Anesthesia and Increased Hypercarbic Drive Impair the Coordination between Breathing and Swallowing

Olivia M. D'Angelo, B.S., Daniel Diaz-Gil, Cand. Med., Danuza Nunn, M.S.-C.C.C.-S.L.P.,
Jeroen C. P. Simons, Cand. Med., Chloe Gianatasio, Noomi Mueller, Cand. Med.,
Matthew J. Meyer, M.D., Eric Pierce, M.D., Ph.D., Carl Rosow, M.D., Ph.D.,
Matthias Eikermann, M.D., Ph.D.

ABSTRACT

Background: Coordination between breathing and swallowing helps prevent aspiration of foreign material into the respiratory tract. The authors examined the effects of anesthesia and hypercapnia on swallowing–breathing coordination.

Methods: In a randomized controlled crossover study, general anesthesia with propofol or sevoflurane was titrated using an up-down method to identify the threshold for suppression of the motor response to electrical stimulation of the forearm. Additional measurements included bispectral index, genioglossus electromyogram, ventilation (pneumotachometer), and hypopharyngeal pressure. During wakefulness and at each level of anesthesia, carbon dioxide was added to increase the end-tidal pressure by 4 and 8 mmHg. A swallow was defined as increased genioglossus activity with deglutition apnea and an increase in hypopharyngeal pressure. Spontaneous swallows were categorized as physiological (during expiration or followed by expiration) or pathological (during inspiration or followed by an inspiration).

Results: A total of 224 swallows were analyzed. Anesthesia increased the proportion of pathological swallows (25.9% *vs.* 4.9%) and decreased the number of swallows per hour (1.7 ± 3.3 *vs.* 28.0 ± 22.3) compared to wakefulness. During anesthesia, hypercapnia decreased hypopharyngeal pressure during inspiration (-14.1 ± 3.7 *vs.* -8.7 ± 2 mmHg) and increased minute ventilation, the proportion of pathological swallows (19.1% *vs.* 12.3%), and the number of swallows per hour (5.5 ± 17.0 *vs.* 1.3 ± 5.5).

Conclusions: Anesthesia impaired the coordination between swallowing and respiration. Mild hypercapnia increased the frequency of swallowing during anesthesia and the likelihood of pathological swallowing. During anesthesia, the risk for aspiration may be further increased when ventilatory drive is stimulated. (**ANESTHESIOLOGY** 2014; 121:1175-83)

THE coordination between breathing and swallowing is important to prevent the aspiration of foreign material into the respiratory tract.[1] In healthy, awake adults, swallowing occurs during or immediately before the expiratory phase of respiration.[2,3] However, in patients with neurodegenerative diseases[4,5] and chronic obstructive pulmonary disease,[6] impaired coordination between breathing and swallowing has been observed, characterized by inspiration after swallowing. This pathological swallowing pattern is associated with an increased risk for aspiration.[7]

Anesthesia is associated with a higher risk of aspiration compared to wakefulness,[8] and one purpose of this study was to evaluate whether general anesthesia, like neurodegenerative or respiratory diseases, can impair the coordination between breathing and swallowing. Previous studies have shown that a hypercapnia-induced increase in ventilatory drive can inhibit airway protective reflexes, similar to the effect of anesthetics.[9] In addition, hypercapnia disrupts the physiological coordination between swallowing and breathing.[10] Since variable levels of hypercapnia occur during anesthesia, an additional

> **What We Already Know about This Topic**
>
> - Anesthesia is associated with a higher risk of aspiration compared to wakefulness
> - The coordination between breathing and swallowing is important to prevent the aspiration of foreign material into the respiratory tract
> - Hypercapnia disrupts the physiological coordination between swallowing and breathing
>
> **What This Article Tells Us That Is New**
>
> - In a pharmacophysiological interaction trial in healthy volunteers, this study demonstrated that compared to wakefulness, sevoflurane and propofol anesthesia decreased spontaneous swallowing frequency (28.0 ± 22.3 *vs.* 1.7 ± 3.3 per hour) and increased proportion of pathological swallows (swallowing during inspiration or followed by an inspiration) (4.9 vs. 25.9%)
> - Mild hypercapnia under general anesthesia augmented this pattern of swallowing impairment
> - During sedation and anesthesia, risk for aspiration may be further increased when ventilatory drive is stimulated

question of interest was whether hypercapnia during anesthesia further impairs the coordination of breathing

---

This article is featured in "This Month in Anesthesiology," page 1A. The first two authors made equal contributions to the manuscript.

and swallowing compared with the effects of anesthesia alone. We hypothesized that:

1. Propofol or sevoflurane anesthesia increases the proportion of pathological swallows compared to the awake state.
2. The administration of carbon dioxide during anesthesia further increases the proportion of pathological swallows.

Materials and Methods

Subjects

After approval by the Partners Human Research Committee (Boston, MA), 11 American Society of Anesthesiologists 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 advertisement to employees at Massachusetts General Hospital. Eligible subjects were 18 to 45 with a body mass index of 18.5 to 28 kg/m^2 and with no history of dysphagia. Before enrollment, a preliminary history and physical was performed. All experiments were conducted at Massachusetts General Hospital in a research facility that was hospital-certified as an anesthetizing location. The study area was equipped with a standard anesthesia workstation with automated record keeping and resuscitation equipment.

Propofol was administered to target concentrations using a Fresenius target controlled infusion pump (Injectomat TIVA Agilia; Fresenius Kabi, Brezins, France). Two board-certified anesthesiologists were present for the duration of each experiment, and one of them was assigned to monitor and care for the subject as his only responsibility. All subjects received standard anesthesia monitoring (electrocardiogram, pulse oximetry, capnography, and oscillometric blood pressure measurements).

