Effects of Depth of Propofol and Sevoflurane Anesthesia on Upper Airway Collapsibility, Respiratory Genioglossus Activation, and Breathing in Healthy Volunteers

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ABSTRACT

Background: Volatile anesthetics and propofol impair upper airway stability and possibly respiratory upper airway dilator muscle activity. The magnitudes of these effects have not been compared at equivalent anesthetic doses. We hypothesized that upper airway closing pressure is less negative and genioglossus activity is lower during deep compared with shallow anesthesia.

Methods: In a randomized controlled crossover study of 12 volunteers, anesthesia with propofol or sevoflurane was titrated using a pain stimulus to identify the threshold for suppression of motor response to electrical stimulation. Measurements included bispectral index, genioglossus electromyography, ventilation, hypopharyngeal pressure, upper airway closing pressure, and change in end-expiratory lung volume during mask pressure drops.

Results: A total of 393 attempted breaths during occlusion maneuvers were analyzed. Upper airway closing pressure was significantly less negative at deep *versus* shallow anesthesia (−10.8 ± 4.5 *vs.* −11.3 ± 4.4 cm H_2O, respectively [mean ± SD]) and correlated with the bispectral index ($P < 0.001$), indicating a more collapsible airway at deep anesthesia. Respiratory genioglossus activity during airway occlusion was significantly lower at deep compared with light anesthesia (26 ± 21 *vs.* 35 ± 24% of maximal genioglossus activation, respectively; $P < 0.001$) and correlated with bispectral index ($P < 0.001$). Upper airway closing pressure and genioglossus activity during airway occlusion did not differ between sevoflurane and propofol anesthesia.

Conclusions: Propofol and sevoflurane anesthesia increased upper airway collapsibility in a dose-dependent fashion with no difference at equivalent anesthetic concentrations. These effects can in part be explained by a dose-dependent inhibiting effect of anesthetics on respiratory genioglossus activity. **(Anesthesiology 2016; 125:525-34)**

GENERAL anesthesia compromises upper airway stability, and anesthesia residents learn early in their training how to manage this increased vulnerability to airway collapse.[1–9] The risk of postoperative upper airway collapse depends on several factors such as pharyngeal and facial anatomy,[10,11] the amount of negative pressure generated by the respiratory muscles, end-expiratory lung volume,[12,13] and upper airway dilator muscle activity.[14] Previous preclinical studies have shown that anesthetics such as propofol, pentobarbital, isoflurane, and ketamine have different effects on airway dilator muscle activity.[15–19]

The effects of isoflurane and propofol on airway collapsibility have been quantified in humans in two landmark studies by Eastwood *et al.*[4,5], but the experiments were not designed to make a head-to-head comparison of the effects of these anesthetics on airway patency.

In this study, we investigate the effects of sevoflurane and propofol given at two equivalent anesthetic doses on upper airway collapsibility. Furthermore, we hypothesize that the mechanism for upper airway collapsibility under general anesthesia is related to the reduction of genioglossus muscle activity.

What We Already Know about This Topic

- Animal studies demonstrated that volatile anesthetics and propofol have different depressant effects on airway dilator muscle activity
- The dose-dependent effects of anesthetics on upper airway collapsibility have not systematically been compared under equivalent anesthesia depth in humans

What This Article Tells Us That Is New

- This randomized controlled crossover study in healthy human volunteers examined effects of equivalent anesthesia doses of sevoflurane and propofol on pharyngeal airway dilating muscle activity and upper airway collapsibility
- Propofol and sevoflurane anesthesia increased upper airway closing pressure in a dose-dependent fashion with no difference at equivalent anesthetic concentrations, possibly mediated by a dose-dependent reduction of genioglossus muscle activation

This article is featured in "This Month in Anesthesiology," page 1A. This article has a video abstract. The first two authors contributed equally.

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We hypothesized that upper airway closing pressure (P_{CLOSE}), defined as the pressure at which mask pressure (P_{MASK}) plateaus and epiglottic pressure decreases further, is less negative and genioglossus activity is lower during deep compared with shallow anesthesia. Additionally, we hypothesized based on preclinical studies that sevoflurane allows for a more negative P_{CLOSE} compared with propofol at the same depth of anesthesia.

Materials and Methods

Subjects

After approval by the Partners Human Research Committee (Boston, Massachusetts), 12 American Society of Anesthesiologists physical status I healthy volunteers were studied in this randomized crossover nested protocol. All subjects provided written informed consent before participation. Subjects were recruited through a recurring broadcast e-mail to employees at Massachusetts General Hospital, Boston, Massachusetts. Eligible subjects were 18 to 45 yr of age with a body mass index of 18.5 to 28 kg/m^2 and no history of sleep apnea or dysphagia. Before enrollment, preliminary history and physical examinations were performed by a board-certified anesthesiologist.

Equipment and Techniques

All experiments were conducted at Massachusetts General Hospital in a research facility hospital certified as an anesthetizing location. The study area was equipped with a standard anesthesia workstation, automated recordkeeping, and resuscitation equipment.

Propofol was administered to target concentrations using a Fresenius target-controlled infusion pump, which is not commercially available in the United States (Injectomat TIVA Agilia, Fresenius Kabi, France). Two board-certified anesthesiologists were present for the duration of each experiment, and one of them was assigned to provide care for the subject as his only responsibility. All subjects received standard anesthesia monitoring (electrocardiogram, pulse oximetry, capnography, and oscillometric blood pressure measurements).

