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ENT • ORIGINAL ARTICLE

Drug-induced sleep endoscopy with target-controlled infusion using propofol and monitored depth of sedation to determine treatment strategies in obstructive sleep apnea

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Abstract

Background Drug-induced sleep endoscopy (DISE) has become an important diagnostic examination tool in the treatment decision process for surgical therapies in the treatment of obstructive sleep apnea (OSA). Currently, there is a variety of regimes for the performance of DISE, which renders comparison and assessment across results difficult. It remains unclear how the different regimes influence the findings of the examination and the resulting conclusions and treatment recommendations. This study aimed to investigate the correlation between increasing levels of sedation (i.e., light, medium, and deep) induced by propofol using a target-controlled infusion (TCI) pump, with the obstruction patterns at the levels of the velum, oropharynx, tongue base, and epiglottis (i.e., VOTE classification). A second goal was the establishment of a sufficient sedation level to enable a reliable decision regarding treatment recommendations.

Material and methods Forty-three patients with OSA underwent a DISE procedure using propofol TCI. Three levels of sedation were defined, depending on entropy levels and assessment of sedation: light sedation, medium sedation, and deep sedation. The evaluation of the upper airway at each level, with increasing sedation, was documented using the VOTE classification. The elapsed time at which each assessment was performed was recorded.

Results Upper airway changes occurred and were measured throughout the DISE procedure. Clinically useful determinations of airway closure occurred at medium sedation; this level of sedation was most probably achieved with a blood propofol concentration of 3.2 μg/ml. In all 43 patients, definite treatment decisions could be made at medium sedation level. Increasing sedation did not result in changes in the treatment decision.

Conclusions Changes in upper airway collapse during DISE with propofol TCI occur at levels of medium sedation. Decisions regarding surgical treatment could be made at this level of sedation.

Clinical trial name Upper Airway Collapse in Patients with Obstructive Sleep Apnea Syndrome by Drug Induced Sleep Endoscopy (URL: https://clinicaltrials.gov/ct2/results?term=NCT02588300&Search=Search)

Registration number NCT02588300

Keywords Obstructive sleep apnea · OSAS · Anesthesia · Sedation · Drug-induced sleep endoscopy procedure · DISE

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Introduction

Obstructive sleep apnea (OSA) is a common disease with a prevalence of 6–13% in the US population [1]. During sleep, complete or partial collapse of the upper airway at different pharyngeal levels leads to reductions in airflow [2]. These obstructions correspond with daytime sleepiness,

hypertension, stroke, and profound effects on morbidity and mortality [3–6]. The first-line treatment in OSA is the application of continuous positive airway pressure (CPAP), which aims to prevent the airway collapse by applying mild air pressure on a continuous basis [7]. While CPAP therapy is effective, it is limited by poor acceptance and compliance [8–11]. Patients who refuse CPAP therapy and other alternative treatments (e.g., mandibular advancement devices) are candidates for surgical interventions. Therefore, identification of the upper airway obstruction sites and patterns of airway collapse is a foundational requirement in staging patients for OSA surgery [12]. Unfortunately, endoscopy of the upper airway during natural sleep is not realizable because of the sleep-disturbing effects of the endoscopic examination. In 1991, Croft and Pringle were the first to describe a drug-induced sleep endoscopy (DISE) procedure to detect changes in the upper airway in OSA patients under sedation [13]. Since then, experts have continued to discuss and debate how findings under sedation correlate with changes during sleep. Eastwood et al. demonstrated that there is a correlation between the propensity for collapse of the upper airway during sleep and under general anesthesia [14]. Additionally, it could be shown that DISE is a useful tool in the individualized decision process for the treatment of OSA, notwithstanding the acknowledged limitation arising from the inconsistent use of sedative drugs and poorly defined levels of sedation during this diagnostic procedure [15–18].

Therefore, it is unclear how the local obstruction pattern may vary depending on confounding factors including sedative drug employed, mode of drug application, and depth of sedation.

The aim of our study was to investigate the correlation of increasing sedation depth induced by propofol using a target-controlled infusion (TCI) pump during DISE with the obstruction patterns and degrees, employing the velum, oropharynx, tongue base, and epiglottis (VOTE) classification [19]. Furthermore, we endeavored to define a sufficient level of sedation at which treatment decisions could properly be made to guide subsequent OSA surgical interventions.