Equipment and Techniques

For measurements of genioglossus activity, breathing, and upper airway closing pressure, subjects were prepared as described previously.[11] Briefly, one nostril was decongested with oxymetazoline and anesthetized with 4% lidocaine spray before insertion of a Millar pressure catheter (Millar Instruments, Houston, TX) nasally into the hypopharyngeal area. Correct placement was confirmed visually (oropharyngeal inspection) and by confirmation of 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 mask (Philips Respironics, Murrysville, PA) which was connected to a high-flow anesthesia circuit. For measurement of electromyogram, two 30-mm needles were used to insert 27-gauge stainless steel wire electrodes into the genioglossus muscle transcutaneously, as described previously.[12] These electrodes were referenced to a ground electrode on the sternum.

The genioglossus electromyogram signal was filtered with a band-pass filter (200 to 1,000 Hz, transition width 40 Hz) and displayed as a moving time average (time constant 100 ms). Both the raw signal and moving time average were recorded for the duration of the experiment. Correct placement of the genioglossus electromyogram electrodes was confirmed by an increase in activity during inspiration and a burst in electromyogram activity upon asking the subject to press her tongue against her teeth.

Ventilatory flow was measured with a pneumotachograph (Hans Rudolph, Kansas City, MO), and tidal volume was obtained by electrical integration of the inspiratory flow signal. End-tidal P_{CO_2} (P_{ETCO_2}) was measured through a port in the nasal mask. A 100% carbon dioxide tank attached to the inspiratory limb of the breathing circuit permitted steady-state P_{ETCO_2} to be increased by 4 or 8 mmHg above baseline. All data were recorded, processed, and filtered using Lab-Chart software (AD Instruments, Colorado Springs, CO). Anesthetic sedative effects were measured with the bispectral index (Covidien, Boston, MA) using a smoothing window of 15 s and recorded at 1 min intervals.

Experimental Protocol

Subjects were fasted for at least 8 h before the start of the experiment. The study was a randomized-crossover study, with nested design. Each subject received propofol and sevoflurane sequentially, randomized for order. The nested design specified three anesthetic conditions (wakefulness, propofol, and sevoflurane); three P_{ETCO_2} conditions (baseline; +4 mmHg; and +8 mmHg); and two depths of anesthesia (high and low) (fig. 1). Measurements of spontaneous swallowing (see Measurements below) were recorded under each condition. The initial measurements during wakefulness were made with no added carbon dioxide in the breathing circuit. Then carbon dioxide was introduced to obtain stable elevations of 4, then 8, mmHg in P_{ETCO_2}. Subjects were then randomized to receive either propofol or sevoflurane first. 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[13] or sevoflurane end-tidal concentration of 1.5%.[14] The anesthetic was administered for 30 min to ensure that the central nervous system reached approximate steady state. A 30 mA tetanic nerve stimulus was applied to the forearm using a peripheral nerve stimulator (Life-Tech, Inc., Stafford, TX), and presence or absence of a motor response was noted. If the subject moved the head or extremities (excluding the stimulated arm), the concentration was increased in 50% increments until a concentration was found that just produced absence of motor response. 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 higher or lower. There were no more than three pain
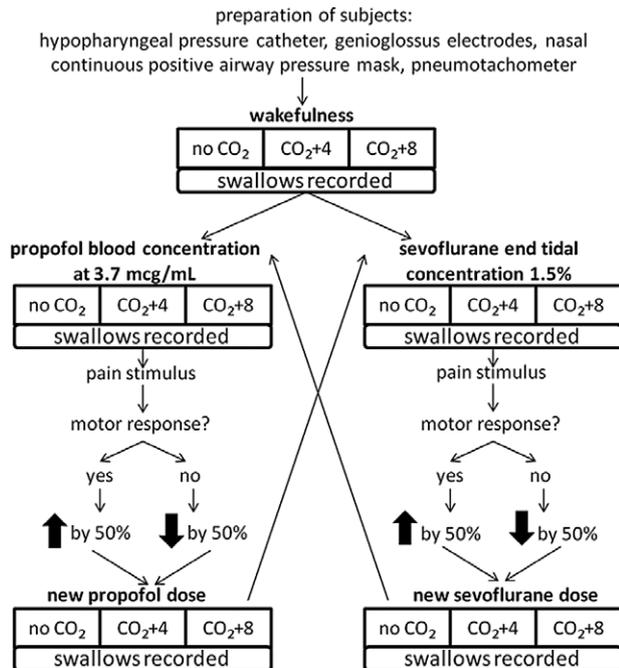
Fig. 1. Protocol design. Baseline measurements were recorded during wakefulness and at three different levels of carbon dioxide (CO_2; 0, +4, and +8 mmHg elevations above baseline). Subjects were then randomized for order to receive either propofol or sevoflurane first, starting at the same dose (estimated ED_{50}) for each volunteer. To establish similar levels of shallow and deep anesthesia for each volunteer, a pain stimulus was applied to assess the depth of anesthesia. Depending on the response, the dosage was increased or decreased by 50% to arrive at a new dose of the drug. The same three levels of carbon dioxide (+0, +4, and +8 mmHg) were applied during anesthesia. Spontaneous swallows were recorded during all conditions.

stimuli applied to one subject to reach two distinct depths of anesthesia. The second concentration of anesthesia was also targeted for 30 min to ensure that the central nervous system reached steady state. At both levels of anesthesia, swallowing measurements were made without added carbon dioxide or with increases of 4 and 8 mmHg.