For measurements of genioglossus activity, breathing, and P_{CLOSE}, subjects were prepared as published previously.[20] Briefly, one nostril was decongested with oxymetazoline and anesthetized with 4% lidocaine spray before insertion of a Millar pressure catheter (Millar Instruments, USA) nasally into the hypopharyngeal area. Correct placement was confirmed visually (oropharyngeal inspection) and by a spike in hypopharyngeal pressure upon asking the subject to swallow. The catheter was taped to the nose and then secured to a nasal continuous positive airway pressure (CPAP) mask (Philips Respironics, USA), which was connected to a high-flow anesthesia circuit, figure 1. For measurement of electromyography (EMG), two 30-mm needles were used to insert 27-gauge stainless steel wire electrodes into the genioglossus muscle transcutaneously.[21] These electrodes were referenced to a ground electrode on the sternum.

For measurement of end-expiratory lung volume, life shirts (LifeShirt; VivoMetrics, USA)[22] were fitted and calibrated using a fixed-volume bag and the calibration protocol provided.[23]

Ventilatory flow was measured with a pneumotachograph (Hans Rudolph, USA), and tidal volume was obtained by electrical integration of the inspiratory flow signal, figure 1.

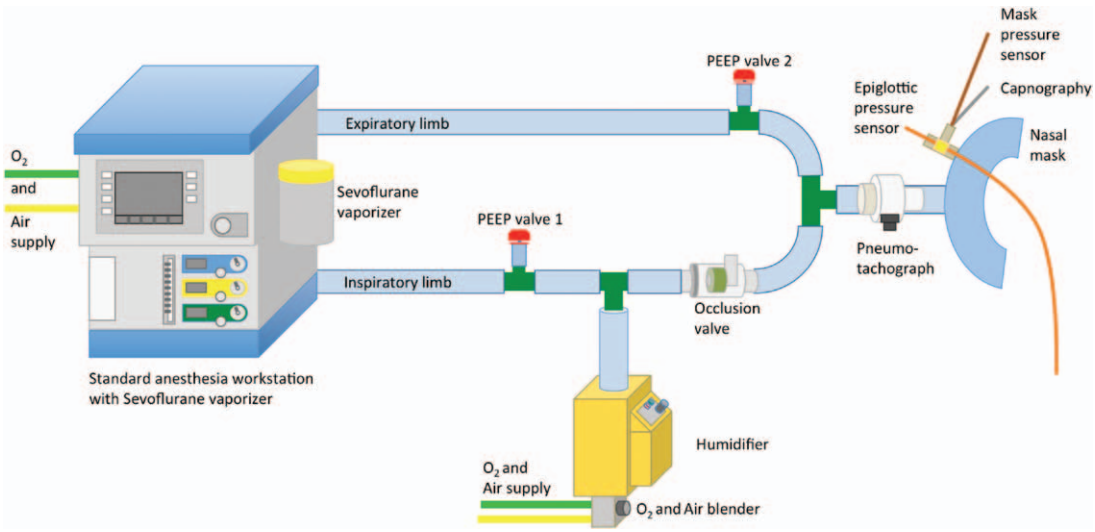

Fig. 1. Drawing of the high flow circuit used to apply 50% oxygenated humidified air at adjustable pressures. Sevoflurane was added by the standard anesthesia workstation using a vaporizer when required. The inspiratory limb of the anesthesia workstation connected to an adjustable positive end-expiratory pressure (PEEP) valve and allowed the insufflation of humidified air before connecting the occlusion valve to the pneumotachograph. The expiratory limb of the anesthesia workstation connected to a second PEEP valve before linking to the pneumotachograph. The nasal mask offered ports that had been modified to connect to the mask and epiglottic pressure sensors. If necessary, the mouth was sealed with a tape to eliminate any leakage of air.

Experimental Protocol

Subjects were asked to fast for at least 8 h before the start of the experiment. The study was conducted in a block (2:2) randomized crossover fashion with nested design. Each subject received propofol and sevoflurane sequentially in a randomized order. The nested design specified three anesthetic conditions (wakefulness and under propofol and sevoflurane anesthesia) and two depths of anesthesia (deeper and lighter anesthesia, defined as no response and positive response to a standardized electrical pain stimulus, respectively), figure 2.

The subject's head was positioned on a gel headrest. We obtained measurements during wakefulness and at two different depths of propofol and sevoflurane anesthesia, figure 2. After loss of consciousness, the mouth was taped with Tegaderm (3M, USA) in order to avoid mouth-breathing.

The initial dose targets were the median concentrations necessary to prevent movement in response to a painful stimulus, established as a propofol-predicted concentration of 3.7 μg/ml[24] or sevoflurane end-tidal concentration of 1.5%.[25] The anesthetic was administered for 30 min in order to ensure that the central nervous system reached approximate steady state before any measurements were recorded.

All data were recorded, processed, and filtered using LabChart software (AD Instruments, USA). Anesthetic sedative effects were measured using bispectral index (BIS; Covidien, USA) recording at 1-min intervals.

Measurement

Breathing was quantified by a pneumotachograph during CPAP (pressure titrated by the clinical anesthesiologists to maintain adequate minute ventilation), as well as during atmospheric pressure. We analyzed 10 consecutive breaths immediately before and after elimination of CPAP during steady-state anesthesia conditions (fig. 2). Baseline respiratory measurements included tidal volume, respiratory rate, minute ventilation, flow rate, peak inspiratory flow, and duty cycle.

End-expiratory lung volume was determined from 5 breaths after the P_{MASK} reduction from CPAP to atmospheric pressure. These were compared to 5 breaths immediately preceding the reduction in pressure.

