulking	1	2	1	1
Spondylodesis				

[N] represents the number of patients undergoing a type of surgery or having a preexisting condition. SAPS is the abbreviation for Simplified Acute Physiology Score II.

Analgosedation

In the operating room, the patients received epidural analgesia if they had no contraindications. In the isoflurane, sevoflurane, and desflurane groups, the number of patients with epidural ropivacaine was 3, 2, and 3, respectively. General anaesthesia was induced with 0.2 µg/kg sufentanil and 2 mg/kg propofol. For anaesthesia maintenance, patients received sevoflurane MAC 1.12 ± 0.18 and sufentanil 0.17 ± 0.10 µg/kg ideal body weight/hour, without significant differences across groups. Postoperatively, the patients were switched to intravenous sedation with propofol for at least 1 hour to allow all accumulated sevoflurane to be exhaled.

In the ICU, we aimed for a BPS ≤ 3 using epidural analgesia (ropivacaine 0.2% + sufentanil 0.75 µg/mL 4 ± 2 mL/hour), anti-inflammatory agents, and intravenous sufentanil µg/kg ideal body weight/hour: 0.25 ± 0.09, 0.26 ± 0.29, and 0.21 ± 0.14 in the isoflurane, sevoflurane, and desflurane groups, respectively (p =

0.83). The analgosedation was supplemented before possible stress-inducing examinations, medical interventions, or nursing care.

The measured end-expiratory MAC did not vary significantly: 0.58 ± 0.03, 0.56 ± 0.07, and 0.58 ± 0.06 for isoflurane, sevoflurane, and desflurane, respectively ($p = 0.32$). The electronically logged N_Index was: 33 [28 to 44], [30 to 45], and 37 [31 to 42] for isoflurane, sevoflurane, and desflurane, respectively ($p = 0.67$).

The N_Index are grouped into the following stages: A = awake (95 to 100 N_Index), B = sedated (80 to 94), C = light anaesthesia (65 to 79), D = general anaesthesia (37 to 64), E_0 to E_1 = general anaesthesia with deep hypnosis (20 to 36), and E_2 to F_1 = general anaesthesia with increasing burst-suppression (0 to 19). In our bootstrap analysis, each patient is equally represented; the corresponding plots are in Fig. 2.

No patient was in stage A or B, and none of the participants needed rescue intravenous sedation. The ratio of moderate versus deep sedation depth was 40%/60%, 52%/48%, and 67%/33% in the isoflurane, sevoflurane, and desflurane groups, and the $\chi 2$ test comparing isoflurane and sevoflurane showed no statistically significant differences ($p = 0.08$). The $\chi 2$ of the sevoflurane - desflurane and isoflurane - desflurane comparisons show *p*-values of 0.03 and 0.0001. Despite comparable MAC values across groups, the deep stages D and F were less frequent in the desflurane group than in the isoflurane or sevoflurane groups.

Sedation depth assessment in the first and last 2 hours

The patient's MAC values showed no significant difference between the first and the last 2 hours of sedation ($p = 0.55$). Across all measurements, the median MAC was 0.58 [0.53 to 0.59].

Despite stable MAC values, mean N_Index in the isoflurane group dropped with a median of − 13.75 [− 4 to − 19] points ($p < 0.01$). In the sevoflurane group, N_Index dropped − 8 points (0.25 to − 13; $p = 0.04$). The difference in the desflurane group − 5.55 [− 1 to − 12] was statistically not significant ($p = 0.07$). These results are displayed in Fig. 3.

In the pairwise (per patient) comparison of the RASS values in the first and last two sedation hours, we obtain the following results: isoflurane $p = 0.02$, sevoflurane $p = 0.04$, desflurane $p = 0.15$. In the first 2 hours, the median [1st quartile, 3rd quartile] was isoflurane − 3 [− 3; −3], sevoflurane − 4 [− 4; −3], desflurane − 3 [− 3.75; −3]. In the last 2 hours, the values were as follows: isoflurane − 4 [− 4; −3], sevoflurane − 4 [− 4: −3.25], desflurane − 3.5 [− 4; −3].

