Effects of spontaneous swallows on breathing in awake goats

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Feroah, Thom R., H. V. Forster, Carla G. Fuentes, Ivan M. Lang, David Beste, Paul Martino, L. Pan, and Tom Rice. Effects of spontaneous swallows on breathing in awake goats. J Appl Physiol 92: 1923–1935, 2002. First published December 7, 2001; 10.1152/japplphysiol.01079.2000.—The effects of spontaneous swallows on breathing before, during, and after solitary swallows were investigated in 13 awake goats. Inspiratory (TI) and expiratory (TE) time and respiratory output were determined from inspiratory airflow (tidal volume [VT]) and peak diaphragmatic activity (Diapeak). The onset time for 1,128 swallows was determined from pharyngeal muscle electrical activity. During inspiration, the later the swallowing onset, the greater increase in Ti and VT, whereas there was no significant effect on TE and Diapeak. Swallows in early expiration increased the preceding TI and reduced TE, whereas later in expiration swallows increased TE. After expiratory swallows, Ti and VT were reduced whereas minimal changes in Diapeak were observed. Phase response analysis revealed a within-breath, phase-dependent effect of swallowing on breathing, resulting in a resetting of the respiratory oscillator. However, the shift in timing in the breaths after a swallow was not parallel, further demonstrating a respiratory phase-dependent effect on breathing. We conclude that, in the awake state, within- and multiple-breath effects on respiratory timing and output are induced and/or required in the coordination of breathing and swallowing.

respiration; deglutition; pharyngeal muscles; diaphragm; electromyography

Both breathing and swallowing are continual ongoing events in mammals, although at different frequencies. As a result of the shared use of the upper airway, it is extremely important that the motor pattern generators associated with breathing and swallowing are tightly coupled to provide effective coordination for cleansing and removing secretions from the lower airways (3, 8, 16). A loss of coordination between these pattern generators is associated with dysphasia, weight loss, coughing, and pulmonary aspiration leading to pneumonia. However, the exact neural and physiological nature of the interconnections between the swallowing and breathing pattern generators is unknown. Nevertheless, the functional relationships between these generators have been investigated for decades.

Although the frequency of spontaneous swallows during the different phases of respiration varies among species, swallowing has been generally reported to inhibit breathing in human, dogs, rabbits, and cats (1, 2, 5, 7, 8, 22, 23, 25, 29). For example, swallows during inspiration or expiration are reported to increase the phase of respiration in which it occurred. In a few studies that measured respiratory output [e.g., tidal volume (VT) and electrical activity of the diaphragm and laryngeal abductors], swallowing reduced inspiratory output (11, 23, 24). In addition, the observations of swallows during the transition between inspiration-expiration or expiration-inspiration are infrequent (18, 22), but if observed they disrupt respiratory timing in humans (27).

The neural substrates that generate and coordinate the motor patterns for swallowing and breathing are located in the dorsomedial and ventrolateral brain stem (1, 4, 16, 14). To understand the interaction between these pattern generators, several interpretative models have been applied, mostly using anesthetized or decerebrate models with superior laryngeal nerve stimulation (7, 19, 27). Few studies have examined this interaction on the swallowing and respiratory pattern generators in unanesthetized animals and humans (20, 23–25).

The aim of this study was to investigate in unanesthetized, awake goats the effect of spontaneous swallows on respiratory output and timing. We hypothesized that a swallow in either phase of respiration would produce a within-breath effect to increase respiratory timing, enough to cause a phase delay but not a resetting of the respiratory rhythm. We also hypothesized that swallows would not have an effect on the timing or VT of the breath before the swallow but would reduce the VT if the swallow occurred during inspiration.

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Methods

Animals. Thirteen adult goats of various breeds that were used in this study received humane care in compliance with the Guide for the Care and Use of Laboratory Animals formulated by the National Research Council, 1996. The study protocol was approved by the Institutional Animal Care Committee of the Medical College of Wisconsin.