P_{CLOSE} and genioglossus function were quantified during airway occlusion maneuvers. Two successive airway occlusion maneuvers were performed at each level of anesthesia to P_{CLOSE}. P_{CLOSE} was defined as the pressure at the inflection point of the P_{MASK} curve during an occlusion while epiglottic pressure continues to decline during an attempted inspiration.[20] During each airway occlusion maneuver, the valve remained

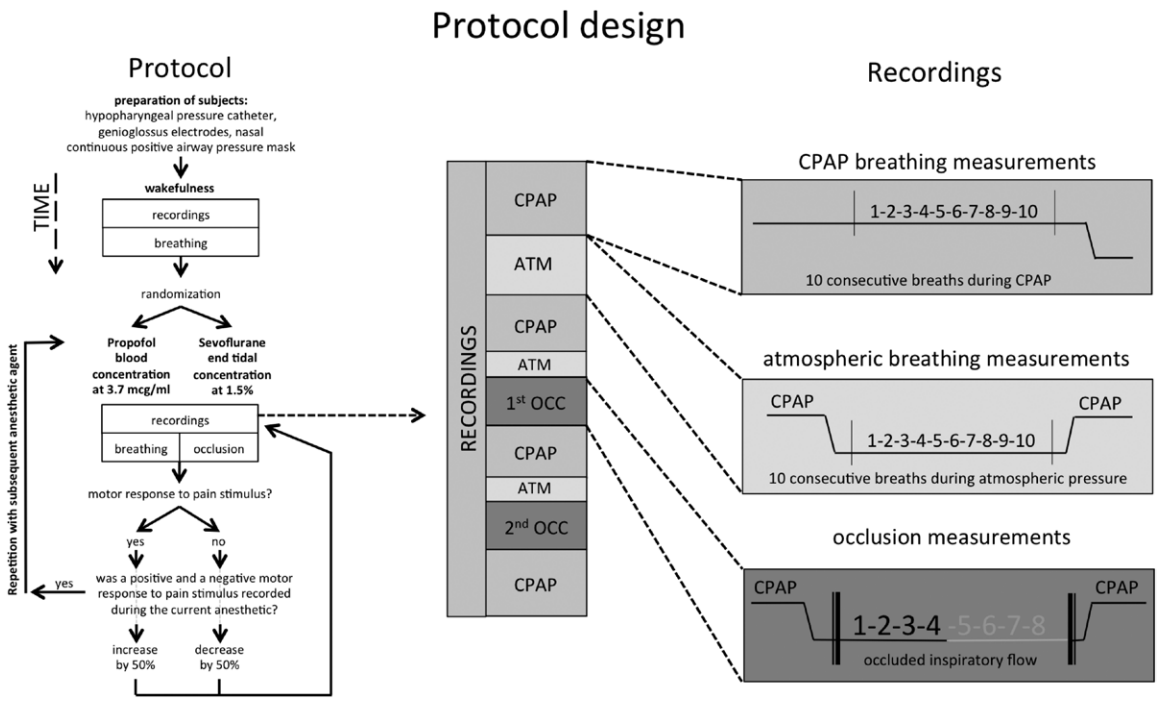

Fig. 2. Protocol used for anesthesia titration and data acquisition. After initial measurement of breathing during quiet wakefulness at atmospheric pressure (ATM), anesthesia was induced with either propofol or sevoflurane. Anesthesia was titrated based on a volunteer's response to a transcutaneous pain stimulus to achieve reproducible level of anesthesia defined as "light" (withdrawal of arm in response to a pain stimulus) and "deep" (no movement). After 30 min of anesthetic agent administration at the same dose, measurements of breathing were conducted at ATM and at a continuous positive airway pressure (CPAP) level (3.7 ± 1.9 cm H_2O) that prevented an inspiratory flow limitation. Ten consecutive breaths immediately before elimination of CPAP and immediately after the drop to ATM were analyzed. In addition, upper airway collapsibility (upper airway closing pressure) was measured at each anesthesia condition studied. Measurements taken during two series of airway occlusions (four to eight respiratory cycles each) were analyzed. OCC = occlusion measurements.

closed for at least four consecutive inspiratory attempts during which the upper airway collapsed, but no more than eight consecutive inspiratory attempts were targeted.

After the breathing and measurements of P_{CLOSE}, a 30-mA tetanic pain stimulus was applied to the forearm using a peripheral nerve stimulator (Life-Tech Inc., USA). Presence or absence of a motor response was noted. If the subject moved head or extremities (excluding the stimulated arm), the concentration was increased in 50% increments until the absence of motor responses, figure 2. If the initial response was no movement, the concentration was decreased by 50% increments until the threshold for motor response to pain was reached. In this way, two levels of anesthesia could be defined for each subject: one corresponding to the level at the initial response and one that was deeper or lighter. Subsequent doses of anesthesia were also administered for 30 min in order to ensure that the central nervous system reached steady state and measurements were performed before a tetanic pain stimulus. Time between the final administration of the initial anesthetic and the first measurement of the subsequent anesthetic was recorded.

In between measurements, CPAP was applied if a subject was unable to tolerate (maintain adequate spontaneous breathing) the study conditions safely over an extended period of time.

Genioglossus Activity

The genioglossus muscle electromyography (GG-EMG) signal was filtered using band-pass filter (200 to 1,000 Hz, transition width 40 Hz) and displayed as a moving time average (time constant 100 ms). Correct placement of the GG-EMG electrodes was confirmed by an increase in activity during inspiration and a burst in EMG activity upon asking the subject to press the tongue against the teeth.

