Supplemental Carbon Dioxide Stabilizes the Upper Airway in Volunteers Anesthetized with Propofol

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ABSTRACT

Background: Propofol impairs upper airway dilator muscle tone and increases upper airway collapsibility. Preclinical studies show that carbon dioxide decreases propofol-mediated respiratory depression. We studied whether elevation of end-tidal carbon dioxide (PETCO2) via carbon dioxide insufflation reverses the airway collapsibility (primary hypothesis) and impaired genioglossus muscle electromyogram that accompany propofol anesthesia.

Methods: We present a prespecified, secondary analysis of previously published experiments in 12 volunteers breathing via a high-flow respiratory circuit used to control upper airway pressure under propofol anesthesia at two levels, with the deep level titrated to suppression of motor response. Ventilation, mask pressure, negative pharyngeal pressure, upper airway closing pressure, genioglossus electromyogram, bispectral index, and change in end-expiratory lung volume were measured as a function of elevation of PETCO2 above baseline and depth of propofol anesthesia.

Results: PETCO2 augmentation dose-dependently lowered upper airway closing pressure with a decrease of 3.1 cm H2O (95% CI, 2.2 to 3.9; P < 0.001) under deep anesthesia, indicating improved upper airway stability. In parallel, the phasic genioglossus electromyogram increased by 28% (23 to 34; P < 0.001). We found that genioglossus electromyogram activity was a significant modifier of the effect of PETCO2 elevation on closing pressure (P = 0.005 for interaction term).

Conclusions: Upper airway collapsibility induced by propofol anesthesia can be reversed in a dose-dependent manner by insufflation of supplemental carbon dioxide. This effect is at least partly mediated by increased genioglossus muscle activity.

What We Already Know about This Topic

- Propofol increases upper airway collapsibility, resulting in upper airway obstruction, particularly in sedated patients with unprotected airways
- Carbon dioxide stimulates both respiratory pump muscles and upper airway dilator muscles
- No previous study has investigated effects of increasing end-tidal carbon dioxide on propofol-induced increased upper airway collapsibility in humans

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What This Article Tells Us That Is New

- Elevation of end-tidal carbon dioxide by inhalation of carbon dioxide dose-dependently stabilized the airway as evidenced by decrease of upper airway closing pressure under propofol anesthesia in 12 nonobese adult volunteers
- Phasic genioglossus activity dose-dependently increased with supplemental carbon dioxide and was a significant effect modifier for stabilizing the upper airway
- Cortical arousal from anesthesia appeared to partly contribute to upper airway stabilization in the light propofol anesthesia group

VOLATILE anesthetics, propofol, benzodiazepines, and barbiturates increase airway collapsibility in a dose-dependent fashion both during and after anesthesia. Partial upper airway collapse can lead to postoperative respiratory complications such as desaturation, atelectasis, and negative pressure pulmonary edema, which may increase hospitalization time, mortality, and cost. While many anesthetics are administered with artificial airways, such as a laryngeal mask airway or an endotracheal tube, propofol is often administered as a mono-anesthetic without a device that bypasses the collapsible upper airway. Propofol administered during monitored anesthesia care has gained popularity for endoscopy, while for some procedures, propofol sedation is even provided by nonanesthesiologists. While the overall rate of overt sedation-related complications due to propofol during endoscopic procedures appears low, patients who are vulnerable to respiratory complications may suffer from sequelae of increased upper airway collapsibility beyond the immediately observable postintervention period. It is certainly a common experience for the anesthesiologist providing moderate to deep propofol sedation to apply airway maneuvers, such as chin lift and jaw thrust, to maintain airway patency of the patient. This puts patients at risk if airway collapse is not immediately noticed and ties up practitioners’ hands during the case. Given that propofol...
Carbon Dioxide Stabilizes the Upper Airway

In patients with obstructive sleep apnea, inhalation of 3 to 6% CO₂ stimulates upper airway inspiratory muscle tonic and phasic electrical activity and decreases apnea time. Furthermore, experiments in rats demonstrate that propofol-mediated respiratory depression can be reversed by carbon dioxide. In this study, we explore the effects of inspiratory insufflation of carbon dioxide on upper airway collapsibility and genioglossus muscle tone in healthy volunteers under propofol anesthesia. We hypothesized that administration of carbon dioxide targeted to a constant degree of end-tidal carbon dioxide (PETCO₂) elevation above baseline under steady-state propofol anesthesia reduces upper airway collapsibility, in a dose-dependent fashion, as measured by a decrease in upper airway closing pressure. If hypercarbia improves airway stability, it could be further explored as a perioperative therapy.