Material and methods

This prospective clinical study (Department of Otorhinolaryngology, Head and Neck Surgery and Department of Anesthesiology, Klinikum rechts der Isar, Munich, Germany) was reviewed and approved by the Local Ethics Board of the Medical Faculty Munich, Germany (study ID number 5782/13). Written informed consent was obtained from all participants. Patients were recruited from the Sleep Disorders Center of the Department of Otorhinolaryngology, Head and Neck Surgery at Klinikum rechts der Isar, Munich, Germany. The clinical trial was registered at ClinicalTrials.gov (NCT02588300).

Subjects

All subjects suffered from documented OSA with an apnea-hypopnea index (AHI) of >10 events/h diagnosed in polysomnography prior to our study examination. The patients were enrolled consecutively. Exclusion criteria included age <18 years; body mass index (BMI) of >35 kg/m^2; active infection; previous oral, head, or neck surgery within the preceding 3 months; pregnancy; American Society of Anesthesiologists (ASA) classification III or higher; chronic use of alcohol (>60 g ethanol per day or >150 g ethanol per week) or sedatives; illicit drug use; and chronic obstructive pulmonary disease.

Drug-induced sleep endoscopy

DISE was performed within the setting of an operating room theater setting with standard anesthesia monitoring including resuscitation equipment and a monitored nearby recovery facility. Vital parameters were recorded on a type F-CM1-04 monitor (GE Healthcare). To control the level of sedation, entropy [state entropy (SE) and response entropy (RE)] was monitored by using self-adhesive, single-use entropy electrodes (GE Healthcare), applied after manual cleansing of the forehead and temple. SE is based on the EEG signal. It is not affected by reactions of the facial muscles in contrast to RE, which is susceptible thereto. For this reason, we chose SE to quantify the depth of sedation.

During the entire procedure, three-channel electrocardiogram (ECG) and pulse oximetry were recorded. Noninvasive blood pressure was measured every 10 min. A head-mounted microphone recorded breathing and snoring noises. The patient was placed in a supine position with or without a pillow per his or her usual sleep habits. All examinations were conducted in a dark, silent, and climate-controlled room to reduce adverse external stimuli during the procedure. Sedation with propofol 10 mg/ml was commenced, using an Alaris Asena PK mkIII TCI pump with an IV access located on the upper limb. Effective dose was calculated using the Schneider protocol [20]. Baseline sedation data were documented, and TCI was started with a target concentration of 2.0 μg/ml. The effect-site concentration was increased in a stepwise manner every 90 s by 0.1 μg/ml.

We defined three levels of sedation: light sedation (the patient appeared asleep for the first time after the initiation of the propofol infusion and showed initial signs of snoring and hypopnea, SE levels >80%), medium sedation (SE levels between 60 and 80 without any arousal or reaction to the manipulation of the endoscope), and deep sedation (SE dropped below 60). Drug infusion was terminated if SE dropped below 50. Patients were monitored post-procedure until complete orientation was restored, and persistent cardiorespiratory stability was ensured.

Every endoscopy was performed by one board-certified ear, nose, and throat (ENT) surgeon and specialist in sleep medicine. A flexible endoscope (Storz, Germany) was inserted transnasally and positioned before the procedure started. It was positioned at each of the different levels of the upper airway throughout the procedure to observe the different levels and patterns of obstructions in the upper airway in accordance with the VOTE methodology. Three different placements of the endoscope were used: (1) at the level of the choanae to assess the soft palate (i.e., velum), (2) at the level of the margin of the soft palate to assess the oropharynx, and (3) just above the level of the tongue base to assess the tongue base and epiglottis. Each patient was evaluated for VOTE at each level of sedation.

The entire DISE procedure was recorded, starting when the endoscope's camera was activated. Furthermore, a jaw thrust (Esmarch) maneuver was performed on every patient. Afterwards, the DISE videos were independently analyzed by four experienced and blinded ENT sleep specialists. The VOTE classification was used to document the obstruction sites, with scoring of both the degree (0 = no obstruction, 1 = partial obstruction, 2 = complete obstruction), and configuration (anterior-posterior, lateral, or concentric) of obstruction [19]. VOTE scoring was performed as soon as each successive predefined sedation level target was reached (light, medium, and deep sedation, in order). For all independent DISE analyses, the entire video was provided to the ENT sleep specialist. These were then viewed in their entirety by each scorer.