Phasic activity of the genioglossus muscle was determined by subtracting the tonic genioglossus activity from peak activity and standardized by comparing it to the maximum recorded activity of each subject. After insertion of the genioglossus muscle electrode, each volunteer was asked to conduct the following maneuvers: maximal tongue protrusion, swallowing, and maximum forced inspiration. The maximum moving time average genioglossus activity observed during these maneuvers was considered as maximum GG activity.[26] Peak activity was identified as the GG-EMG at the time of attempted inspirations during occlusion maneuvers. Tonic activity was determined from GG-EMG at the time of attempted expirations during occlusion maneuvers.

End-expiratory Lung Volume

End-expiratory lung volume was measured by respiratory inductance plethysmography (LifeShirt; VivoMetrics, USA).[22] The transducers were fitted and calibrated using a fixed-volume bag and the calibration protocol provided.[23] Data were recorded and stored on a memory card (LifeShirt200 recorder; VivoMetrics) before being analyzed on a computer (VivoLogic V 3.1 software; VivoMetrics).[21]

History of Sleep Apnea

On recruitment, patients with a history of sleep apnea were excluded. We specifically asked for witnessed apneas, observed evidence of gasping or choking during sleep, and unexplained excessive daytime sleepiness.

We also used the Epworth Sleepiness Scale[27] and the Perioperative Sleep Apnea Prediction (P-SAP)[28] score to objectively quantify signs of obstructive sleep apnea.

Statistical Analysis

The primary endpoint was P_{CLOSE}, and the secondary endpoint was the respiratory genioglossus activity.

For the evaluation of the effects of depth of anesthesia on upper airway collapsibility, we used mixed models including the main effect of depth of anesthesia on P_{CLOSE} (primary) and genioglossus activity (secondary) as fixed effects, while allowing intercepts to vary (random intercepts model). In order to adjust for an effect of different number of breaths within an occlusion maneuver on P_{CLOSE} measurements, we included the number of the inspiratory attempts (1 to 8) within an occlusion maneuver as a random effect in the regression model.

All other analyses were conducted with an exploratory intention, utilizing the same mixed linear model as for our primary aim. We tested for a fixed main effect of BIS on P_{CLOSE} and respiratory genioglossus activity. We also conducted additional exploratory breathing analysis to evaluate the different fixed effects of depth and type of anesthesia on breathing (fixed main effects of depth of anesthesia and compound on respiratory rate, minute ventilation tidal volume, flow rate, duty cycle, and peak flow, allowing for random intercept).

Based on our preclinical data,[17] we also hypothesized that sevoflurane allows for a more stable upper airway at the same depth of anesthesia compared to propofol, expressed as a more negative P_{CLOSE}. Using the same mixed linear model as for our primary aim, we tested for an interaction effect of anesthetic agent and anesthetic depth (below and above median effective dose) on the dependent variables P_{CLOSE} and genioglossus activity.

All model assumptions were examined through model diagnostic plots including residual plots and Q–Q plots. We examined whether the variance estimates were indistinguishable from zero and examined residual distribution plots. Model comparison, if applied, was presented and conducted using ANOVA and comparing Bayesian information criterion values.

Our power analysis was based on the study of Eastwood *et al.*[4] We expected a difference in P_{CLOSE} between shallow and deep anesthesia of 1.6 cm H_2O with a SD of 1.3 cm H_2O. By using paired *t* tests, we calculated that a comprehensive data of eight volunteers would provide us with a more than 80% power to identify a significant dose-dependent difference in

P_{CLOSE} between high- and low-dose anesthesia at an α error $P = 0.05$. We recruited 12 volunteers in order to account for inadequate readings and to achieve high-quality P_{CLOSE} and respiratory genioglossus activity data from eight patients.

Data are presented as mean ± SD unless otherwise specified. A value of $P < 0.05$ was used as the threshold for statistical significance. Statistical analysis was performed using SPSS 22.0 (SPSS Inc., USA).

Results

Subjects

Data from 12 American Society of Anesthesiologists physical status I healthy volunteers (age, 24 ± 3 yr, 20 to 29 yr; body mass index, 23 ± 2.3 kg/m^2) were analyzed. The results of the P-SAP revealed absence of high sleep apnea risk in all volunteers and evidence of daytime sleepiness in one volunteer. The mean observed end-tidal concentration of sevoflurane and mean targeted propofol with a positive response to pain stimulus were 1.2 ± 0.2 Vol% and 3.1 ± 0.6 μg/ml, respectively. At a mean observed end-tidal concentration of 1.7 ± 0.4 Vol% sevoflurane and targeted 4.2 ± 0.8 μg/ml propofol, no response to pain stimulus was observed.

Effect of Anesthesia on Upper Airway Closing Pressure (Primary Endpoint)

The occlusion maneuvers were recorded and analyzed in 393 breaths from 9 out of 12 volunteers. Three volunteers did not tolerate repetitive occlusion maneuvers, and we therefore did not obtain valid data. Of the remaining 9 volunteers, 34 measurement conditions were analyzed, and one measurement at the low propofol anesthesia level was not included since the subject moved during the occlusion maneuver. At one deep level of propofol anesthesia, the subject was unable to sustain spontaneous breathing without a jaw thrust being performed, and the propofol dose was reduced before making P_{CLOSE} measurements. The upper airway collapsed 295 times during occlusions and remained stable during 98 occlusions.

During anesthesia, we observed a dose-dependent impairment of P_{CLOSE} using the predefined exposure variable depth of anesthesia (fixed main effect of depth of anesthesia, no response *vs.* positive response to pain stimulus, −10.7 ± 4.5 *vs.* −11.3 ± 4.4 cm H_2O, $P = 0.001$). Of note, the dose-dependent impairment of P_{CLOSE} was also observed when using the electroencephalographic exposure variable BIS instead of a pain-related measure of depth of anesthesia (fixed main effect of BIS on P_{CLOSE}, $P < 0.01$) as the exposure variable, figure 3.