Materials and Methods

Study Subjects

This study is a prespecified, secondary analysis of a previously performed experimental series, of which two prior analyses have been published, and is registered at clinicaltrials.gov (NCT01557920; supplemental methods described in Supplemental Digital Content, http://links.lww.com/ALN/B716). Following approval by the Partners Human Research committee, Somerville, Massachusetts, subjects were recruited at the Massachusetts General Hospital, Boston, Massachusetts. Volunteers with an American Society of Anesthesiologists physical classification score of I, ages 18 to 45, with a body mass index of 18.5 to 28 kg/m², and no history or physical findings of obstructive sleep apnea were enrolled in a randomized controlled crossover study as previously described. Thirteen of 18 enrolled subjects completed the study, and 12 had an adequate signal to noise ratios for data analysis. See Supplemental Digital Content, http://links.lww.com/ALN/B716, for further details.

Experimental Protocol

Our nested design protocol included three levels of arousal (awake, light anesthesia and deep anesthesia) and three degrees of PETCO₂ elevation: baseline PETCO₂, 4 mmHg above baseline, and 8 mmHg above baseline.

After initial measurements of breathing at atmospheric pressure while awake, anesthesia was induced and maintained with propofol for a mean ± SD duration of 2 h and 44 ± 37 min. Propofol was administered using a target controlled infusion pump (Injectomat TIVA Agilia, Fresenius Kabi, France; see Supplemental Digital Content, http://links.lww.com/ALN/B716, for further details). The initial propofol target plasma concentration was 3.7 µg/ml. The light and deep anesthetic doses were determined from the response to an electrical pain stimulus delivered by a peripheral nerve stimulator (Life-Tech Inc., USA). Propofol dose was increased in increments of 50% until the absence of motor response, or decreased by 50% if there was no response to pain. The individualized light anesthetic level was defined as the propofol dose with a motor response, while the deep anesthetic level was the propofol dose without motor response. Each propofol dose was administered for at least 30 min before recording measurements to ensure that steady-state had been reached. The mean ± SD light and deep propofol anesthesia target blood concentrations were 3.1 ± 0.7 µg/ml and 4.3 ± 0.8 µg/ml, respectively (supplemental methods and table S1, Supplemental Digital Content, http://links.lww.com/ALN/B716).

At each propofol level, subjects underwent a sequence of greater than or equal to 10 consecutive breaths at atmospheric pressure followed by two airway occlusions maneuvers with 7 ± 3 inspiratory attempts (Supplemental Digital Content, http://links.lww.com/ALN/B716). This sequence was repeated at two stepwise increasing PETCO₂ elevations (fig. 1). Between sequences, rescue continuous positive airway pressure was applied if a subject was unable to maintain adequate unassisted breathing. Figure 2 illustrates a typical experimental sequence under deep propofol anesthesia in which continuous positive airway pressure was applied to eliminate flow-limited breathing, continuous positive airway pressure was removed, and occlusion maneuvers were performed at three levels of PETCO₂. The mean ± SD baseline PETCO₂ before carbon dioxide administration was 45.9 ± 8.4 mmHg, and 47.7 ± 12.7 mmHg for light and deep propofol anesthesia, respectively (see table S2, Supplemental Digital Content, http://links.lww.com/ALN/B716, for individual PETCO₂ levels).