Surgical procedures. Surgery was performed to implant chronic electromyographic (EMG) electrodes in the diaphragm (EMGdiam), thyropharyngeus (EMGTP), posterior cricoarytenoid (EMGPCA), and thyroarytenoid (EMGTYA) muscles. In four goats, a tracheostoma was created at the level of the eighth tracheal ring to isolate the upper airway. The animals received an intravenous injection of ketamine (Ketaset) and xylazine (12:1 ratio, 15 mg/kg) for induction of anesthesia before intubation. After intubation for mechanical ventilation, general anesthesia was maintained with 1.5–2.5% halothane in oxygen (sufficient to eliminate the withdrawal reflex and any signs of pain.)

EMG electrode placement has been previously described (10). Briefly, Teflon-coated 32-gauge stainless steel bipolar microelectrodes were inserted into the muscles defined above. For implants into airway muscles, a midline incision was made on the ventral surface of the neck from the hyoid bone to 4 cm below the thyroid cartilage, exposing the lateral aspect of the pharynx. The EMGTP electrode was sewn into the thyropharyngeus midway between the posterior midline of the pharynx and the insertion on the thyroid cartilage 0.5 cm below the cranial laryngeal nerve. To implant the EMGPCA, a small window was made at the inferior edge of the thyroid cartilage 1 cm below the cranial laryngeal nerve. For implantation of the EMGPCA, the cricoid cartilage to expose the posterior cricoarytenoid. For placement of the EMGTYA electrode, a U-shaped window was made in the lateral wall of the thyroid cartilage to expose the thyroarytenoid. The EMGTP electrode was sewn into the stylopharyngeus muscle close to its disappearance under the hypopharyngeus. The wires were looped in the subcutaneous layer of connective tissue and exited on the lateral ventral surface of the neck. For the EMGdiam, a lateral thoracotomy was performed between the ninth and tenth ribs midway between the sternum and spine. The diaphragm electrodes were implanted in the costal portion of the diaphragm and exteriorized next to the incision. After the above instrumentation, the carotid arteries were elevated bilaterally so that they could be easily catheterized for monitoring of arterial blood pressure during the experimental studies. A 5-cm segment of each carotid artery was elevated subcutaneously and sutured in place.

For at least 24 h after surgery, laboratory personnel frequently inspected the animals. The animals received daily intramuscular antibiotics (cefotiofur sodium, 2 mg/kg), and their rectal temperature, eating habits, and behavior were monitored daily. These measures indicated that the goats were in good health and fitness during recovery from surgery and the subsequent experimental period.

Methods of measurement and experimental design. For measurements of airflow in the animals without a tracheostoma, a tight-fitting, custom facemask was connected to a one-way breathing circuit. In the animals with a tracheostoma, airflow measurements were made via an 8-Fr cuffed tracheostomy tube that was inserted into the trachea, cuff inflated, and connected to a one-way breathing circuit with a two-way nonrebreathing valve (model 2600, Hans Rudolph). A pneumotachograph was connected in-line on the inspiratory side of the nonrebreathing valve and connected to a differential pressure transducer to measure inspiratory airflow only. The proximal ends of the EMG wires were connected via microclips to a Grass recorder for signal processing and recording. The EMG signals were filtered at a band pass of 3–500 Hz. A carotid artery was catheterized at least 2 days before initiation of experimental studies. Arterial blood pressure was monitored during all studies by connecting the arterial catheter via a Statham blood pressure transducer to a Grass recorder. The airflow, raw EMG signals, and arterial blood pressure were sent to a CODAS computer data acquisition system at a sampling rate of 250 Hz for display, digital recording, and analysis.

Before initiation of data collection, the goats were acclimatized for several hours a day for a week in a stanchion where they were connected to the recording system. On the days the goats were studied, respiration, upper airway EMG activity, and blood pressure were continuously monitored for a minimum of 2 h. Chewing and other movement artifacts were eliminated from the analysis. All goats were studied in the awake state in the prone recumbent position. Respiratory and arterial blood pressure were normal throughout the experimental period, indicating that the goats were in good health, relaxed, and free of pain.