Measurements

The presence of a spontaneous swallow was identified by all of the following three criteria:

1. Rapid increase in the genioglossus electromyogram moving time average of at least 200% above tonic baseline
2. Rapid increase of hypopharyngeal pressure of 15 cm H_2O or more
3. Deglutition apnea

In a pilot study, the methodology was validated with electroglottography, a clinical tool used to detect changes in glottic impedance.[15] Electroglottography changes indicate laryngeal movement that occurs during swallowing.[15] The timing of

respiration and swallowing was determined as previously described.[10] Expiratory swallows (E) were preceded and followed by expiratory flow; inspiratory–expiratory (I–E) swallows were preceded by inspiratory flow and followed by expiratory flow; inspiratory swallows (I) were preceded and followed by inspiratory flow; and expiratory–inspiratory (E–I) swallows were preceded by expiratory flow and followed by inspiratory flow. We further categorized swallows into physiological or pathological. Physiological swallows were followed by expiratory flow (E or I–E). Pathological swallows were followed by inspiration (I and E–I), and termed "pathological" because I and E–I swallows present a higher risk for aspiration[7] (fig. 2).

To analyze the effects of anesthesia and hypercapnia on respiration, a breath-by-breath analysis was conducted on the five breaths before and after each swallow. Tidal volume was calculated as the integral of the flow signal. Respiratory rate and minute ventilation were calculated by averaging the values from the five breaths before and after each swallow. To examine the effect of carbon dioxide on the pharyngeal pressure generated during inspiration, we measured the maximum pharyngeal pressure during expiration and minimum pharyngeal pressure during inspiration and calculated the difference.

Statistical Analysis

The primary aim of this study was to evaluate the effects of anesthesia (propofol and sevoflurane) on the proportion of pathological swallows. This was expressed as a percentage of total spontaneous swallows. The secondary aim was to evaluate the effect of adding carbon dioxide during anesthesia on the proportion of pathological swallows. To test the hypothesis that anesthesia increases the proportion of pathological swallows, we included all measurements of swallows across anesthetic state (wakefulness vs. anesthesia), doses (awake, low, and high), and carbon dioxide levels (0, 4, and 8 mmHg above baseline). We created a mixed linear model (compound symmetry repeated covariance type) to test our hypothesis and modeled a binominal distribution with a logit link.

To evaluate the effect of general anesthesia on the proportion of pathological swallows, we modeled a binominal distribution with a logit link and included anesthetic state (anesthesia vs. wakefulness), anesthetic dose (shallow vs. deep), and carbon dioxide level (0, 4, and 8 mmHg above baseline) as repeated independent variables. The type of swallow (pathological vs. physiological) was the dependent variable. In addition to testing the main effect of anesthesia on the proportion of pathological swallows, we also tested the main effect of bispectral index values. To address the secondary aim, we tested for an interaction between anesthesia and hypercapnia on the proportion of pathological swallows using the same mixed model modeled with a binominal distribution with logit link. For testing the secondary hypothesis, we adjusted the P value (Bonferroni–Holm).
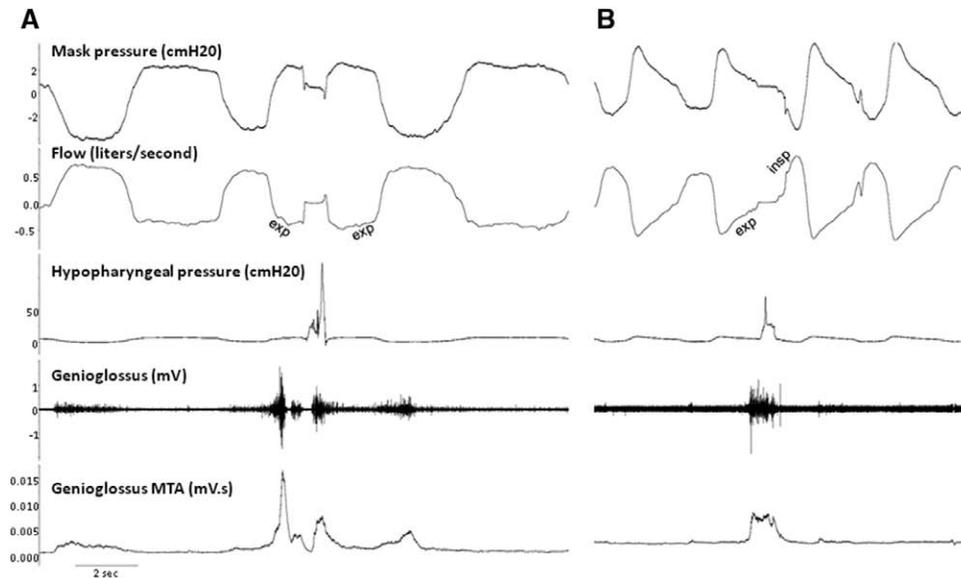
Fig. 2. Experimental recordings of physiological and pathological swallows during wakefulness and anesthesia. The proportion of spontaneous swallows was indicated by an increase of genioglossus activity by at least 200%, along with an increase in hypopharyngeal pressure by at least 15 cm H_2O, and deglutition apnea. (*A*) Expiratory swallow during wakefulness. (*B*) Pathological expiratory–inspiratory swallow during propofol anesthesia. Exp = expiratory flow, insp = inspiratory flow; MTA = moving time average.

All other comparisons were made with an exploratory intention. We used the same mixed model to evaluate the main effect of pharyngeal pressure generated during inspiration on type of swallow. To evaluate the effects of anesthesia and hypercapnia during anesthesia on respiratory rate, minute ventilation, and the frequency of spontaneous swallows (expressed as swallows per hour), we used the same linear mixed model but modeled a normal distribution with an identity link function. The statistical analyses for respiratory rate and minute ventilation were conducted as described for the primary outcome. To address the effect of carbon dioxide during anesthesia on swallows per hour, we weighted the residual for number of swallows. To examine the relationship between respiratory rate and pathological swallows, we used Spearman nonparametric correlation analysis.

For our prospective power analysis, we used preliminary data to project a 10% difference in the fraction (in percent) of pathological swallows during anesthesia compared with wakefulness, with a standard deviation of 10%. Based on these assumptions, we calculated by using a paired t test that 11 volunteers would provide us with a power greater than 0.8 to 0.84 to identify a difference in pathological swallowing rate between wakefulness and anesthesia at alpha error P of 5%. Data are presented as percentage of total for primary outcome and mean ± SD for other outcomes. Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL).