Equipment

All measurements were conducted in a research facility equipped with a standard anesthesia workstation (Dräger Medical, USA), automated recordkeeping, resuscitation equipment, and an anesthesiologist dedicated solely to managing the volunteer. Standard monitors were used...
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Fig. 1. Study flow of anesthesia titration and data acquisition. Eighteen subjects were enrolled, and 13 completed the study. After initial recordings at atmospheric pressure while awake, anesthesia was induced with propofol. After 30 min at a constant targeted blood propofol concentration, measurements were conducted at atmospheric pressure and at a given continuous positive airway pressure (CPAP) level. Ten consecutive breaths with three different levels of end-tidal carbon dioxide pressure (PETCO₂) elevation at atmospheric pressure and with CPAP under propofol anesthesia were recorded. Twelve subjects were included in the final analyses. CO₂ + 0 = elevation of PETCO₂ by 0 mmHg; CO₂ + 4 = elevation of PETCO₂ by 4 mmHg, CO₂ + 8 = elevation of PETCO₂ by 8 mmHg.

Measurements

Respiratory airflow was determined using a pneumotachograph. Respiratory rate, inspiratory tidal volume, minute ventilation, peak inspiratory flow, and duty cycle (inspiratory time/total breath time) were calculated from an average of 10 sequential breaths from the respiratory airflow curves. Mask pressure was monitored with a catheter at the inlet of the nasal mask attached to a pressure transducer (Hans Rudolph Inc., USA). Negative pharyngeal pressure was measured at the level of the epiglottis with the intranasal catheter-tip pressure transducer. Upper airway collapse was induced by external airway occlusion. Occlusion maneuvers were performed only during propofol anesthesia. Airway closure can be quantified by measuring the difference between nasal pressure and tracheal pressure during airway occlusion (fig. 2). Closing pressure is defined as the inspiratory mask pressure plateau during occlusion while negative pharyngeal pressure continues to decrease until the end of the inspiratory attempt (fig. 2 inset). PETCO₂ was measured continuously through a port in the nasal mask using a gas analyzer (Datex Ohmeda, Finland). The genioglossus electromyogram signal was rectified and a moving time averaged signal was used. The tonic genioglossus activity baseline was subtracted from peak phasic genioglossus activity during occlusions and normalized to a subject-specific maximal genioglossus electromyogram to obtain genioglossus electromyogram activity as a percent of maximum. The quantitative difference in end-expiratory lung volume between consecutive breaths was measured using respiratory inductive plethysmography. Breaths were excluded in end-expiratory lung volume analysis if the inspiratory volume from respiratory

electrocardiography, pulse oximetry, capnography, and oscillometric blood pressure measurements). Subjects fasted for at least 8 h before the start of the experiment. They were positioned supine on a gel headrest with a 5-cm head elevation and neck flexion (Frankfort plane). One nostril was anesthetized with 4% lidocaine spray and a pressure catheter (Millar Instruments, USA) was inserted while awake with its tip close to the epiglottis. Correct positioning was confirmed by visual oropharyngeal inspection and the characteristic negative pharyngeal pressure peak during swallowing. The breathing circuit is depicted in figure S1 (Supplemental Digital Content, http://links.lww.com/ALN/B716). In brief, subjects wore a nasal mask connected to a high-airflow circuit with positive end-expiratory pressure valves on the inspiratory and expiratory limbs to deliver continuous positive airway pressure. The mouth was sealed with Tegaderm (3M, USA) after loss of consciousness to avoid oral breathing. The inspiratory limb of the circuit included an air humidifier and an inflatable balloon occlusion valve (Hans Rudolph Inc., USA) to perform external airway occlusions by preventing inspiratory flow while allowing expiration. The fraction of inspired oxygen was maintained at 0.5. A 100% carbon dioxide tank side-streamed to the inspiratory limb of the breathing circuit permitted steady-state PETCO₂ to be increased by 4 or 8 mmHg above baseline. Two 27-gauge stainless steel wire electrodes were inserted into the genioglossus muscle transcutaneously while the volunteer was awake and referenced to a sternal ground electrode. Correct placement was confirmed by an increase in activity during inspiration and an electromyogram activity burst when the volunteers pressed the genioglossus against their teeth. A respiratory inductive plethysmography device (LifeShirt200, VivoMetrics, USA) was fitted around the volunteers’ thorax and abdomen and calibrated per the manufacturer’s instructions (fig. 1, Supplemental Digital Content, http://links.lww.com/ALN/B716).
inductive plethysmography and gold-standard spirometry had a correlation factor of less than 0.8, if unreasonably high inspiratory volumes of more than 3,500 ml were measured by respiratory inductive plethysmography (consistent with a movement artifact), or if the respiratory inductive plethysmography recording was of obvious poor quality. During a period of breathing in which continuous positive airway pressure was either applied or removed, interbreath quantitative difference in end-expiratory lung volume were added until the summation reached a plateau, typically over more than five breaths, to obtain the total change in end-expiratory lung volume ($\Delta_{\text{end-expiratory lung volume}}$) that occurred due to a change in airway pressure ($\Delta_{\text{continuous positive airway pressure}}$). The $\Delta_{\text{end-expiratory lung volume}}$ was then normalized to $\Delta_{\text{continuous positive airway pressure}}$ to obtain $\Delta_{\text{end-expiratory lung volume}}/\Delta_{\text{continuous positive airway pressure}}$ (ml/cm H$_2$O). The bispectral index (BIS) was recorded in 1 min intervals throughout the experiment in an electronic anesthesia record (MetaVision, iMDsoft, USA).