Effect of Anesthesia on Genioglossus Muscle Activity (Secondary Endpoint)

During an occlusion of the respiratory circuit, the average phasic and tonic genioglossus activity at predicted anesthesia levels resulting in positive pain response amounted to 31 ± 22% (phasic) and 26 ± 20% (tonic) of the maximum recorded activity. At predicted anesthesia levels resulting in no pain response, phasic and tonic activity amounted to 19 ± 17 and 22 ± 22%, respectively. The depth of anesthesia had a significant inhibiting effect on the phasic genioglossus muscle activity as measured by the moving time average of the electromyography ($P < 0.01$; fixed main effect of depth of anesthesia). The difference in tonic genioglossus activity was not significant ($P = 0.18$; fixed main effect of depth of anesthesia).

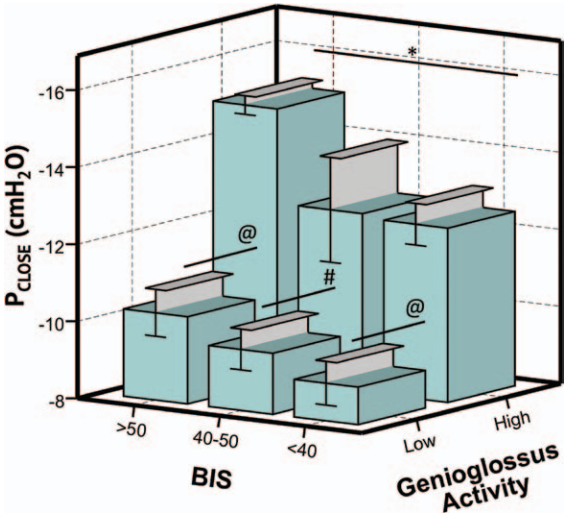

Fig. 3. Effects of anesthesia-induced unconsciousness level (defined by bispectral index [BIS]) and phasic genioglossus electromyography (EMG) activity (moving time average; dichotomized data) on upper airway closing pressure (P_{CLOSE}) during propofol and sevoflurane anesthesia. The two genioglossus activity groups are defined as activity higher or lower than 21% of maximum activity. With decreasing BIS levels (indicating decreasing levels of arousal), upper airway closing pressure increased (less negative values indicating increased collapsibility; fixed main effect of BIS on P_{CLOSE}, $^*P < 0.001$). Across BIS levels, high genioglossus activity was associated with more negative P_{CLOSE} values indicating a more stable airway (fixed main effect of dichotomized genioglossus EMG on P_{CLOSE}; $@P < 0.001$; $\#P < 0.05$; mean ± SEM).

Exploratory Analyses

Association between Genioglossus Muscle Activity and Upper Airway Closing Pressure during Anesthesia. For analysis of the relation between P_{CLOSE} and genioglossus activity, we built two groups: occlusion maneuvers with low genioglossus activity (21% of maximum genioglossus activity or lower, 9 ± 6% [mean ± SD]) and those with high genioglossus activity (higher than 21% of maximum genioglossus activity, 41 ± 17%). Analyzing all airway occlusions, we found a significant association between more negative (more stable) P_{CLOSE} (fixed main effect of P_{CLOSE} on phasic genioglossus activity, correlation of fixed effect estimates = −0.6, $P = 0.018$) and higher phasic genioglossus activity, figure 3.

Effect of Bispectral Index on Upper Airway Closing Pressure. Low BIS (lower than 40), indicating deep anesthesia–induced

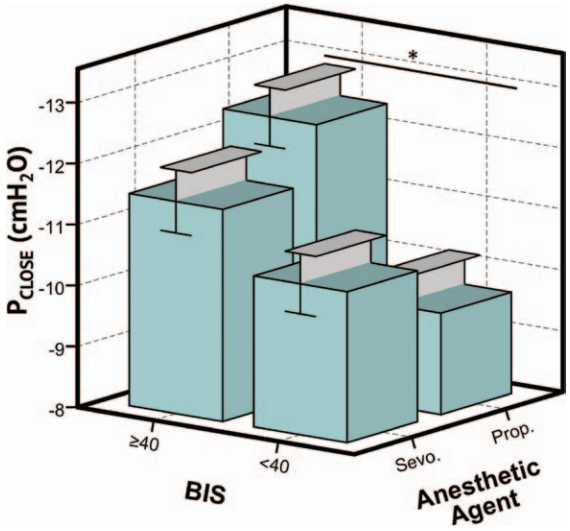

Fig. 4. Effects of sevoflurane (Sevo.) and propofol (Prop.) anesthesia at different levels of arousal (bispectral index [BIS] lower than 40 *vs*. BIS of 40 and higher) on upper airway closing pressure (P_{CLOSE}). Deep anesthesia predicted high upper airway collapsibility compared with more shallow levels of Sevo. and Prop. anesthesia (fixed main effect of BIS on P_{CLOSE}; *$P < 0.001$). In contrast, there were no anesthetic agent–specific effects on P_{CLOSE} (fixed main effect of compound, Sevo. *vs*. Prop. , on P_{CLOSE}; $P = 0.233$) across BIS values (mean ± SEM).

loss of consciousness, predicted high upper airway collapsibility during sevoflurane and propofol anesthesia compared with more shallow levels of anesthesia (BIS of 40 and higher; 10.5 ± 3.5 *vs.* −11.5 ± 5.3 cm H_2O during sevoflurane and −9.7 ± 3.7 *vs.* −12.4 ± 3.9 cm H_2O during propofol, $P < 0.001$, fixed main effect of BIS on P_{CLOSE}). In contrast, there was no anesthetic agent–specific effect on P_{CLOSE} across arousal states measured in this study (−11.0 ± 4.8 *vs.* −11.0 ± 4.0 cm H_2O, $P = 0.233$ for fixed main effect of compound, sevoflurane *vs.* propofol, on P_{CLOSE}, fig. 4).