Statistical analysis

Normally and nonnormally distributed data are presented by mean ± standard deviation and median (5th percentile–95th percentile), unless otherwise stated. Absolute and relative frequencies are given for qualitative data. Exact two-sided 95% confidence intervals were computed for effect measures on the binomial scale. Linear regression models with robust Huber-White covariance estimates—to account for repeated measurements within subjects—were used to assess differences in TCI values between VOTE scores adjusted for BMI and AHI. Likewise, linear discriminant analysis (LDA) [21] and evolutionary trees [22] were applied to infer the conditional probabilities of VOTE scores given TCI values (i.e., Pr(VOTE|TCI)). In LDA, the latter is derived through application of the Bayes theorem on the estimated class probabilities (i.e., Pr(VOTE)) and the estimated distribution of TCI values within the VOTE scores (i.e., Pr(TCI|VOTE)), which are assumed to follow a normal distribution. Evolutionary trees conduct binary splits of the data to produce subsets with divergent empirical distributions of the outcome. The latter serve as estimates of the respective conditional distributions. The splitting process is guided by the BIC criterion as a goodness-of-fit measure [21]. Hypothesis testing for differences in dependent samples was performed by the Friedman rank sum tests on two-sided 5% significance levels. All statistical analyses were conducted in R 3.2.0 (R Core Team 2015, R Foundation for Statistical Computing, Vienna, Austria).

Data analysis is based on the score of the most experienced scorer. Measuring the interrater variability with Cohen's kappa (values of >0.85) for each possible score insured a high consistency among the four scorers.

Table 1 Patient characteristics

	Median [5% quantile; 95% quantile]
Age (years)	46.0 [27.2; 71.8]
BMI (kg/m^2)	26.0 [22.8; 32.1]
Overall AHI (events/h)	19.5 [5.3; 51.1]

BMI body mass index, *AHI* apnea-hypopnea index

Results

Forty-three male patients were included in this trial. Table 1 gives an overview of the patients' characteristics. All patients suffered from OSA were diagnosed by prior polysomnography.

In order to reach the predefined sedation levels, significantly different target concentrations of propofol had to be administered with a mean target concentration of 2.2 μg/ml at light sedation, 3.0 μg/ml at medium sedation, and 3.4 μg/ml at deep sedation (Fig. 1).

The probabilities of being evaluated for VOTE score at either point in time depending on TCI concentration are derived from LDA (Fig. 2). There are no distinct cutoff points that define a

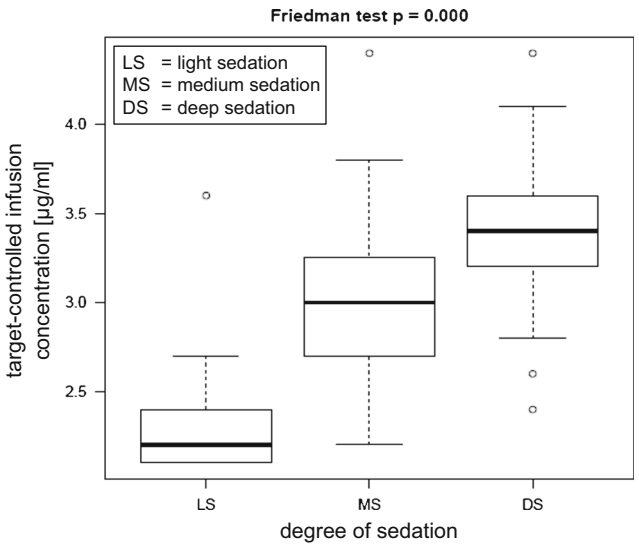

Fig. 1 Required target-controlled infusion concentration in order to reach the predefined sedation levels. The *black bar* shows the median, the *square* shows the range between 25% and 75% quantile and the *error bars* shows the total range except for the outliers, which are presented by the circles