Data analysis. Respiratory airflow and EMG signals were processed and analyzed (WinDaq, DATAQ Instruments). Raw EMG data were full-wave rectified and passed through a moving time averager (time constant of 0.1 s) to obtain an integrated EMG signal. The integrated EMGTP, EMGPCA, and EMGTYA signals were analyzed to obtain the occurrence of swallowing. The absolute time of a swallow was determined at the peak of a 10-fold increase in the integrated EMGTP and EMGTYA activity with a 200-ms duration and without signs of movement artifacts. The start of a swallow was then set at 0.15 s before peak EMGTP activity. Even though the TP muscle is activated in the later part of the recruitment order of pharyngeal muscles, the onset of activation is within 0.2 s of the initiation of the oropharyngeal phase of swallowing (8, 9, 18). In this study, spontaneous swallows were considered as nonfeeding swallows that were initiated reflexively by the accumulation of oropharyngeal secretions. These secretions were presumably sensed by afferent receptors in the laryngeal mucosa innervated by the trigeminal, glosopharyngeal, and vagal nerves (1, 8, 15, 16). None of the swallows analyzed were related to mastication.

For the analysis of ventilation, a two-state computer algorithm (inspiration-expiration) was used for the automatic detection of the breath-by-breath calculations for VT, duration of inspiration (TI), and duration of expiration (TE) from the airflow signal. Peak EMGdiam activity (Dia peak) was obtained for each breath. In this two-state computer algorithm, inspiration was determined when flow exceeded zero respiratory flow by 0.01 l/s for a minimum duration of 0.2 s. The start of expiration was determined when a pause in the EMGdiam activity and in the inspiratory flow longer than 0.35 s was detected. Although this period was shorter than the reported deglutition apnea in animals and humans (5, 17, 22–24, 27, 30), we felt that it was a conservative estimate of the establishment of expiratory cycle. In addition, our observations in goats led us to the use of these criteria, because deglutition apneas, if present during inspiration, were very short. Therefore, we believe that the determination of the phase of breathing was accurately and reliably determined. The absolute time for the start of inspiration for each breath was recorded along with the time of each swallow. The total duration of a breath (Ttot) was calculated as the sum of TI and TE. The inspiratory duty cycle (TI/Ttot) and the ratio of VT to TI (VT/TI) were calculated for each breath.
Three types of analysis of the effects of swallowing on breathing were made. First, to examine the general effects of swallowing on breathing, swallows were categorized into one of four phases of ventilation (Fig. 1): expiration (SwE), the transition from expiration to inspiration (SwEI), inspiration (SwI), and the transition from inspiration to expiration (SwIE). The effects of SwE, SwEI, SwI, and SwIE on Ti, Te, Ttot, VT, T/v, and Diapeak (expressed as a percentage of control) on the breath before (n − 1), during (n), and after (n + 1) the swallows were evaluated. Second, the gamma analysis (γ) evaluated whether the time of occurrence of a swallow, within either inspiration (γI) or expiration (γE), had an effect on the breath before or during a swallow (23, 24). For this analysis, five consecutive breaths were evaluated, with a solitary swallow in the fourth breath (Fig. 2, A and B). In this analysis, a breath was considered to start with expiration followed by inspiration. Swallows with movement or augmented breaths within the set of five consecutive breaths were eliminated from this analysis. Averages for Ti, Te, Vt, and Diapeak were calculated from the first, second, and fifth breaths of the set of five breaths and used as control values. The value for γI was calculated as the time from the beginning of inspiration to the onset of the solitary swallow, expressed as percentage of the control Ti. The value for γE was calculated as the time from the beginning of expiration to the onset of the solitary swallow, expressed as percentage of the control Te. Values for Ti, Te, Vt, and Diapeak for the previous breath (n − 1) and the breath during (n) the swallow were expressed as a percentage of its control value and were plotted against γI or γE.