Results

A total of 224 spontaneous swallows from 11 American Society of Anesthesiologists I healthy volunteers (age 24.3 ± 3.3, body mass index 23.7 ± 1.8) were observed. Of

the spontaneous swallows, 196 (87.5%) were physiological, and 28 (12.5%) were pathological. In this study, we titrated to two different levels of propofol and sevoflurane anesthesia, defined by a response *versus* absence of response to a pain stimulus, and the corresponding level of consciousness was also evaluated by using bispectral index. There was no significant difference in bispectral index values between propofol and sevoflurane.

Primary Aim: Effects of Anesthesia on the Proportion of Pathological Swallows

Anesthesia was associated with a significantly higher proportion and occurrence of pathological swallows compared to wakefulness (25.9 *vs.* 4.9%, $P = 0.001$, fig. 3A and 21 *vs.* 7 swallows, table 1). Lower bispectral index levels indicating lower level of consciousness were associated with a higher proportion of pathological swallows ($P = 0.01$, fig. 3B). There was no difference in the proportion of pathological swallows between propofol and sevoflurane (31.1 *vs.* 10%, $P = 0.241$). Pathological swallows occurred with a slightly higher proportion at the low dose of anesthesia compared to high dose (28.4 *vs.* 14.3%, $P = 0.153$), but this difference was not significant statistically. Under propofol anesthesia, the proportion of pathological swallows was slightly higher at lower doses compared to the high dose (36.2 *vs.* 14.3%, $P = 0.062$), but this difference was not significant statistically. No swallows occurred during the deep level of sevoflurane. Respiratory rate was higher during anesthesia compared to wakefulness (19.8 ± 2.1 *vs.* 14.9 ± 3.6, $P < 0.001$), although minute ventilation did not differ. This observed increase in respiratory rate was positively correlated with the proportion of pathological swallows ($P = 0.02$).
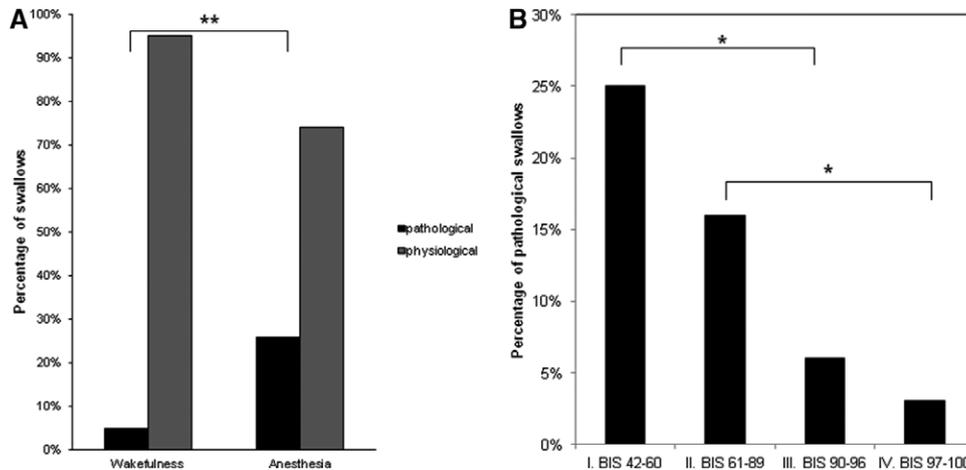
Fig. 3. Impairing effect of anesthesia on coordination between breathing and swallowing. (*A*) Significantly higher proportion of pathological swallows (inspiratory or expiratory–inspiratory swallows) defined as swallows followed by inspiration observed under anesthesia compared to wakefulness. (*B*) Lower bispectral index (BIS) electroencephalogram values were associated with higher proportion of pathological swallows. *$P < 0.05$; **$P < 0.001$.

Table 1. Swallow Characteristics during Wakefulness and Anesthesia

Swallow Classification	Swallows under Wakefulness	Swallows under Anesthesia	Number
Physiological	136	60	196
Pathological	7	21	28
Total number	143	81	224

Swallows are categorized as physiological (during expiration or followed by expiration) or pathological (during inspiration or followed by an inspiration) and displayed within conditions of wakefulness *vs.* anesthesia.

Secondary Aim: Effects of Induced Hypercapnia on Proportion of Pathological Swallows

The average baseline end-tidal carbon dioxide level during wakefulness was 39.4 ± 5.36 mmHg, during propofol was 44.9 ± 9.5 and 51.6 ± 10.3 mmHg for the low and high dose, respectively, and during sevoflurane was 42.44 ± 13.32 and 43.29 ± 13.87 mmHg for the low and high dose, respectively ($P < 0.05$ for higher end-tidal carbon dioxide level during propofol compared with sevoflurane). The end-tidal concentration was increased by 4 and 8 mmHg at all of these levels. Hypercapnia (6 ± 2 mmHg above baseline) was associated with a higher proportion of pathological swallows compared to normocapnia (23.9% *vs.* 5.1%, $P < 0.001$). The vulnerability to carbon dioxide–induced pathological swallows was significantly higher during anesthesia compared to wakefulness (increase in rate of pathological swallows by 19.1% *vs.* 12.3%, respectively, $P < 0.001$; fig. 4). Hypercapnia increased minute ventilation and respiratory rate both during wakefulness and anesthesia (table 2). During wakefulness, minute ventilation increased from 9.1 ± 2.5 to 13.3 ± 3.3 l during carbon dioxide insufflation ($P < 0.001$), and respiratory rate increased from was 15.7 ± 5.3 to 16.2 ± 3.9 breaths/min ($P = 0.048$). During anesthesia, minute ventilation increased from 8.3 ± 3.0 to 12.9 ± 3.2 l during hypercapnia ($P < 0.001$), and respiratory rate increased from 19.8 ± 2.1 to 22.3 ± 3.2 breaths/min ($P = 0.004$), respectively. Hypercapnia during anesthesia also augmented the negative pharyngeal pressure generated during inspiration to more negative values (fig. 5A). Furthermore, pathological swallows were associated with greater pharyngeal pressure generated during inspiration compared to physiological swallows (fig. 5B).