Data regarding mask pressure, epiglottic pressure, and ventilatory flow were collected in Labchart (AD Instruments, USA) with a sample rate of 20,000 Hz. The genioglossus muscle electromyography signal was band-pass filtered (200 to 1,000 Hz, transition width 40 Hz) and a moving time average (time constant 100 ms) was created. BIS data was extracted from MetaVision. Data from the respiratory inductive plethysmography was reported by VivoLogic (VivoMetrics, Inc., USA). All the data were organized in Excel (Microsoft, USA). Statistical analysis was performed using STATA IC 14 (StataCorp LLC, USA) and SPSS 23.0 (SPSS Inc., USA).

**Statistical Analysis**

Our primary endpoint was closing pressure and our secondary endpoint was phasic genioglossus activity. To test our primary hypothesis that PETCO$_2$ elevation via carbon dioxide insufflation decreases closing pressure (i.e., stabilizes the airway) under propofol anesthesia, we applied a linear mixed effects model with volunteers’ identification as random intercepts. Closing pressure was dependent on the degree of PETCO$_2$ elevation and depth of anesthesia as fixed effects. We also tested an interaction term between PETCO$_2$ and anesthetic depth as a fixed effect on closing pressure and conducted post hoc pairwise comparisons using Bonferroni adjustment to compare the effect of subgroups of PETCO$_2$ elevation (three comparison groups; baseline PETCO$_2$, 4 mmHg PETCO$_2$ elevation, and 8 mmHg PETCO$_2$ elevation) and anesthetic depth (two groups: light vs. deep anesthesia) on closing pressure. We analyzed our secondary endpoint of genioglossus activity in a similar fashion using a linear mixed effects model with the same fixed effects, random intercepts model, and post hoc as for the primary analysis. Data from 12 volunteers was included in analysis of closing pressure and of nine volunteers in analysis.
of genioglossus activity. Closing pressure was by necessity analyzed during airway occlusion maneuvers leading to full airway collapse. Genioglossus activity was analyzed for all breaths, and during airway occlusion maneuvers. The modification of genioglossus activity on the effect of PETCO2 elevation on closing pressure was explored with a linear mixed effects model of closing pressure by the fixed effects of carbon dioxide with genioglossus activity as a continuous variable during occlusion maneuvers leading to airway collapse.