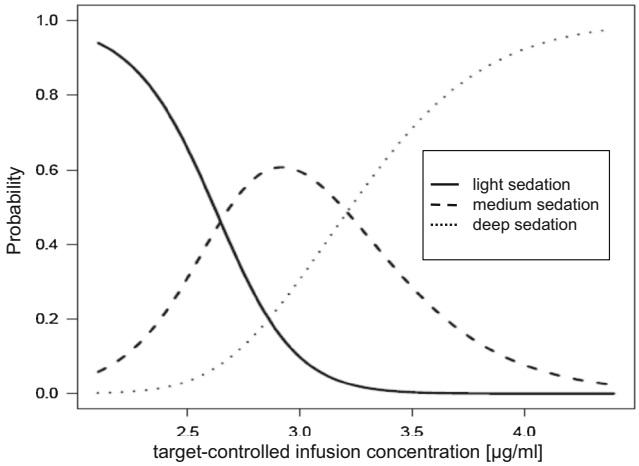

Fig. 2 Probabilities of being evaluated for VOTE score depending on target-controlled infusion concentration

complete separation of diagnostic windows. In order to present an optimal separation by adequate cutoff values, an evolutionary tree was created (Fig. 3). Our results show that a concentration of up to 2.5 μg per ml provides the highest probability of reaching the light sedation level. Concentrations between 2.5 to 3.2 μg per ml seem to be most suitable for evaluating VOTE score at medium sedation. According to our protocol, deep sedation levels were reached at concentrations beyond 3.2 μg per ml.

The data show changes in the different sites and their obstruction configurations in the upper airway according to the VOTE classification from light sedation to deep sedation, expressed as relative frequencies of their occurrence (Fig. 4). At the velum level, there were significant changes concerning the anterior-posterior assessment (Fig. 4a) and the concentric assessment (Fig. 4c) detected between light sedation and medium sedation but no significant changes between medium sedation and deep sedation. Only minor changes appear on the velum level concerning the lateral evaluation. At the level of the oropharynx, in the lateral assessment, there were significant changes in the degree of obstruction detected between light sedation and medium sedation and between medium sedation and deep sedation (Fig. 4d). At the level of the tongue, there were also significant changes between light sedation and medium sedation as well as between medium sedation and deep sedation (Fig. 4e). At the level of epiglottis in the anterior-posterior assessment, changes between light sedation and medium sedation were significant (Fig. 4f), whereas there were no changes in the lateral assessment (Fig. 4g).

From light to medium sedation, 42 patients changed the degree of obstruction. From medium to deep sedation, six patients changed the degree of obstruction—mainly partial to complete obstructions.

A linear regression analysis for the differences in TCI between light, medium, and deep sedation, which was adjusted for AHI and BMI (Table 2), revealed that for a median AHI of 19.5 n/h and a median BMI of 26.0 kg/m^2, the expected average (95% CI) TCI at light sedation, medium sedation, and deep sedation is 2.3 (2.2; 2.4), 3.0 (2.8; 3.2), and 3.4 (3.2; 3.6), respectively ($p < 0.001$). A 1-unit increase in AHI and BMI led to a TCI increase of 0.004 ($p = 0.199$) and 0.001 ($p = 0.939$) units on average.

In all 43 patients, a medium sedation level sufficed to guide the differential diagnosis for further surgical treatment of the OSA. A further propofol infusion towards deep sedation did not change treatment decision for any patient compared to the decision made at a medium level of sedation.

Discussion

During the preceding several years, DISE has emerged as a useful method for guiding the surgical treatment in patients with