Other Outcome Variables: Frequency of Spontaneous Swallows during Anesthesia versus Wakefulness, and during Hypercapnia

The number of swallows per hour during anesthesia (1.7 ± 3.3) was significantly lower compared to wakefulness (28.0 ± 22.3, $P < 0.001$, fig. 6), with no difference between propofol (2.3 ± 4.1) and sevoflurane (0.93 ± 2.3) ($P = 0.38$). Hypercapnia applied during anesthesia was associated with an increased number of swallows per hour compared to anesthesia alone (5.1 ± 17.0 *vs.* 1.3 ± 5.5, $P = 0.006$, fig. 7). We did not observe effects of carbon dioxide on the number of swallows per hour when hypercapnia was applied during wakefulness (22.3 ± 24.3 *vs.* 30.4 ± 23.6).

Discussion

Sevoflurane and propofol increased the likelihood of pathological swallows and decreased the frequency of swallowing. In addition, an increase in minute ventilation and an augmentation of the negative pharyngeal pressure generated during inspiration induced by carbon dioxide, increased both the frequency of swallowing and proportions of pathological swallows during anesthesia. These effects of hypercapnia during anesthesia may further increase the vulnerability to aspiration.

The most important finding of this study was that anesthesia impaired the coordination between breathing and swallowing, leading to a higher proportion of pathological swallows. Our data confirm the findings of several studies
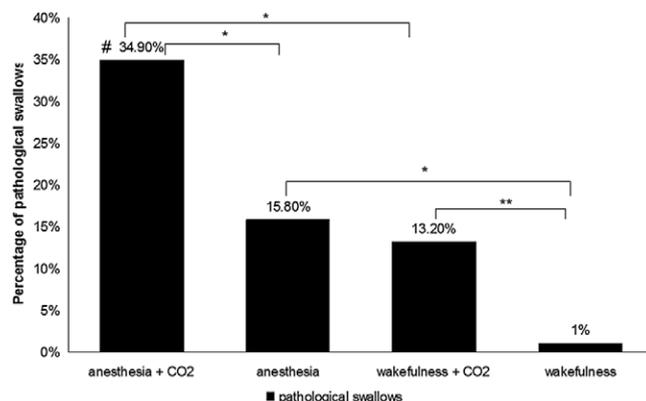
Fig. 4. Proportion of pathological (inspiratory) swallows during wakefulness and anesthesia with and without evoked hypercapnia. Carbon dioxide (CO_2) induces an increase in the proportion of pathological swallows during wakefulness and anesthesia. Anesthesia augmented the effects of carbon dioxide to impair breathing–swallowing coordination compared with wakefulness. *$P < 0.05$; **$P < 0.001$; #interaction effect between anesthesia and carbon dioxide, $P < 0.05$.

that physiological swallows during wakefulness typically either occur during expiration or are followed immediately by the expiratory phase.[3,16] There was no difference in the proportion of pathological swallows between propofol and sevoflurane. However, the absence of significant difference in pathological swallow proportion between sevoflurane and propofol does not indicate significance of absence, and further studies may be needed to address differential effects of γ-aminobutyric acid–mediated anesthetics on breathing swallowing coordination.

Sundman *et al.*[17] demonstrated that propofol and sevoflurane increase the incidence of pharyngeal dysfunction measured by manometry, and the incidence of laryngeal penetration detected by fluoroscopy. While we did not formally quantify aspiration, our data taken together with other published findings[7] suggest that impaired coordination between swallowing and breathing may be a contributing mechanism of anesthesia-associated aspiration.

Nishino and Hiraga[18] did not find a difference in the incidence of strictly inspiratory *versus* expiratory swallows in intubated, anesthetized patients after surgery but, in accordance with our finding, reported a higher incidence of swallows occurring at the transition between inspiration and expiration. These investigators examined intubated subjects in the postoperative period and measured volitional swallows after the presentation of a saline bolus. In contrast,

our study examined reflexive swallowing, a scenario similar to that seen during procedural sedation in which a patient receives anesthetics without enteral fluid administration or an endotracheal tube, conditions that affect physiological airway reflexes. We believe that our methodology examined the interaction of breathing and swallowing in a more clinically relevant manner. The observed pattern of post-swallow inspiration in pathological swallowing has been reported in patients with high aspiration risk such as those with Parkinson disease[19,20] and chronic obstructive pulmonary disease.[6,21] It has been demonstrated that swallows followed by inspiration in patients with Parkinson disease are associated with a higher risk of aspiration indicated by higher penetration–aspiration scores.[7]

A decrease in the frequency of spontaneous swallows has been shown to be associated with a higher risk of aspiration in hospitalized patients.[22] Our finding of decreased frequency of swallows during anesthesia may also represent a contributing factor to the association between anesthesia and aspiration. However, we did not formally quantify the effectiveness of swallowing and therefore cannot draw any firm conclusions regarding the risk of aspiration.