Finally, to evaluate the effect of swallows on the oscillations of the respiratory pattern generator, a phase response...
Fig. 2. Illustration of inspiratory (γI; A) and expiratory (γE; B) gamma analysis. γI was calculated as the period of time from the beginning of inspiration to the start of the swallow during inspiration. γE was calculated as the period of time from the beginning of expiration to the start of a swallow during expiration. Inspiratory time (T_in), expiratory time (T_out), tidal volume (V_T), and peak diaphragmatic activity (Dia_peak) for the breaths before and during the swallow were calculated. Control values were calculated from the 2 breaths before and 1 breath after the breaths used in this analysis.

Analysis (similar to the analysis of biological oscillators) was performed (26, 27, 31). In this analysis, six consecutive breaths were evaluated, with a solitary swallow in the fourth breath. The old phase (φ) was defined as the time from the beginning of inspiratory flow of the fourth breath to the onset of the swallow (Fig. 3A). The subsequent cophases (θ) were defined as the time from the onset of swallow to the beginning of inspiratory flow of breaths 5 (θn,1) and 6 (θn,2) and to the end of expiration of breath 6 (θn,3). The cophase for the breath before the swallow (θn−1) was calculated as the time from the beginning of the swallow backward to the beginning of inspiratory flow of breath 3. Movement or augmented breaths in any of these breaths eliminated the set from analysis. Ventilatory values from breaths 1, 2, and 6 of the set were averaged and used as controls. All values of φ and θ were expressed as a fraction of control values. Values of VT and Dia_peak in this analysis were calculated as a percent of control values.

Following the above definitions of φ and θ, the effect of swallowing on the respiratory rhythm can be assessed, as previously presented by Paydarfar et al. (27). As defined in Fig. 3A, the normalized measures of φ and θ would equal 1 (φ + θ = 1) if swallowing had no effect on rhythm at any time during the respiratory cycle, and the slope of θn,1 vs. φ would be −1. Furthermore, as demonstrated in Fig. 3B, the effect on any subsequent breaths (n) would be anticipated by the equation, θn = −φ + n with a similar slope. A phase advance or delay in the onset of breathing would be anticipated if swallowing had an effect on the respiratory rhythm generator to shorten or lengthen inspiration or expiration. If swallowing had more than a transient effect on the respiratory rhythm, then a permanent shift or resetting of the subsequent start of ventilation would occur. To evaluate the possible phase shift in the phase response curves, the difference in the onset from the previous breath (θn−1 − θn−1,1, θn−1 − θn−1,2, θn−1 − θn−1,3) for each swallow in all the animals was calculated and averaged every 0.05 interval of φ. Given sequential breaths and the above equation for φn, a parallel shift in the θn curves would result in a difference of 1. A phase delay would result in an increase in the difference between the θn curves relative to the previous swallow, whereas a phase advance would result in a decrease in the difference. To estimate the potential phase shift of the breath before the swallow, the difference between θn−1,1 and a nonaffected old phase (θn,ideal) with a slope of −1 was calculated and averaged every 0.05 interval of φ. In this latter comparison

Fig. 3. Phase response analysis. In this analysis, a set of 6 consecutive breaths (without movements and augmented breaths) was evaluated, with a solitary swallow in the 4th breath. A: the old phase (φ) was calculated from the start of inspiration to the start of the swallow. Cophases (θ) were calculated from the start of the swallow to the start of inspiration of the previous breath (θn−1) and the start of the 3 subsequent breaths (θn,1, θn,2, θn,3, respectively). In a hypothetical model in which swallowing had no effect on respiration rhythm, the normalized measures of φ and θ (expressed as a fraction of control) would be equal to 1 (φ + θ = 1). B: plot of subsequent θn vs. φ in which a family of swallows that occurred during respiration had no effect on respiratory rhythm. In this hypothetical example, the slope of θn,1 vs. φ would be −1, and the effect on any subsequent breaths (n) would also be anticipated by the equation θn = −φ + n. As a result, the slope of the relationship between the onset of swallowing and respiration rhythm would be represented by a series of linear parallel lines with a slope of −1.
The phase transition from inspiration to expiration (IE) for the breaths with swallows was estimated by calculating the half-cycle period relative to a specific old phase that began at the start of inspiration. The cophase (\(\gamma_{IE}\)) in this analysis was calculated as the period of time from the start of the swallow to the start of expiration. The average phase transition was then estimated for the breaths with swallows by solving for the relationship of \(\phi\) vs. \(\gamma_{IE}\) by using a third-order polynomial equation for an intercept of zero.