Analysis of longitudinal data

In the second step of the analysis, we applied an autoregressive hierarchical linear model to all 21.208 longitudinal measurements, with clustering per patient. This regression identified a robust negative correlation between time under sedation and the N_Index ($R^2 = 0.76$): the regression model is presented in Table 2. Both the linear intercept and slope have a significant *p*-value < 0.001. The regression formula:

N_Index = 43 − 0.72 × hours, this translates into a N_Index drop of approximately − 17 points after one inhalative sedation day.

Table 2
The hierarchical linear model

Terms	Estimates	Confidence-intervals
Intercept	42.85*, p < 0.001	39.05 to 45.65
Slope	-0.72*, p < 0.001	-1.00 to -0.44
$N_{patients}$	30	R^2 = 0.76
$N_{paired-measurements}$	21208	

In the last step of the statistical analysis, three bootstrapped linear models estimated the effect of time on N_Index for each study group; the results are presented in Fig. 4. All three model's intercepts and slopes had *p*-values < 0.01. Table 3 summarises the corresponding linear equations. The slope of desflurane − 0.4 x hours is almost half of isoflurane (− 0.9 x hours) and sevoflurane (− 0.8 x hours). The N_Index downdrift in the desflurane group appears less pronounced than in patients receiving isoflurane or sevoflurane.

Table 3
Statistical output of the bootstrapped linear regressions per subgroup

Subgroup	Easy formula	Intercept	Sedation hours	P-value
Isoflurane	43–0.9 x hours	42.82 ± 2.28	− 0.92 ± 0.21	< 0.01
Sevoflurane	43–0.8 x hours	45.19 ± 1.96	− 0.82 ± 0.19	< 0.01
Desflurane	43–0.4 x hours	43.18 ± 1.51	− 0.42 ± 0.13	< 0.01

Discussion

Sedation depth drifts downward over time

This study's primary focus was to examine the difference in the N_Index between the first and last 2 hours of sedation (Figs. 2 and 3). All statistical tests confirmed the sedation time-dependent down-drift in the isoflurane and sevoflurane groups on the EEG-derived index. In the desflurane group, the N_Index drop was smaller than in the isoflurane or sevoflurane study arm. Considering the small number of included patients, the regression formulas per each group has an exploratory character. However, the time-dependent down-trend of all three investigated inhalative anaesthetics suggests that MAC-monitoring alone is not sufficient, even by constant end-expiratory concentrations, to prevent a slow drift into excessive sedation depth (Stage E and F). The RASS values analysis grouped per patient and group conveys the same interpretation as the longitudinal analysis of the N_Index.

Our results highlight the importance of frequent clinical sedation-depth assessments, MAC titration, or (when feasible) a sedation pause to prevent the detrimental effects of excessive sedation, as advocated in the international guidelines on analgosedation-delirium prophylaxis in ICU patients.

MAC and the sedation depth

The literature reports a weak drug–response relationship in both inhalational and intravenous sedative agents, partly attributed to polypharmacy and the high pathophysiological heterogeneity of mechanically ventilated patients (16, 17).

A recent investigation of natural sleep reported EEG-derived values of 41 ± 9.8 in the deepest stage of non-REM sleep (18). Below this range, the critical care patient remains in long-term sedation in the deep stages E and F, which correlates with significant adverse effects.

In our data, the N_Index oscillates around 43 to 45; only after long-term exposure of the neurons to the volatile anaesthetic, we observe a negative drift towards EEG ranges with increasing burst-suppression phases.