Several other analyses were conducted with an exploratory intent, utilizing linear mixed effects models as for our primary endpoint. To better understand the effect of carbon dioxide and stimulus-guided propofol concentration on processed electroencephalogram output, we tested for a fixed effect of PETCO2 elevation, anesthetic depth, and their interaction term on BIS. We similarly explored negative pharyngeal pressure, Δ end-expiratory lung volume/Δ continuous positive airway pressure, and breathing variables using the same linear mixed effects model approach with the same fixed effects and post hoc analysis. With an intent to explore the effect modification of genioglossus activity by negative pharyngeal pressure, we performed a linear mixed effects model of phasic genioglossus activity by the fixed effect of negative pharyngeal pressure as a continuous variable. BIS and negative pharyngeal pressure were analyzed for occlusion maneuvers which collapsed the airway as this was a strong arousal stimulus. For analysis of breathing variables, unassisted breaths before occlusion maneuvers were used.

Our power analysis was based on previously published data. We expected a difference in closing pressure (between baseline PETCO2, and elevation by 8 mmHg) of 2 cm H2O with a SD of 2 cm H2O. By using paired t tests, we calculated that data from 10 volunteers would provide greater than 80% power to identify a significant dose-dependent difference in closing pressure between different degrees of PETCO2 elevation at an alpha error of 0.05. We thus expected that our preexisting dataset from 12 volunteers would provide an adequate number of measurements to proceed with further analysis.

Data are presented as mean ± SD, or estimated marginal mean (95% CI) for modeled data. A two-tailed P value of less than 0.05 was considered statistically significant.

Results

Participants in the study had a low-risk of obstructive sleep apnea by STOP-Bang score, were 58% male, age 24 ± 3 yr, height 1.7 ± 0.1 m, weight 70 ± 13 kg, and BMI 23 ± 2 kg/m2 (table S3, Supplemental Digital Content, http://links.lww.com/ALN/B716).

Effect of PETCO2 Elevation and Depth of Propofol Anesthesia on Upper Airway Closing Pressure (Primary Endpoint)

Inspiratory attempts during occlusion maneuvers leading to airway collapse were analyzed under light and deep propofol anesthesia, and three levels of PETCO2 elevation. Insufflation of supplemental carbon dioxide to raise PETCO2 significantly improves closing pressure (fixed effect of PETCO2 elevation on closing pressure; P < 0.001) in a dose-dependent fashion (fig. 3, A and B; tables S4 and S5, Supplemental Digital Content, http://links.lww.com/ALN/B716). Propofol anesthetic depth and an interaction term between PETCO2 elevation and anesthetic depth also have a significant fixed effect on closing pressure (P < 0.001 and P = 0.044, respectively). We obtained pairwise comparisons of the effect of various levels of PETCO2 elevation and anesthetic depths on closing pressure via post hoc analyses. Under both propofol conditions, PETCO2 by 8 mmHg conferred airway stabilization compared to baseline PETCO2 with a mean modeled decrease in closing pressure of 1.8 cm H2O (95% CI, 0.6 to 3.0; P = 0.01) and 3.1 cm H2O (2.2 to 3.9; P = 0.001) for light and deep propofol anesthesia, respectively. For all three PETCO2 levels, a less negative closing pressure was observed under deep versus light anesthesia for the same PETCO2 elevation, indicating airway destabilization with a deeper level of anesthesia.

Phasic Genioglossus Activity during Airway Occlusion (Secondary Endpoint)