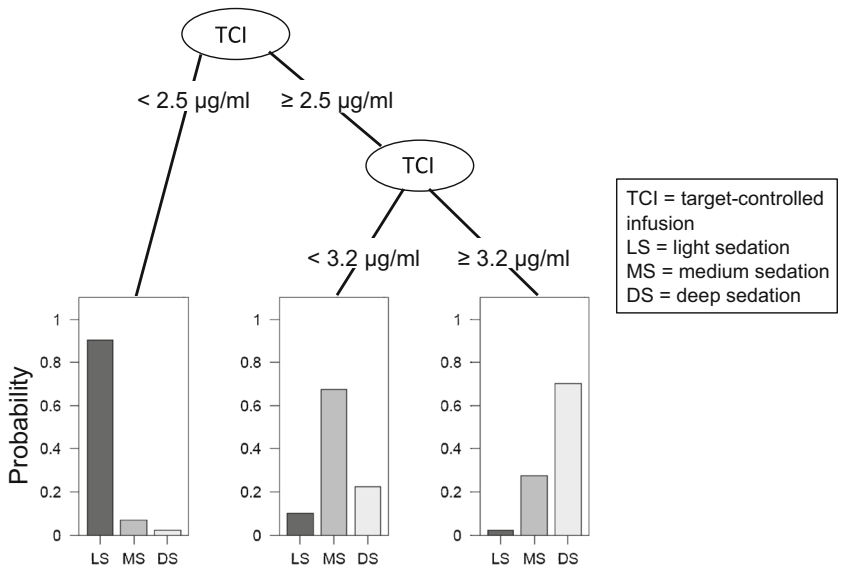

Fig. 3 Conditional distribution of the VOTE score depending on target-controlled infusion (evolutionary tree)