Another study by the same author revealed a pharmacodynamic plateau similar to this study's findings (19). Data from 26 ASA II patients anaesthetized with sevoflurane and monitored with N_Index and BIS formed a biphasic dose-response curve, with a plateau at the change between the maximum δ power and the increase in the burst-suppression rates. Similar to our results, Bomberg et al. reported N_Index values under ICU sedation with isoflurane of 38 ± 10 (20).

Differences across isoflurane, sevoflurane, and desflurane groups

As displayed in Fig. 3, the negative regression slope of desflurane is almost half of those in the other two subgroups, suggesting that the time-dependent negative drift is smaller in patients receiving desflurane. According to the fitted linear equations, after a day of sedation with desflurane, the N_Index should remain above 33, which is not associated with burst suppression. Following the regression formulas, after 24 hours of sedation with isoflurane and sevoflurane, we expect N_Index values of 21 and 25, respectively, which correspond to deep substages of stage E and stage F. Moreover, only 33% of the N_Index observations were in the deep stages, compared to sevoflurane and isoflurane (48% and 60%, respectively).

Meiser et al. compared the awakening times after long-term sedation with desflurane versus propofol and noted that the former offers greater control of sedation, narrower distribution of values, and significantly quicker emergence (15). Our measurements suggest that desflurane could be a better choice for long-term sedation, for example, in patients without EEG-monitoring under neuromuscular blocking drugs. Nonetheless, a higher number of patients and studies with more patients is necessary to confirm the difference between desflurane and isoflurane/sevoflurane inhalational sedation.

Limitations of the study

Although the secondary variables are comparable across the study groups, hidden non-linear interactions between different demographic variables cannot be excluded. Therefore, the differences across the three subgroups should be interpreted with caution. Future studies with larger study samples are needed to confirm the secondary endpoints of this study.

The MIRUS system provided automatic control of the end-expiratory concentration in a given target, independent of the tidal volume or breathing rate. Nonetheless, drastic changes in ventilation ('patient fighting the ventilator') combined with the sudden need to deepen the sedation may require an intravenous agent, such as propofol, at the bedside. Moreover, opioids, like sufentanil, also have a sedative effect. An ICU study with an opioid and non-opioid group may provide more accurate results regarding the drug-response over time of inhalative anaesthetics.

Conclusions

The time under inhalative sedation shows a suppressive effect on both the clinical assessment (RASS) and the EEG-monitoring (N_Index). When relying only on MAC-monitoring, the ICU patients receiving long-term sedation may drift to an excessive sedation depth (stage E and F). In the desflurane subgroup, this time-suppressing effect seems less pronounced.

Abbreviations

Intensive care unit (ICU); minimum alveolar concentration (MAC); electroencephalography (EEG); Richmond-Agitation-Sedation-Scale (RASS)

Declarations

Ethical approval and consent to participate

The Institutional Review Board of the Ruhr University Bochum (No. 4780-13, Chair Prof. M. Zenz), approved the study, registered at ClinicalTrials.gov (NCT03860129, on 24 September 2018). This study was conducted in complete compliance with the Declaration of Helsinki (2013), and all patients provided written informed consent before study participation.

Consent for publication

All authors consented for the publication.

Availability of data and materials

The data is available in tabular format per request to the authors.

Competing interests

Bellgardt und Herzog-Niescery received speaker's honoraria from Pall Medical, Dreieich, Germany. The other authors declare that they have no conflict of interest.

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Authors' contributions Study conception/design: MB, TPW**.** Data acquisition: LP, AIG**.** Data analysis and model construction: AIG. Interpreting results: MB, AIG, LP. Initial drafting of manuscript: AIG. Critical revision of the manuscript: JHN, SL, LP, MB, TK, TPW. All authors have read and approved the final draft. All authors had full access to all the data and took responsibility for the data analysis's integrity and accuracy.