During occlusion of the airway circuit, phasic genioglossus activity increases during inspiratory attempts (fig. 2). PETCO2 elevation significantly increases mean phasic genioglossus activity in percentage as a function of end-tidal carbon dioxide pressure (PETCO2) elevation and anesthetic depth. P CLOSE and normalized phasic genioglossus activity as a percent of maximum (GG-EMG) as a function of 3 PETCO2 elevation levels under light anesthesia (A, C) and deep anesthesia (B, D), respectively. P CLOSE was measured during evoked airway collapse in 12 volunteers and GG-EMG was measured during all breaths in nine volunteers. Means ± SD are shown. Significant difference between groups (P < 0.05) is indicated by asterisk and was determined by mixed modeling. CO2 + 0 = elevation of PETCO2 by 0 mmHg; CO2 + 4 = elevation of PETCO2 by 4 mmHg; CO2 + 8 = elevation of PETCO2 by 8 mmHg.
activity during airway collapse (fixed effect of $P_{ETCO_2}$ elevation level on genioglossus muscle electromyography; $P < 0.001$) in a dose-dependent fashion (table S4 and S5, Supplemental Digital Content, http://links.lww.com/ALN/B716). We see the same result when all breaths are included in the analysis, regardless of whether there is airway occlusion (fig. 3, C and D). Deeper propofol anesthesia decreases genioglossus activity ($P < 0.001$). Carbon dioxide supplementation mitigates this effect of propofol on genioglossus activity ($P < 0.001$ for the interaction term between $P_{ETCO_2}$ elevation level and propofol anesthetic depth). At the highest level of $P_{ETCO_2}$ (elevation by 8 mmHg), genioglossus activity increased by a mean of 7% (95% CI, 3 to 11) and 19% (16 to 23) for light and deep propofol anesthesia, respectively ($P < 0.001$ for both; fig. 3, C and D). Using linear mixed models of our measurements of closing pressure and genioglossus activity during occlusion maneuvers resulting in airway collapse, we found that phasic genioglossus activity is a significant modifier of the effect of $P_{ETCO_2}$ elevation on closing pressure ($P = 0.005$; fixed effect of interaction term $P_{ETCO_2} \times$ genioglossus).

Exploratory Analyses

BIS Activity with Carbon Dioxide Insufflation under Anesthesia. We explored whether supplemental carbon dioxide improves airway patency and genioglossus activity simply by increasing cortical arousal. $P_{ETCO_2}$ elevation, depth of propofol anesthesia, and their interaction term have a significant fixed effect on BIS ($P < 0.001$ for all). As expected, for each $P_{ETCO_2}$ condition, BIS was significantly lower (i.e., deeper level of anesthesia) under high-dose propofol compared to low-dose propofol with a mean modeled decrease of 8.3 (95% CI, 6.8 to 9.7), 8.6 (7.2 to 10.0), and 15.2 (13.4 to 16.9) for baseline $P_{ETCO_2}$, 4 mmHg $P_{ETCO_2}$ elevation, and 8 mmHg $P_{ETCO_2}$ elevation, respectively ($P < 0.001$ for all three). Under light propofol anesthesia, BIS increased dose-dependently with $P_{ETCO_2}$ elevation, with 8 mmHg $P_{ETCO_2}$ elevation raising BIS by 6.9 (5.0 to 8.7) compared to baseline $P_{ETCO_2}$ ($P < 0.001$), indicating a cortical arousal effect of carbon dioxide during light propofol anesthesia. In contrast, under deep propofol anesthesia, BIS did not significantly change with $P_{ETCO_2}$ manipulation (fig. 4; table S5, Supplemental Digital Content, http://links.lww.com/ALN/B716). Therefore, $P_{ETCO_2}$ elevation may cause some of its airway stabilizing benefits by increasing cortical arousal in lightly anesthetized individuals, but not under deeper anesthetic conditions.

Negative Pharyngeal Pressure Variation with Different $P_{ETCO_2}$ Conditions. We explored the effects of $P_{ETCO_2}$ elevation on negative pharyngeal pressure under different propofol conditions. $P_{ETCO_2}$ elevation, depth of propofol anesthesia, and their interaction term have a significant fixed effect on negative pharyngeal pressure ($P < 0.001$ for all). Negative pharyngeal pressure dose-dependently decreased during airway collapse with insufflation of supplemental carbon dioxide (fig. 5; table S5, Supplemental Digital Content, http://links.lww.com/ALN/B716).

Phasic Genioglossus Activity as a Function of Different Negative Pharyngeal Pressure Levels. To explore if the increase in genioglossus activity we see with $P_{ETCO_2}$ elevation may be partly explained by changes in negative pharyngeal pressure, we studied the association between change in genioglossus activity and change in negative pharyngeal pressure. Negative pharyngeal pressure has a significant fixed effect on genioglossus activity ($P < 0.001$). When negative pharyngeal pressure is divided into quintiles, genioglossus activity increases as negative pharyngeal pressure becomes more negative (fig. S2, Supplemental Digital Content, http://links.lww.com/ALN/B716).