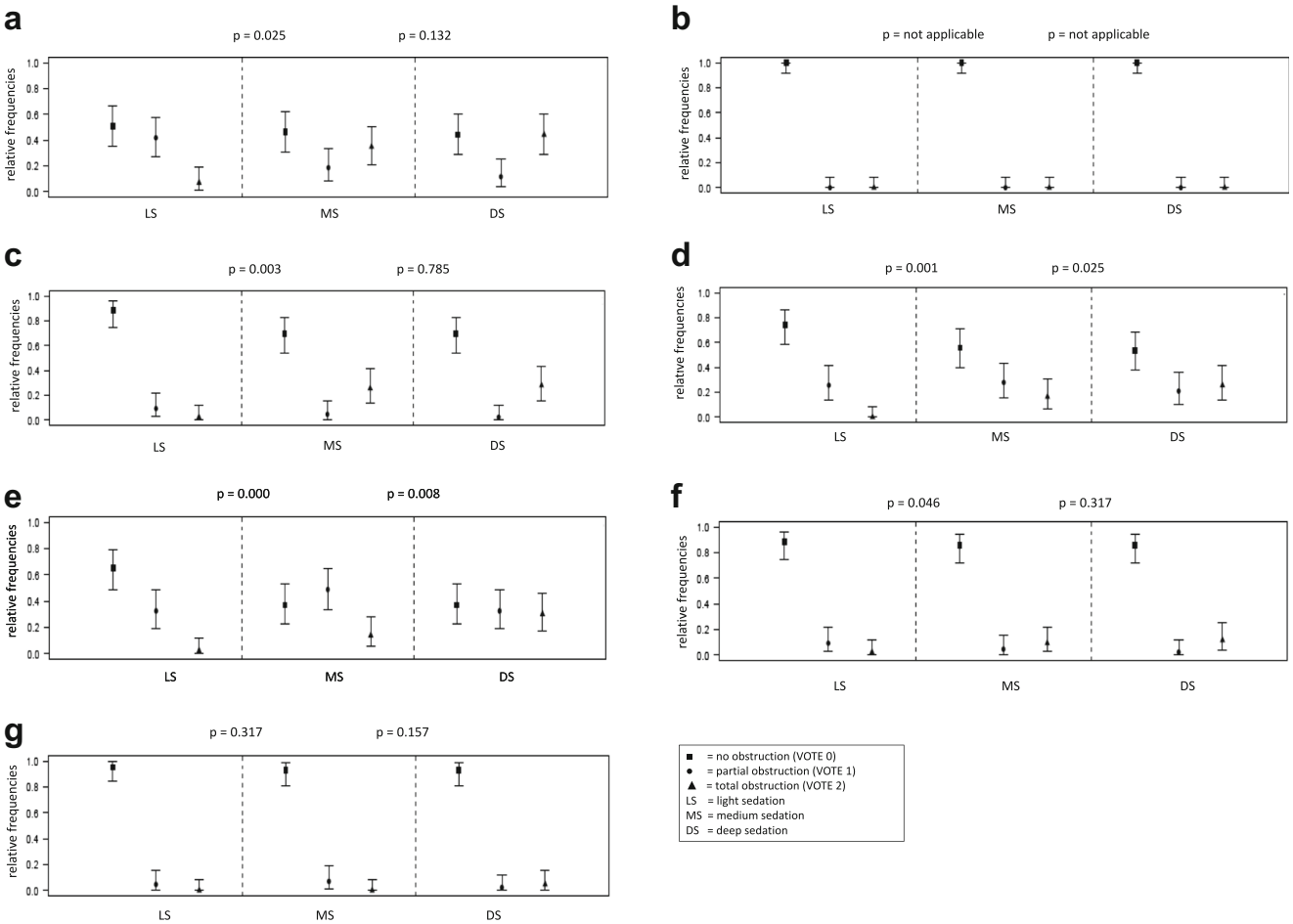

Fig. 4 Relative frequencies with exact 95% confidence intervals of the levels of obstruction configurations across VOTE scores. **a** Velum anterior-posterior. **b** Velum lateral. **c** Velum concentric. **d** Oropharynx lateral. **e** Tongue anterior-posterior. **f** Epiglottis anterior-posterior. **g** Epiglottis lateral

OSA. DISE has been performed with a wide range of procedural regimes and varying sedative agents, applied by either bolus or continuous infusion [23–26]. In 2014, a group of European experts in the field of sleep endoscopy published a position paper on the indications for DISE, how to perform the sedation, and how to report the DISE findings [12]. They recommended propofol, midazolam, or a combination of both, with either a bolus or continuous infusion technique or a combination of both techniques.

A DISE procedure is normally performed as an outpatient procedure. With the use of propofol, patients are generally awake and oriented within 10 min after termination of the infusion, which is a particular advantage compared to midazolam. Furthermore, we used propofol in our study due to the availability of a well-established target-controlled infusion (TCI) algorithm. Administering propofol by TCI is currently considered to be a safe and useful option to have reasonably steady drug concentrations over time [27–31]. The intersubjective variability is less with TCI than with a bolus technique [32]. TCI systems further reduce variability by incorporating pharmacokinetic covariates and eliminating parts of the time-varying variabilities. Using conventional infusions, the ratio between infusion rate and plasma drug concentration changes considerably over time and with duration of infusion. Using TCI, the ratio between target drug concentration and actual drug at effect-site concentration shows far less variability, being relatively insensitive to both time and infusion history [31]. Our results show that TCI facilitated optimal comparability among the enrolled patients and practicability in a clinical setting. Individual differences in the susceptibility to propofol concerning the collapse of the upper airway have been reported [33]. However, in our study, TCI concentrations and predefined sedation levels were unaffected by the apnea-hypopnea index (AHI) and the body mass index (BMI). This finding commends the procedure and favors the use of the TCI pump because the important parameters AHI and BMI are sufficiently covered by the Schneider protocol within our TCI regime. De Vito et al. compared a bolus versus a continuous infusion procedure and showed more severe oxygen desaturation in the bolus technique [25]. This can be avoided

Table 2 Relation of the AHI and BMI to the required TCI concentrations (μg/ml)

	Regression coefficient	*p* value
VOTE at LS (intercept)	2.185	<0.001
VOTE at MS	+0.698	
VOTE at DS	+1.128	
AHI	+0.004	0.199
BMI	+0.001	0.939

VOTE velum, oropharynx, tongue base, and epiglottis; *LS* light sedation; *MS* medium sedation; *DS* deep sedation; *BMI* body mass index; *AHI* apnea-hypopnea index