Strengths and Weaknesses of the Study

Our study examined the coordination between breathing and reflexive swallows in volunteers who were spontaneously breathing through the regular anatomic route during anesthesia. The absence of an artificial bolus for induction of swallowing (*i.e.*, water or other liquid administered) permitted our study to directly examine the breathing–swallowing coordination under physiological conditions. Furthermore, the timing of an artificial bolus required to study volitional swallowing may influence the timing of respiration and swallowing (*i.e.*, if the bolus was presented during inspiration *vs.* expiration). In addition, we administered carbon dioxide through the patent airway in a way that the laryngeal receptors could be directly exposed to carbon dioxide and the induced increase in negative pharyngeal pressure during

Table 2. Effects of Hypercapnia on Respiratory Rate and Minute Ventilation

	Minute Ventilation		Respiratory Rate	
	Wakefulness	Anesthesia	Wakefulness	Anesthesia
Normocarbia	9.1 ± 2.5 l	8.3 ± 3.0 l	15.7 ± 5.3	19.8 ± 2.1
Hypercarbia	13.3 ± 3.3 l	12.9 ± 3.2 l	16.2 ± 3.9	22.3 ± 3.2
P value	<0.001	<0.001	0.048	0.004

Effects of hypercapnia compared to normocapnia on both minute ventilation and respiratory rate are presented and categorized into wakefulness *vs.* anesthesia.
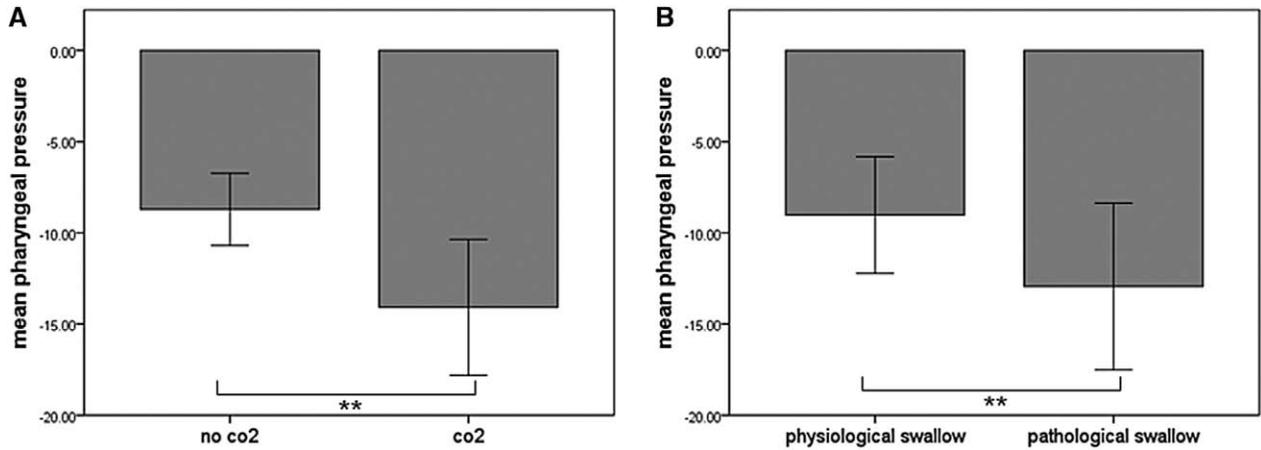
Fig. 5. Association between hypercapnia, pharyngeal pressure during inspiration, and pathological swallows. (*A*) Carbon dioxide (CO_2) insufflation increases the pharyngeal pressure generated during inspiration. (*B*) Increased pharyngeal pressure is associated with occurrence of pathological swallows. Error bars represent ±1 standard deviation. **$P < 0.001$.

inspiration.[23] This is important because laryngeal hypercapnia can directly activate superior laryngeal nerve fibers[24] and the (carbon dioxide–induced) augmentation of negative pharyngeal pressure during inspiration should activate the genioglossus muscle.[23] These effects of hypercapnia on the genioglossus negative pressure reflex cannot be studied in endotracheally intubated patients.

We were not able to visualize the pharynx to provide detailed information about the efficiency of the swallow. Further understanding of the quality of swallows in addition to its relation to respiratory timing is likely to provide important information about the effect of anesthesia and hypercapnia on aspiration rate. The use of any type of catheter in the hypopharynx could potentially lower the threshold for pharyngeal swallowing as it stimulates pharyngeal mechanoreceptors. To minimize this unwarranted stimulating effect, we used a very small catheter and secured the catheter with tape at the nostril to minimize any movement of the catheter

Fig. 6. Box-plot (median, quartiles, 10/90 percent percentile, and outer fence [*small open circles*]) of number of swallows per hour. The frequency of swallows was lower during anesthesia compared with wakefulness. **$P < 0.001$ for lower occurrence of swallows during anesthesia compared with wakefulness.

and also kept the subject's head and neck position constant throughout the experiment.

Possible Biological Explanations

Several studies have reported that hypercapnia is associated with impaired coordination between breathing and swallowing, leading to a higher proportion of pathological (I and I–E) swallows.[2,10] Our study confirms these observations and adds the information that hypercapnia has stronger effects on breathing–swallowing coordination during anesthesia than during wakefulness.

Under the conditions in our study, carbon dioxide administered to the inspired air during anesthesia increased both the number of swallows per hour and the proportion of pathological swallows. In contrast, Nishino *et al.*[9] found in anesthetized, endotracheally intubated volunteers, airway reflexes were attenuated during administration of carbon dioxide. Reflexive carbon dioxide–induced genioglossus activation *via* hypopharyngeal mechanoreceptors and laryngeal chemoreceptors cannot be studied in endotracheally intubated patients.[24]