Effect of $P_{ETCO_2}$ Elevation on Change in End-expiratory Lung Volume. We analyzed the end-expiratory lung volume change during transitions between continuous positive airway pressure and atmospheric pressure in our experiment and found that the change in end-expiratory lung volume per change in cm H$_2$O continuous positive airway pressure ($\Delta$ end-expiratory lung volume/$\Delta$ continuous positive airway pressure) averaged 50 ± 29 ml/cm H$_2$O. The value was similar whether continuous positive airway pressure was being turned on or off (51 ± 33 vs. 48 ± 25 ml/cm H$_2$O). We next explored whether elevation of $P_{ETCO_2}$ affects the magnitude of $\Delta$ end-expiratory lung volume/$\Delta$ continuous positive airway pressure. When analyzed as pooled data, or differentiated into continuous positive airway pressure–on and continuous positive airway pressure–off subgroups, we did not find a significant change in $\Delta$ end-expiratory lung volume/$\Delta$ continuous positive airway pressure for different levels of $P_{ETCO_2}$ elevation.

Ventilatory Variables as a Function of $P_{ETCO_2}$ Elevation and Depth of Propofol Anesthesia. From periods of steady breathing without continuous positive airway pressure or occlusion maneuvers, ventilatory variables were measured, including minute ventilation, duty cycle, and peak
Discussion

Our data show that moderate elevation of P_{ETCO2} by exogenous carbon dioxide administration stabilizes airway patency in a dose-dependent fashion under light and deep propofol anesthesia. This can partly be explained by a stimulating effect of elevated P_{ETCO2} on upper airway dilator muscle activity, as genioglossus activity is a significant modifier of the effect of P_{ETCO2} elevation on closing pressure.

Our findings are consistent with canine models, where hypercarbia decreases critical closing pressure and upper airway resistance (stabilizing the airway). Under both light and deep propofol anesthesia, phasic genioglossus activity dose-dependently increased with elevation of P_{ETCO2}. This is consistent with our previous work in rats, where supplemental carbon dioxide increased phasic genioglossus activity during propofol anesthesia. Increased genioglossus activity with hypercarbia has likewise been found in healthy subjects during non–rapid eye movement sleep and wakefulness.

Given that propofol dose-dependently destabilizes the upper airway in parallel with its depressing effects on consciousness, we hypothesized that airway stabilization via inhaled carbon dioxide may be partly due to hypercapnia-mediated arousal causing an effectively lighter plane of anesthesia. We show that carbon dioxide inhalation increased BIS values under light anesthesia. This is concordant with findings showing that rebreathing 7% CO\textsubscript{2} during sleep results in increased wakefulness at an alveolar carbon dioxide pressure between 55 to 65 mmHg. Likewise, during dexmedetomidine sedation, which has some resemblance to deep hypercarbia induced by rebreathing 5% CO\textsubscript{2} results in cortical arousal, as measured by an increased BIS and cessation of a slow-wave sleep pattern in the electroencephalogram. Though the absolute value of BIS has questionable utility, in a given patient, deepening propofol anesthesia as measured by the Observer’s Assessment of Alertness/Sedation Scale score results in lower BIS. While light propofol anesthesia is distinct to sleep, our results in the light propofol anesthesia group are consistent with the hypercapnic
ventilatory wakefulness (cortical arousal) response that occurs during natural sleep and dexamethasone sedation.

Propofol not only affects upper airway stability, but also depresses the hypoxic ventilatory response. In our study, we can exclude hypoxia-mediated increase in the drive to the upper airway dilator genioglossus muscle, since we applied hypoxia throughout the experiment. Rather, stimulation of carotid body chemoreceptors by carbon dioxide may in part explain the observed increase in minute ventilation and respiratory arousal via activation of the nucleus tractus solitarius. Perhaps more importantly, some of the effects of carbon dioxide inhalation on arousal and genioglossus activity may be directly explained by the increased level of (mechanical) inspiratory effort. Prior work in healthy subjects has shown that arousal to a variety of respiratory stimuli (hypercapnia, hypoxemia, and resistive loading) occurs at a similar level of negative intrathoracic pressure. When negative pharyngeal pressure is eliminated by application of nasal continuous positive airway pressure in humans during non–rapid eye movement sleep, hypercarbia-mediated dilator muscle activation is attenuated, which suggests that afferents from respiratory mechnoreceptors or central respiratory drive play an important role in the arousal mechanism. In our study, we observed dose-dependent effects of hypercarbia on hypopharyngeal pressure during inspiration toward more negative values—up to 7.8 cm H2O more negative with elevation of PETCO2 by 8 mmHg. The decrease in pharyngeal pressure represents a mechanical arousal stimulus and is known to activate the genioglossus muscle via the premotoneurons in the perireticular region.