Statistical analysis. The average rate of swallowing and its standard deviation were calculated for each goat, and a Kolmogorov-Smirnov test was performed to test whether the rate of swallowing significantly deviated from Gaussian distribution (\(P < 0.05\)). For the categorization of swallows, a Student’s t-test was performed on the means of the percent change of Ti, Te, Ttot, Vr, Tst/Tti, and Diapeak for the breaths before, during, and after the swallows, compared with no change (100%) within SwE, SwEi, SwI, and SwIE (\(P < 0.02\)). A comparison was also made using a one-way ANOVA between the means of the percent change for the breaths before, during, and after the swallows within SwE, SwEi, SwI, and SwIE (\(P < 0.02\)).

In the gamma distribution, a linear regression analysis was performed on Te, Ti, Vr, and Diapeak (expressed as a fraction of its control) on the previous breath, and the breath in which the swallow occurred was evaluated for \(\gamma_1\) and \(\gamma_2\) (\(P < 0.02\)). The slopes and intercepts were compared to determine whether the time of occurrence of the swallow (\(\gamma_1\) or \(\gamma_2\)) during inspiration or expiration had an effect on respiratory parameters from the breath before and during the swallow.

In the evaluation of the phase shift, the mean value of \(\theta_{1-1} = \theta_n - \theta_1\), \(\theta_{1-2} = \theta_{n+1} - \theta_1\), and \(\theta_{n-1} - \theta_{2-2}\) at every 0.05 interval of \(\phi\) was tested to determine whether it differed significantly from a hypothetical value of 1 using a Student’s t-test (\(P < 0.02\)). Similarly, the mean of \(\theta_{n-1} - \theta_1 = \theta_{ideal}\) was compared with a value of 0 by using a Student’s t-test (\(P < 0.02\)).

RESULTS

During expiration, the normal phasic respiratory activity of EMGTP was inhibited just before its recruitment for a swallow (Fig. 1B, a). Commonly associated with the swallows during expiration was a small burst of activity in the EMGDia (Fig. 1B, b). During late expiration, swallows were associated with a burst of inspiratory airflow, usually termed a “swallow breath” or Schluckatmung. However, if a swallow occurred during the first third of expiration, inspiratory flow was not seen. During inspiration, phasic EMGPS activity was inhibited at the onset of EMGTP swallow activity (Fig. 1B, c). A short inhibition, or pause, in EMGDia activity occurred midway through EMGTP swallow activity (Fig. 1B, d). In all goats (with an intact upper airway or with a tracheostomy), a short pause (<0.1 s) and a significant decrease in inspiratory airflow were seen during swallows after increases in EMGTP activity and decreases in EMGDia.

The average rate of swallowing for all the goats was 2.88 ± 1.22 swallows/min (Table 1). Goats with tracheotomies had an average rate of 1.86 ± 0.31 swallows/min, whereas goats with intact airways presented with an average rate of 3.3 ± 1.9 swallows/min. On average, 12.4% of the swallows from each goat were not used in the analysis because of movement artifacts or the presence of more than one swallow within a breath. The average duration of the moving time average of a swallow in the TP signal was 0.25 ± 0.03 s. No pharyngolaryngeal or swallowing dysfunction was observed in any goat in this study.