Breathing Data. At deep anesthesia (no response to pain stimulus), flow rate and peak flow were about 30% lower compared to at shallow anesthesia (0.29 ± 0.07 *vs.* 0.23 ± 0.06 l/s and 0.41 ± 0.14 *vs.* 0.33 ± 0.09 l/s, respectively, fixed main effect of depth of anesthesia on flow rate, $P < 0.01$; fixed main effect of depth of anesthesia on peak flow, $P < 0.01$). This difference was observed at atmospheric pressure but not when subjects were breathing at CPAP (3.7 ± 1.9 cm H_2O, fixed main effect of depth of anesthesia, $P = 0.976$). The effects of anesthesia on other breathing variables were similar as can be seen in table 1.

Of note, respiratory rate was significantly higher during all depths of sevoflurane-induced anesthesia compared to propofol anesthesia (18 ± 2 *vs.* 16 ± 2 min^{-1}; fixed main effect of compound, $P < 0.001$). See figure 5 for a representative response to a reduction of airway pressure (fig. 5A) and airway occlusion (fig. 5, B and C) during sevoflurane anesthesia.

The decrease in end-expiratory lung volume during the switch from CPAP decreases to atmospheric pressure did not significantly differ between sevoflurane and propofol (60 ± 30 *vs.* 45 ± 26 ml, fixed main effect of compound, $P = 0.238$) at equivalent anesthetic concentrations.

At least 40 min (53 ± 9 min) passed after the final application of the first anesthetic and before any measurements during the second anesthetic were conducted.

Table 1. The Effects of Anesthesia on Breathing Variables

		Sevoflurane		Propofol	
	Awake	Low Dose	High Dose	Low Dose	High Dose
Respiratory rate (min^{-1})					
ATM	13.7 ± 3.9	17.8 ± 1.3	18.7 ± 2.2	16.4 ± 2.3	15.9 ± 1.8
CPAP		17.6 ± 1.9	18.6 ± 3.1	17.1 ± 2.6	15.8 ± 2.0
Minute ventilation (l/min)					
ATM	7.9 ± 1.7	6.7 ± 1.3	5.6 ± 1.5	7.2 ± 1.7	5.7 ± 1.3
CPAP		6.8 ± 1.1	7.1 ± 1.7	7.3 ± 1.7	6.7 ± 1.7
Tidal volume (l)					
ATM	0.63 ± 0.25	0.38 ± 0.06	0.30 ± 0.08	0.44 ± 0.11	0.36 ± 0.10
CPAP		0.39 ± 0.06	0.38 ± 0.09	0.42 ± 0.07	0.43 ± 0.15
Flow rate (l/s)					
ATM	0.31 ± 0.07	0.27 ± 0.05	0.22 ± 0.06	0.30 ± 0.09	0.24 ± 0.07*
CPAP		0.30 ± 0.03	0.32 ± 0.06	0.31 ± 0.04	0.31 ± 0.10
Duty cycle					
ATM	0.42 ± 0.03	0.42 ± 0.05	0.43 ± 0.04	0.40 ± 0.03	0.41 ± 0.03
CPAP		0.38 ± 0.04	0.37 ± 0.03	0.39 ± 0.06	0.37 ± 0.04
Peak inspiratory flow (l/s)					
ATM	0.45 ± 0.10	0.41 ± 0.16	0.33 ± 0.09	0.42 ± 0.13	0.33 ± 0.09*
CPAP		0.42 ± 0.06	0.44 ± 0.09	0.42 ± 0.06	0.44 ± 0.16

All values are presented as mean ± SD.

*$P < 0.01$ when comparing deep to shallow anesthesia at atmospheric pressure.

ATM = atmospheric pressure; CPAP = continuous positive airway pressure; Duty cycle = inspiratory time/total time.