Another respiratory variable influencing upper airway patency is the end-expiratory lung volume, and greater end-expiratory lung volume correlates with airway stabilization in sleeping obstructive sleep apnea patients, while lowering the lung volume has been associated with greater genioglossus responsiveness to negative pharyngeal pressure in sleeping healthy volunteers. We found that end-expiratory lung volume increases with continuous positive airway pressure and decreases with continuous positive airway pressure removal, however, Δ end-expiratory lung volume/Δ continuous positive airway pressure did not significantly change with supplemental carbon dioxide. Thus, we did not find that changes in end-expiratory lung volume contribute to carbon dioxide mediated stabilization of the upper airway under propofol anesthesia.

Carbon dioxide has long been known to stimulate the respiratory system via central and peripheral chemoreflexes, and the ventilatory sensitivity to carbon dioxide, which determines the apneic threshold is altered by many factors. In obstructive sleep apnea, supplemental carbon dioxide decreases apnea time. We found that during spontaneous breathing without flow limitation or obstruction, both in awake subjects and under propofol anesthesia, carbon dioxide increases minute ventilation, as expected. In obstructive sleep apnea, mild to moderate flow limitation can be compensated for by an increase in duty cycle, or during severe obstruction, with an increase in peak inspiratory flow. We do not find significant changes in duty cycle or peak inspiratory flow with PETCO2 elevation during breaths without flow-limitation or occlusion. Thus, the protective mechanisms compensating for airway collapse during sleep in obstructive sleep apnea patients may be distinct to the airway stabilizing effects of hypercarbia in healthy volunteers under propofol anesthesia.

While this study shows a role for hypercarbia to reverse the dose-dependent airway instability caused by propofol anesthesia, it has several limitations. First, we studied healthy volunteers, and it is unclear how our results translate to the population particularly prone to airway collapse, namely those who are obese and have sleep apnea. Our study also employed a pure propofol anesthetic, however, in many clinical scenarios where propofol is used without an artificial airway, benzodiazepines and opioids are sometimes used and we don’t know how these agents would impact our findings. Furthermore, the pain level we elicited with an electrical stimulus may not reflect the level of discomfort experienced by patients during a surgical procedure and thus our deep anesthesia level may not correspond to deep anesthetic levels used during certain surgical procedures. A small pH shift presumably occurred from hypercarbia; whether our effects were primarily a carbon dioxide or pH-mediated effect could also be explored in future studies. Evidence in animals and humans suggests that propofol modulates the ventilatory response primarily via central rather than peripheral effects. A functional magnetic resonance imaging approach could help further elucidate how much cortical versus brainstem-mediated arousal contributes to the effects we see.

In conclusion, increasing PETCO2 with supplemental carbon dioxide dose-dependently stabilizes the airway (decreases closing pressure) under propofol anesthesia. This airway stabilization is likely due to improved phasic genioglossus activity, as genioglossus activity dose-dependently increases with supplemental carbon dioxide, and genioglossus activity is a significant modifier of the effect of PETCO2 elevation on closing pressure. Under light propofol anesthesia, these effects may be mediated in part by cortical arousal from anesthesia, while under deep propofol anesthesia, airway stabilization may occur independently of cortical arousal. Deliberate elevation of PETCO2 with supplemental carbon dioxide during propofol anesthesia improves airway stability and should be further explored as a potential perioperative therapy.

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Competing Interests

The authors declare no competing interests.

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