We speculate based on our data that carbon dioxide–induced augmentation of the negative hypopharyngeal pressure (generated by respiratory pump muscles) contributes to our finding of increased frequency of swallows during anesthesia.[23] Carbon dioxide and the negative hypopharyngeal pressure are sensed by chemoreceptors, and mechanoreceptors activate the nucleus tractus solitarius *via* the superior laryngeal nerve and lower the threshold for swallow initiation.[25,26] Furthermore, the increased negative hypopharyngeal pressure also activates the genioglossus muscle *via* the premotoneurons in the periobex region.[23] In our study, in parallel with carbon dioxide insufflation, we observed an augmentation of the negative pharyngeal pressure generated during inspiration, which was associated with high proportion of pathological swallows. This supports the view that hypercarbia-induced augmentation of negative pharyngeal
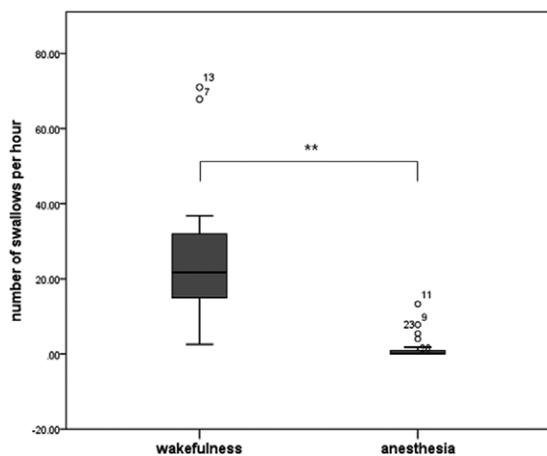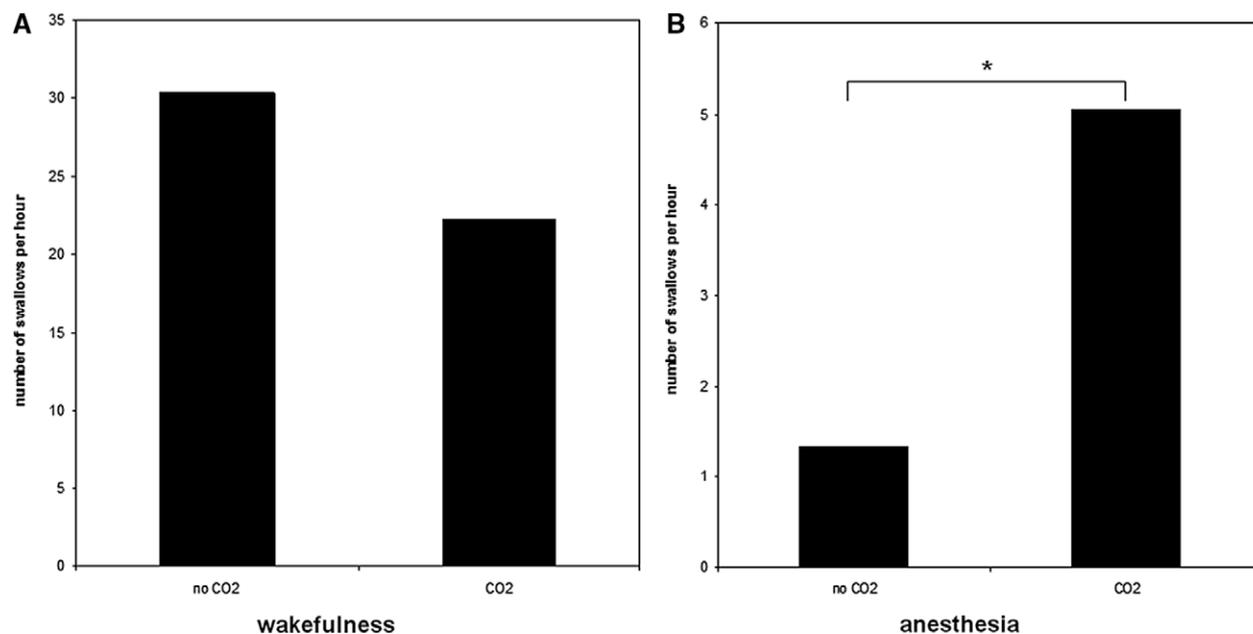
Fig. 7. Swallows per hour with and without hypercapnia during wakefulness and anesthesia. (*A*) The frequency of swallows was not significantly different with and without carbon dioxide (CO_2) during wakefulness. (*B*) Hypercapnia increased the number of swallows per hour during anesthesia. *$P < 0.05$.

pressure during inspiration may lower the threshold for swallow initiation. In agreement with the observation of others, we did not find an increasing effect of hypercapnia on the number of swallows per hour during wakefulness.[2,10] During wakefulness, reflexive swallows can be cortically modulated. It is possible that volunteers elected not to swallow in these short periods of evoked hypercapnia during which they perceived shortness of breath. Anesthesia allowed us to study the effect of hypercapnia on reflexive swallowing without cortical control.

Meaning of the Study: Implications for Clinicians

Anesthesia impaired the coordination between swallowing and breathing, which has been demonstrated to increase the risk of aspiration.[7] The intravenous anesthetic propofol and the volatile anesthetic sevoflurane had similar effects impairing the coordination of swallowing and breathing.

Our data indicate that anesthetized patients not only have less chances to clear the airway due to decrease in the number of swallows, but also have an increased chance of aspiration because of poor performance of the swallowing act (increased proportion of the pathological swallows). Clinically, one meaningful aspiration may be sufficient to translate into a bad respiratory outcome postoperatively. We therefore speculate based on our data that the combination of the decreased incidence of swallowing and increased pathological swallowing may contribute to an increased aspiration risk during anesthesia.[7,22]

It is a common clinical observation that during the emergence from anesthesia, an increase in swallowing frequency is observed.[18] An increased ventilatory drive during anesthesia was associated with increased risk of pathological swallows. In addition, our data support the view that conditions associated with increased ventilatory drive (such as a pain stimulus) may impose a greater risk for pathological swallows during anesthesia. We speculate that in a setting of procedural sedation where the upper airway is not protected by a tracheal tube, shallow levels of anesthesia, also known to increase ventilatory drive, may increase the aspiration risk.

In summary, our data show that sevoflurane and propofol increase the likelihood of pathological swallows and decrease overall the frequency of swallowing. In addition, an increase in ventilatory drive induced by hypercapnia increases the vulnerability to pathological swallows.