Effects of spontaneous SwE, SwEi, SwI, and SwIE on breathing. In this analysis, shown in Fig. 4, a total of 1,128 solitary swallows met the criteria for evaluation during the observation of 7,573 breaths. In the SwE analysis (317 swallows, 28% of total), Te was significantly increased in the breathes before, during, and after the swallow. In contrast, Ti decreased during the inspiration after the SwE. As a result, Ttot was increased in the breathes before, during, and after the swallows despite the decrease in Ti after the swallow. The inspiratory duty cycle, Ti/Ttot, was decreased in the subsequent breath after SwE because of the decrease in Ti and increase in Te. The Vr just before and after SwE was significantly reduced, as well as Vr/Ti. Similarly, Diapeak activity was decreased in the inspirations before and after the SwE. Therefore, swallows during early and mid expiration had an immediate effect on timing during expiration (increasing) and the subsequent inspiration (decreasing), while having a wider effect over time by decreasing respiratory output, as indicated by Vr and Diapeak on the breaths before and after the swallow.

Swallows during the EI transition (296 swallows, 26% of total) provided a slightly different pattern (Fig. 4). Immediately after SwEi, Ti was significantly decreased, whereas no significant changes were found in Te or Ttot in the breathes before, during, or after the swallow. A small increase in Ttot was observed in the breath after SwEi. After SwEi, Vr was significantly decreased and then increased in the subsequent breath. No changes in Vr/Ti were seen, demonstrating that Vr and Ti decreased proportionally in the immediate inspiration but then increased in the subsequent breath. In contrast, Diapeak was not significantly altered in the breaths before, during, or after SwEi.

### Table 1. Intact vs. tracheostomy goats and general swallowing data

<table>
<thead>
<tr>
<th>Goat</th>
<th>Tracheostomy</th>
<th>Number of Swallows</th>
<th>Swallows/min, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>42</td>
<td>1.87 ± 0.42</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>72</td>
<td>2.28 ± 0.93</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>47</td>
<td>1.58 ± 1.01</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>58</td>
<td>1.70 ± 1.30*</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>123</td>
<td>3.51 ± 1.23*</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>108</td>
<td>3.09 ± 1.02</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>190</td>
<td>2.11 ± 1.66*</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
<td>76</td>
<td>2.17 ± 1.13</td>
</tr>
<tr>
<td>9</td>
<td>No</td>
<td>186</td>
<td>4.97 ± 1.56</td>
</tr>
<tr>
<td>10</td>
<td>No</td>
<td>174</td>
<td>5.14 ± 1.91</td>
</tr>
<tr>
<td>11</td>
<td>No</td>
<td>109</td>
<td>2.88 ± 1.34*</td>
</tr>
<tr>
<td>12</td>
<td>No</td>
<td>282</td>
<td>2.02 ± 1.11</td>
</tr>
<tr>
<td>13</td>
<td>No</td>
<td>150</td>
<td>4.12 ± 1.97*</td>
</tr>
</tbody>
</table>

*Swallowing data for this animal was not normally distributed as determined by Kolmogorov-Smirnov test.
Therefore, swallows during the EI transition solely affected the subsequent inspiratory timing and, consequently, VT, but not total output, as suggested by Diapeak.

In the SwI analysis (507 swallows, 45%), TI was greatly increased during SwI, whereas no effect was seen in TI in the breaths before or after (Fig. 4). Swallows during SwI had no effect on TE. As a consequence, VT/Ttot was significantly increased. VT was slightly increased in the breath with a swallow and in the subsequent breath, whereas a significant decrease in DIapeak was observed during SwI. However, VT/TI was significantly decreased during the inspiratory swallow, primarily as a result of the increases in TI. These results suggest that swallows during inspiration affected respiratory timing but not output.

Because so few swallows were observed during the IE transition (8 swallows; 0.01%), great variability and lack of significant changes were observed in these data.

Within-breathe effects of swallows: gamma inspiratory and expiratory analysis. In the gamma inspiratory analysis, the slope of the TI-vs.-TI relationship for the n breaths was significantly different (P < 0.01) from zero and from the n - 1 breaths (Fig. 5B, Table 2). In addition, the estimated y-intercept of the TI-vs.-TI relationship was significantly above control (P < 0.02).