by the utilization of a TCI pump, as done in this study. The slow onset led to a longer duration of the procedure in comparison with the bolus technique. In our case, the average procedure duration was 24 min and 20 s. The degree of obstructions did change significantly in some parameters of the VOTE classification between medium and deep sedation. No major changes were observed at the velum between medium and deep sedation, whereas changes at the tongue base were detected between medium and deep sedation. These findings were seen in the change of obstruction degrees (from partial to complete). However, the determination of subsequent therapeutic intervention did not change, notwithstanding the changes observed in progressing from medium to deep. Therefore, the level of medium sedation is sufficient for a proper diagnosis, and seeking deeper sedation is unwarranted, as it confers no additional advantage while lengthening the procedure and exposing the patient to an overall increased burden of propofol. Considering this, the time of our procedure going forward can be reduced to a mean of 15 min and 10 s. Atkins et al. describe a DISE procedure by using a probability ramp propofol infusion system [23]. They reach the point of obstruction in less than 4 min, which is even faster, compared with the bolus technique described [25]. However, they made no statement about the obstruction pattern or the possible indication for further treatment. We are convinced that a slow onset of sedation is important for performing a reliable examination and assessing the sites of obstructions at multiple levels. In preliminary examinations, the bolus technique led to a fast onset of airway obstructions and a very high percentage of complete concentric collapse, and a likely false positive finding due to abruptly crossing the narrow boundary between a sedated and anesthetized patient. In the aforementioned study of De Vito et al., the bolus group showed a sudden pharyngeal collapse without snoring or apneic events. A fast pharmacological-time effect was postulated rather than a slow natural muscle relaxation. One possible explanation was that fast sleep induction skips the diagnostic window in which pharyngeal collapse would most probably occur [25]. Hillman et al. showed that a slow increase of propofol sedation is associated with a nonlinear increase in collapsibility of the upper airway. They concluded that those changes might parallel changes during onset of sleep [33]. Hillman et al. also showed that the upper airway collapsibility occurs abruptly beyond loss of consciousness within a narrow range of propofol concentration. This concentration band differs between individuals according to their susceptibility to the sedating effect of the drug. These changes happen nonlinearly to the increasing propofol concentrations and are accompanied by an accelerated decrease in bispectral index score (BIS) values [33]. Instead of BIS, we used entropy, which is an alternative, substantially equivalent EEG technique for assessment of depth of sedation. Due to a light level of sedation targeted as a first point of scoring for VOTE classification, our clinical assessment of the patient's state of consciousness had to be limited to mere observation: Auditory or tactile stimuli would have likely made it difficult to evaluate sedation measured by entropy in our effort to assess it. For medium and deep sedation, we employed spectral entropy as a nonreactive, EEG-based sedation score. Quantitative evaluation of a patient's state of consciousness using processed EEG is a common method in monitoring general anesthesia. BIS by Covidien and GE Healthcare's pair of spectral entropy measures, state entropy (SE) and response entropy (RE), are well-established realizations of such technology. Schmidt et al. evaluated the performance of BIS and SE/RE during slow propofol induction, using TCI to establish gradually increasing plasma levels until loss of response. Within an induction protocol like ours, both BIS and SE/RE detected changes in state of consciousness, with no significant difference between BIS and SE/RE [34]. In deference to a method demonstrably more reliable, we chose to imply the applicability of EEG-based depth-of-anesthesia monitoring to states of sedation. This is also in line with the procedure presented by Hillman et al., who utilized BIS monitoring to discriminate sedation levels.

Our results indicate that the optimal level of sedation for relevant therapeutic information regarding the upper airway in OSA patients is within the medium sedation window. This level reflects the aforementioned accelerated decrease. A concentration of 3.2 μg/ml or higher seems to be neither favorable nor necessary as the patients at this concentration have already reached at least a medium level of sedation (see Figs. 2 and 3). The changes in the obstruction patterns according to the VOTE classification from light to medium sedation are significant and mirror the increased airway collapsibility, which has been also described by Hillman et al. The fact that the concentration of propofol at which an individual loses consciousness varies greatly favors the use of an appropriately sophisticated—and expensive—medical tool to monitor anesthetic depth, with TCI serving well in this clinical trial. In this study, we identified a concentration ceiling of 3.2 μg/ml propofol in patients with OSAS at which a reliable diagnosis is

possible in most cases, and levels higher than 3.2 μg/ml are, therefore, inadvisable in the vast majority of patients.

In conclusion, we showed that changes in the upper airway occur throughout the DISE procedure with propofol TCI. The most useful, differentially diagnostic changes occur at the level of medium sedation. In this stage, a decision regarding therapy could be made. A further increase in sedation does not change the treatment and should be avoided to increase the safety of DISE. For the identification of the level of medium sedation, a sedation depth monitoring method like entropy or BIS is favorable. We identified a target concentration of 3.2 μg/ml to be sufficient to make treatment decisions in patients with OSAS. The AHI and the BMI do not affect the dosing of the TCI during DISE.

Compliance with ethical standards

Conflict of interest Clemens Heiser is a consultant of Inspire Medical Systems (Maple Grove USA) and Sutter Medizintechnik GmbH (Freiburg, Germany). He received personal fees from Neuwirth Medical Products (Obernburg, Germany) and Heinen und Lösenstein (Bad Ems, Germany). Benedikt Hofauer received grants and research support from Inspire Medical Systems (Maple Grove USA).

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