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Figures

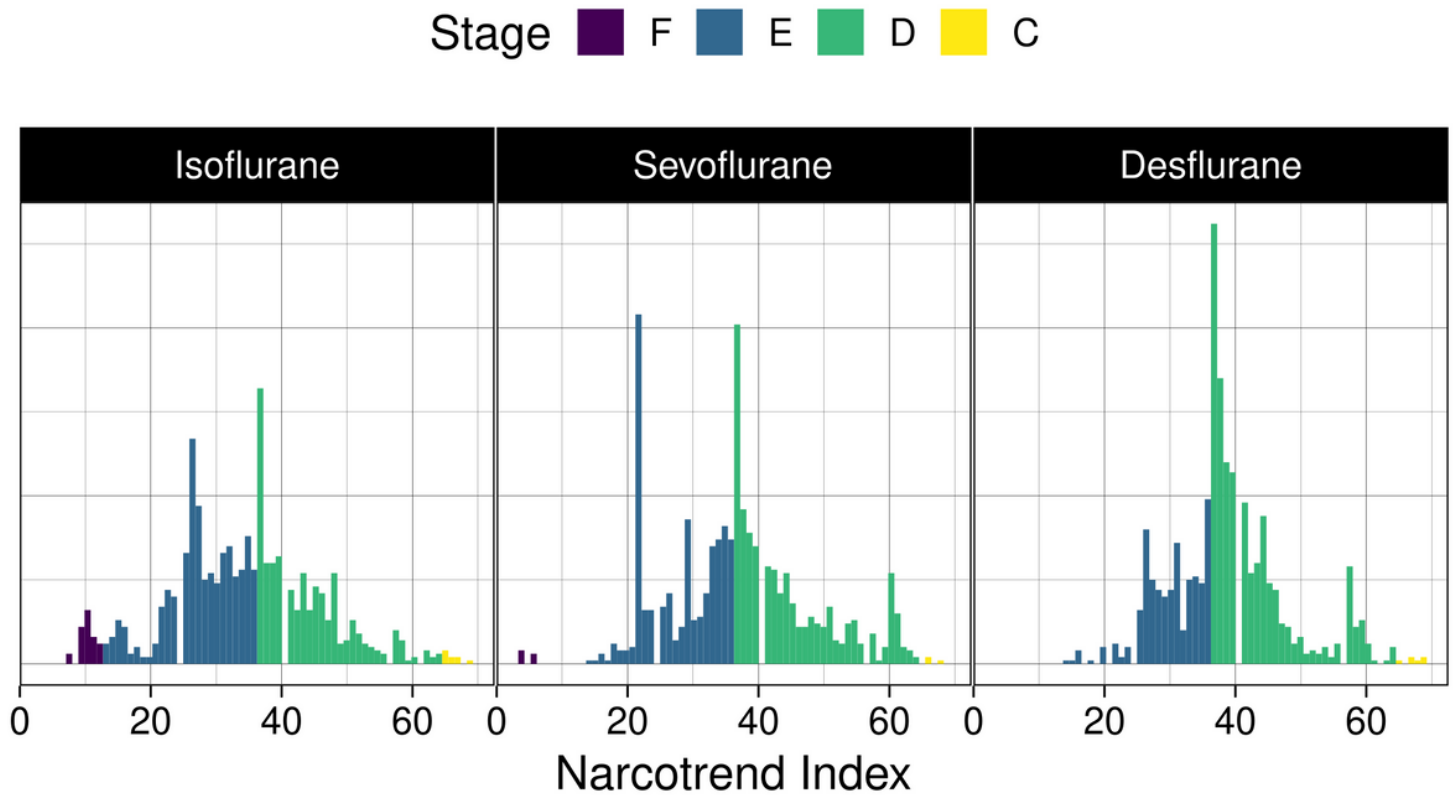

Figure 2

Histrograms (bootstrapped), each patient is equally represented.