Acknowledgments

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Eikermann: Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114. meikermann@partners.org. This article may be accessed for

personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Cedborg AI, Sundman E, Bodén K, Hedström HW, Kuylenstierna R, Ekberg O, Eriksson LI: Pharyngeal function and breathing pattern during partial neuromuscular block in the elderly: Effects on airway protection. ANESTHESIOLOGY 2014; 120:312–25

2. Sai T, Isono S, Nishino T: Effects of withdrawal of phasic lung inflation during normocapnia and hypercapnia on the swallowing reflex in humans. J Anesth 2004; 18:82–8

3. Hårdemark Cedborg AI, Bodén K, Witt Hedström H, Kuylenstierna R, Ekberg O, Eriksson LI, Sundman E: Breathing and swallowing in normal man – Effects of changes in body position, bolus types, and respiratory drive. Neurogastroenterol Motil 2010; 22:1201–8, e316

4. Butler SG, Stuart A, Pressman H, Poage G, Roche WJ: Preliminary investigation of swallowing apnea duration and swallow/respiratory phase relationships in individuals with cerebral vascular accident. Dysphagia 2007; 22:215–24

5. Terzi N, Orlikowski D, Aegerter P, Lejaille M, Ruquet M, Zalcman G, Fermanian C, Raphael JC, Lofaso F: Breathing-swallowing interaction in neuromuscular patients: A physiological evaluation. Am J Respir Crit Care Med 2007; 175:269–76

6. Gross RD, Atwood CW Jr, Ross SB, Olszewski JW, Eichhorn KA: The coordination of breathing and swallowing in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009; 179:559–65

7. Troche MS, Huebner I, Rosenbek JC, Okun MS, Sapienza CM: Respiratory-swallowing coordination and swallowing safety in patients with Parkinson's disease. Dysphagia 2011; 26:218–24

8. Brock-Utne JG, Winning TJ, Rubin J, Kingston HG: Laryngeal incompetence during neuroleptanalgesia in combination with diazepam. Br J Anaesth 1976; 48:699–701

9. Nishino T, Hiraga K, Honda Y: Inhibitory effects of CO_2 on airway defensive reflexes in enflurane-anesthetized humans. J Appl Physiol (1985) 1989; 66:2642–6

10. Nishino T, Hasegawa R, Ide T, Isono S: Hypercapnia enhances the development of coughing during continuous infusion of water into the pharynx. Am J Respir Crit Care Med 1998; 157(3 Pt 1):815–21

11. Eikermann M, Jordan AS, Chamberlin NL, Gautam S, Wellman A, Lo YL, White DP, Malhotra A: The influence of aging on pharyngeal collapsibility during sleep. Chest 2007; 131:1702–9

12. Herbstreit F, Peters J, Eikermann M: Impaired upper airway integrity by residual neuromuscular blockade: Increased airway collapsibility and blunted genioglossus muscle activity in response to negative pharyngeal pressure. ANESTHESIOLOGY 2009; 110:1253–60

13. Baars JH, Tas S, Herold KF, Hadzidiakos DA, Rehberg B: The suppression of spinal F-waves by propofol does not predict immobility to painful stimuli in humans. Br J Anaesth 2006; 96:118–26

14. Baars JH, Kalisch D, Herold KF, Hadzidiakos DA, Rehberg B: Concentration-dependent suppression of F-waves by sevoflurane does not predict immobility to painful stimuli in humans. Br J Anaesth 2005; 95:789–97

15. Perlman AL, Grayhack JP: Use of the electroglottograph for measurement of temporal aspects of the swallow: Preliminary observations. Dysphagia 1991; 6:88–93

16. Boden K, Cedborg AI, Eriksson LI, Hedström HW, Kuylenstierna R, Sundman E, Ekberg O: Swallowing and respiratory pattern in young healthy individuals recorded with high temporal resolution. Neurogastroenterol Motil 2009; 21:1163–e101

17. Sundman E, Witt H, Sandin R, Kuylenstierna R, Bodén K, Ekberg O, Eriksson LI: Pharyngeal function and airway protection during subhypnotic concentrations of propofol, isoflurane, and sevoflurane: Volunteers examined by pharyngeal videoradiography and simultaneous manometry. ANESTHESIOLOGY 2001; 95:1125–32

18. Nishino T, Hiraga K: Coordination of swallowing and respiration in unconscious subjects. J Appl Physiol (1985) 1991; 70:988–93

19. Pinnington LL, Muhiddin KA, Ellis RE, Playford ED: Non-invasive assessment of swallowing and respiration in Parkinson's disease. J Neurol 2000; 247:773–7

20. Gross RD, Atwood CW Jr, Ross SB, Eichhorn KA, Olszewski JW, Doyle PJ: The coordination of breathing and swallowing in Parkinson's disease. Dysphagia 2008; 23:136–45

21. Cvejic L, Harding R, Churchward T, Turton A, Finlay P, Massey D, Bardin PG, Guy P: Laryngeal penetration and aspiration in individuals with stable COPD. Respirology 2011; 16:269–75

22. Murray J, Langmore SE, Ginsberg S, Dostie A: The significance of accumulated oropharyngeal secretions and swallowing frequency in predicting aspiration. Dysphagia 1996; 11:99–103

23. Chamberlin NL, Eikermann M, Fassbender P, White DP, Malhotra A: Genioglossus premotoneurons and the negative pressure reflex in rats. J Physiol 2007; 579(Pt 2):515–26

24. Bradford A, Nolan P, O'Regan RG, McKeogh D: Carbon dioxide-sensitive superior laryngeal nerve afferents in the anaesthetized cat. Exp Physiol 1993; 78:787–98

25. Jean A: Brain stem control of swallowing: Neuronal network and cellular mechanisms. Physiol Rev 2001; 81:929–69

26. Feindel W: The neural pattern of the epiglottis. J Comp Neurol 1956; 105:269–85