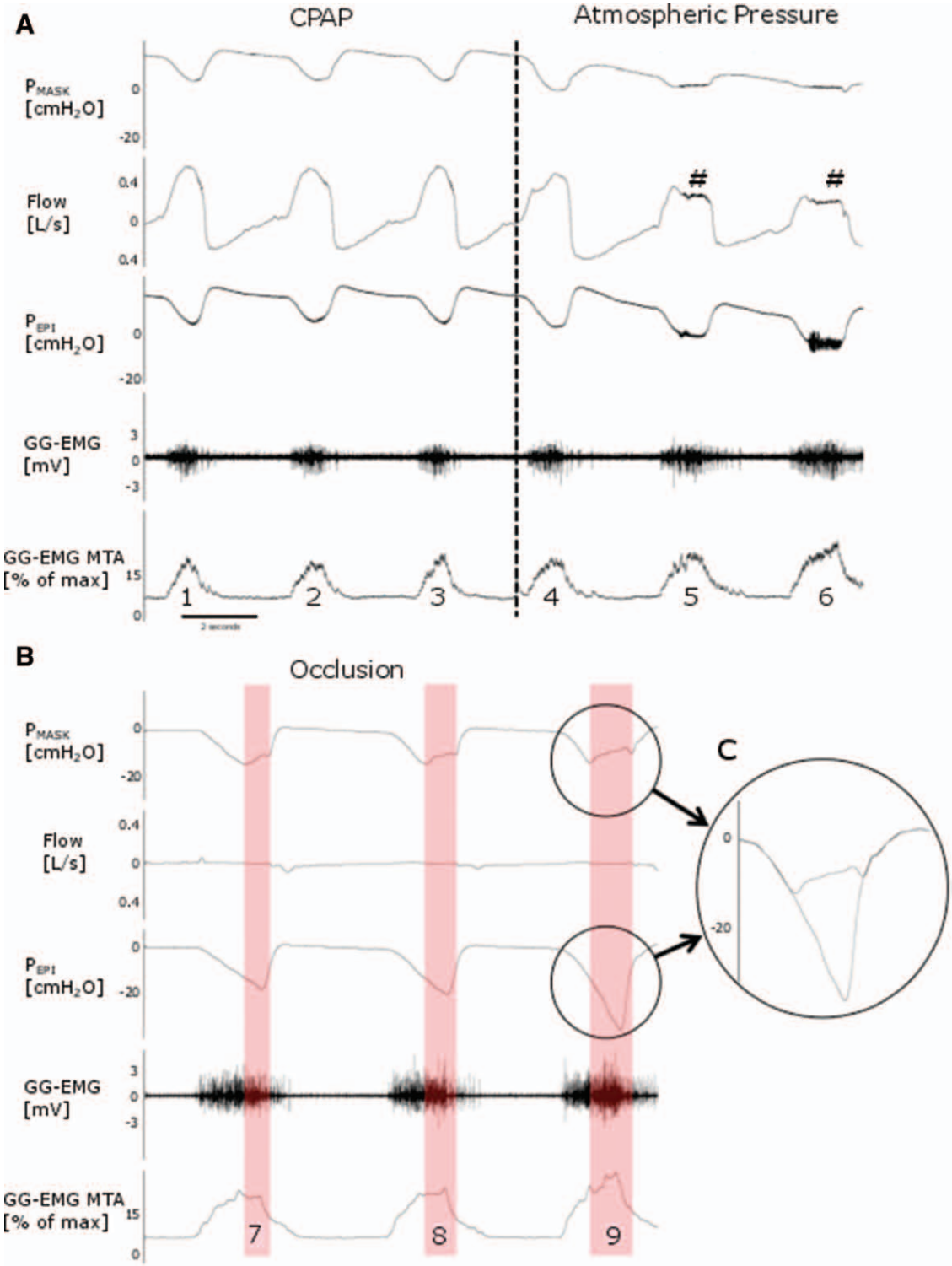

Fig. 5. Representative response to a reduction of airway pressure and airway occlusion during light sevoflurane anesthesia. (*A*) During breaths 1 to 3, continuous positive airway pressure (CPAP) was applied and no flow limitations were detectable. Subsequently, pressure was reduced to atmospheric level (*vertical dotted line*) causing flow limitations (#) and genioglossus electromyography activity to increase. (*B*) The inspiratory limb was occluded, each inspiratory effort produced a decrease in mask (P_{MASK}) and epiglottic pressure (P_{EPI}). While P_{EPI} progressively decreased to a minimum value, P_{MASK} separated from P_{EPI} during breaths 7 to 9 as the result of upper airway collapse. The inflection points (upper airway closing pressure [P_{CLOSE}]) of the P_{MASK} trace were defined as the points at which airway collapse occurred (*red shade*). (*C*) Superimposition of P_{MASK} and P_{EPI}. GG-EMG = genioglossus muscle electromyography; GG-EMG MTA = genioglossus muscle electromyography moving time average.

Discussion

This study compared the effects of equivalent anesthetic doses of propofol and sevoflurane anesthesia on P_{CLOSE} in healthy volunteers and evaluated the relationship between anesthesia-induced changes in respiratory genioglossus activity and P_{CLOSE}.

Our data show that propofol and sevoflurane anesthesia dose-dependently and similarly impair upper airway collapsibility. These effects of anesthesia on airway collapsibility can in part be explained by the inhibitory effects of anesthetics on genioglossus muscle activity. Similar to Malcharek *et al.*,[29] we used both electroencephalographic exposure variable BIS and pain-related measure of depth of anesthesia as study endpoints. The association between increasing depth of anesthesia, blunted respiratory genioglossus response, and increased airway collapsibility was stable across electroencephalographic and motor response–related assessments of depth of anesthesia.

The effects of isoflurane on upper airway collapsibility and genioglossus muscle control have been studied by Eastwood *et al.*[5] Similar to our study, the authors observed an increase in the P_{CLOSE} at high doses of a volatile anesthetic compared to shallow levels of anesthesia. In contrast to our study, Eastwood *et al.*[5] did not observe a significant effect of the volatile anesthetic agent dose on genioglossus activity. The difference between the results of Eastwood *et al.*[5] and our study may be explained by differences between compounds (isoflurane *vs.* sevoflurane) and differences in study design. Furthermore, Eastwood *et al.*[5] measured the critical closing pressure (P_{CRIT}; averaged 3 to 5 breath responses to a decrease in P_{MASK}) and genioglossus activity after multimodal anesthesia (propofol and fentanyl for induction, nitrous oxide, and isoflurane for maintenance) and surgery. Carryover effects of anesthetics and narcotics as well as the effects of surgery (pain, possible interference with vagus nerve activity) may have complicated the quantification of isoflurane's effects on airway patency and phasic genioglossus activity. In contrast to our study, Eastwood *et al.*[5] used a chin strap that may have improved airway patency similar to a jaw thrust. Our data, which were collected in healthy volunteers without the use of airway-stabilizing devices, show that the decreased airway patency during sevoflurane can in part be explained by a sevoflurane-induced impairment of phasic genioglossus muscle activation.