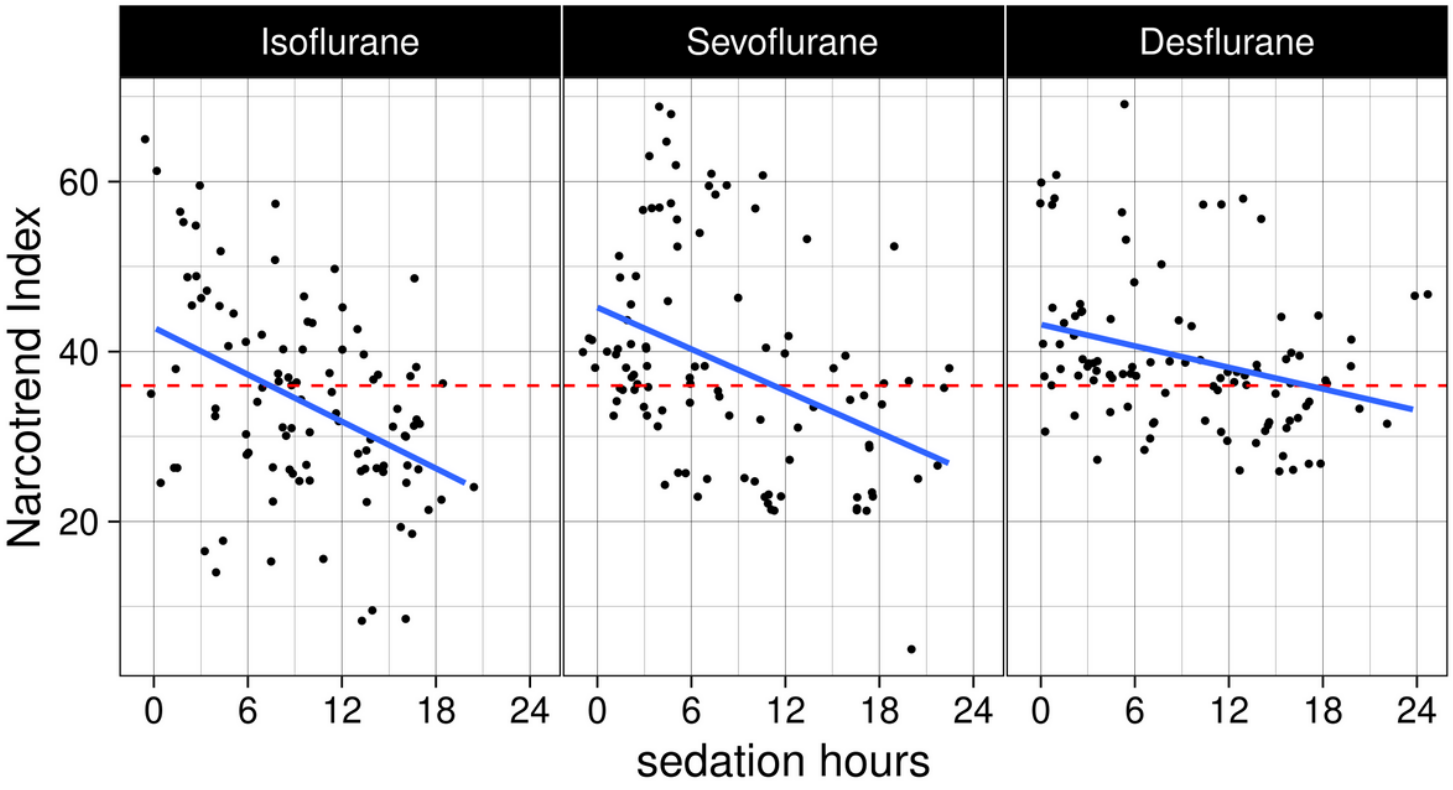

Figure 4

The three blue lines represent the bootstrapped linear regressions in the isoflurane, sevoflurane, or desflurane subgroup (the confidence interval of the models is marked with grey). The horizontal axis is the duration of uninterrupted volatile sedation; the vertical axis is the EEG-derived sedation depth. Below the dotted red line are the Stages E and F corresponding to deep sedation.