In another landmark study, Eastwood *et al.*[4] evaluated in patients before surgery the sole effects of propofol on upper airway patency and genioglossus muscle activity. Our data confirm their results, the dose-dependent impairment of airway patency by propofol. Interestingly, Eastwood *et al.*[4] only observed significant inhibiting effects of propofol on phasic genioglossus muscle activity when making comparisons between anesthetic doses (target-controlled infusion, 2.5 to 6 μg/ml) and low sedative doses given for insertion of percutaneous electrodes (1 μg/ml). Their sedative dose was substantially lower than the lowest anesthetic dose applied in our study. In our study, the correlation between respiratory (phasic) genioglossus activity and P_{CLOSE} during propofol anesthesia suggests that a propofol-induced inhibition of the genioglossus activity contributes to its impairing effects on upper airway patency. Of note, in contrast to Eastwood *et al.*,[4,5] we did not use an airway-stabilizing device (chin strap), which may have increased the sensitivity to identifying effects of propofol on upper muscle control.

Another methodologic difference between the studies of Eastwood *et al.*[4,5] and our study relates to the different approach used to quantify airway collapsibility. To assess upper airway collapsibility, we measured the P_{CLOSE}, as described by Issa and Sullivan[30]: the P_{MASK} at which the upper airway collapses in reaction to a sudden and complete occlusion of inspiratory airflow. The P_{CLOSE} is considered to be the summation of anatomical properties and a neuromuscular response to an external occlusion, whereas P_{CRIT} as measured by Eastwood *et al.*[4] examines the collapsibility of the passive upper airway. It is likely that P_{CLOSE} measurements are more sensitive than P_{CRIT} to quantify effects of anesthetics on respiratory upper airway activity. In fact, the magnitude of respiratory (phasic) genioglossus activity observed in our study during airway occlusion was substantially higher (25 to 35%) compared with the genioglossus activity measured previously under conditions where the upper airway was not occluded during inspiration (1 to 11%).[4]

Our group has previously shown in a preclinical study in rats that the volatile anesthetic isoflurane, compared to propofol, causes dose-dependent increased phasic genioglossus activity, a finding at odds with this human study. We speculate that the differences between the findings in rats and humans may be explained by species-specific interactions between the vagus nerve and upper airway muscle control. The vagus nerve is important for mediating the interplay between lung volume[31,32] and upper airway muscle activity, and isoflurane may have vagolytic effects.[33,34] The latter may be more relevant in the rat than in humans. In fact, our current findings of decreased genioglossus activity with increased sevoflurane doses reflect our preclinical finding in vagotomized rats where the genioglossus activity decreased with increasing isoflurane doses. In the rat, vagotomy leads to an approximately twofold increase in both flow rate and phasic genioglossus activity, and isoflurane has opposite effects on these variables in vagotomized rats compared to those with intact vagus nerves. In humans, the effects of the vagus nerve on breathing appear to be less relevant.[35] Therefore, vagolytic effects of isoflurane observed to stimulate breathing and genioglossus activity in the rats seem to be less relevant in humans.

Topical anesthesia decreases the response of the genioglossus muscle to negative pressure since nasal trigeminal nerves and the internal branches of the superior laryngeal nerves mediate an important component of the negative pressure reflex. Horner *et al.*[36] achieved a complete anesthesia of the upper airway using high doses of benzocaine, cocaine, and lidocaine administered locally over a long application time.

In our study, low-dose lidocaine was sprayed in the nasopharynx before insertion of a Millar pressure catheter for the subjects' comfort but not for complete topical anesthesia. The first measurements of P_{CLOSE} were conducted 108 ± 26 min after administration of the lidocaine spray. We believe it is unlikely that P_{CLOSE} values reported in our study were affected by local anesthesia of the upper airway in our randomized crossover study.

Our study has some limitations, namely mask occlusion and naturally occurring upper airway collapse are not precisely the same, and it may be possible that mechanoreceptors are more stimulated during mask occlusion compared with more physiologic stimuli. Since we applied the same model of airway occlusion throughout both anesthetic doses and agents, our study allows us to compare the different effects as reliably as possible. Half-life of propofol is 2 to 6 min after injection; however, redistribution half-life is up to 60 min.[37] Despite the long washout period used in our protocol, we cannot exclude the fact that active substances of the first anesthetic were active during measurements of the effects of the second. We are confident that this does not affect the conclusion of our randomized controlled crossover study. We did not conduct polysomnography in our volunteers such that obstructive sleep apnea cannot formally be excluded. However, none of our volunteers reported evidence of sleep apnea during prescreening, and P-SAP did not provide any evidence of a high likelihood of sleep apnea.

Our study has clinical implications. Sevoflurane and propofol both potentiate γ-aminobutyric acid–mediated inhibition.[38] Clinicians using γ-aminobutyric acid–mediated volatile anesthetics and IV anesthetics have to expect a dose-dependent increase in upper airway collapsibility. During procedural sedation when patency of the upper airway is not secured by an airway device, hypoxia may occur despite capnographic monitoring.[39] This supports the view that trained anesthesia providers improve safety of patients undergoing procedural sedation. Of note, the impairing effects of anesthetics on airway patency are still clinically relevant at the end of surgery in the postanesthesia care unit, and treatment with CPAP may help stabilize breathing immediately after anesthesia.[40]

In summary, our data show that propofol and sevoflurane anesthesia dose-dependently and equally increase upper airway collapsibility. These effects of anesthesia on airway collapsibility can in part be explained by dose-dependent inhibiting effects of anesthetics on genioglossus activity.

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Competing Interests

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Reproducible Science

Full protocol available from Dr. Eikermann: meikermann@partners.org. Raw data available from Dr. Eikermann: meikermann@partners.org.

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