However, the observed Ti did not show a linear increase from the estimated intercept but, rather, an abrupt increase around 0 to 15 yI. In contrast, no differences were found in the TE-vs.-TI relationship either for the breaths before (n - 1) or during (n) the swallow (Fig. 5A and Table 2). Swallows during early inspiration tended to reduce VT as indicated by the significantly reduced y-intercept of the VT-vs.-TI relationship over the n breaths (P < 0.02), whereas swallows in the later part of inspiration increased VT, as indicated by the significant positive slope of the VT-vs.-TI relationship (P < 0.01; Fig. 5C, Table 2). In contrast, the slope of DIapeak vs. yI was not significantly different from zero for both the n and n - 1 relationships. However, a significant reduction in the y-intercept of the DIapeak vs. yI was seen for the n breaths (Fig. 5D, Table 2). Primarily because of the lengthening of TI above control in the n breaths (Fig. 5D), values greater than control (100%) were observed for yI.

In the gamma expiratory analysis (yIE), swallows during expiration had a different effect on the respiratory pattern generator. In the n - 1 breaths, the slope of the TE-vs.-yIE relationship, although significantly greater than zero, was small (Fig. 6A, Table 3). However, in the n breaths, swallowing during expiration had a significant effect on TE, although there was...
The effects of swallowing on breathing were studied, focusing on the impact of swallows on respiratory timing. The data show a significant attenuation of VT and increased TI, with a moderate effect on TE in the cycle before the swallow. However, swallows during expiration demonstrated a lesser effect than those during inspiration.

**Table 2. Inspiratory gamma analysis**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Slope</th>
<th>Intercept</th>
<th>R²</th>
<th>Slope</th>
<th>Intercept</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE</td>
<td>240</td>
<td>0.02 ± 0.03</td>
<td>99.4 ± 1.84</td>
<td>0.002</td>
<td>-0.03 ± 0.03</td>
<td>98.6 ± 1.56</td>
<td>0.005</td>
</tr>
<tr>
<td>Ti</td>
<td>240</td>
<td>0.02 ± 0.02†</td>
<td>100 ± 1.23</td>
<td>0.004</td>
<td>0.37 ± 0.003‡</td>
<td>110 ± 1.82‡</td>
<td>0.368</td>
</tr>
<tr>
<td>VT</td>
<td>240</td>
<td>0.03 ± 0.03†</td>
<td>97.1 ± 1.39</td>
<td>0.008</td>
<td>0.23 ± 0.03‡</td>
<td>88.8 ± 1.65‡</td>
<td>0.21</td>
</tr>
<tr>
<td>Dia peak</td>
<td>121</td>
<td>0.05 ± 0.07</td>
<td>96.5 ± 3.16</td>
<td>0.006</td>
<td>0.04 ± 0.06</td>
<td>94.2 ± 2.86‡</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are means ± SD. TE, expiratory time; Ti, inspiratory time; VT, tidal volume; Dia peak, peak diaphragmatic activity. *Slope is significantly different from zero (P < 0.01); †slopes (n - 1 vs. n) are significantly different from each other (P < 0.01); ‡y-intercepts are significantly different from control (100%) (P < 0.02).

The occurrence of spontaneous swallows that meet the criteria for the phase response analysis (427) demonstrated a bimodal distribution (Fig. 7A), with ~53% occurring during inspiration (average IE transition 0.47 ± 0.006; see arrow in Fig. 7A) and 47% during expiration. The 0.1 curve in Fig. 7B illustrates the effect of swallowing on respiratory timing in the breath before the swallow. A linear regression analysis demonstrated a strong within-phase dependency of TE on the timing of the onset of a swallow, whereas, in contrast, the following inspiratory period is attenuated irrespective of when the swallow occurred in the previous expiration. Similar to what was observed in γE analysis above, the increases in Ti and TE produced γE values >100%.

The slopes of VT vs. γE for both the n - 1 and n breaths were not significantly different from zero. However, only the y-intercept for the n breaths relationship was significantly less (88%) than control (P < 0.02; Table 3). In contrast, neither the slopes nor the intercepts for either Dia peak vs. γE relationships were significant (Fig. 6, Table 3). These results suggest that total respiratory output was not altered, but the overall attenuation of VT was similar to the decrease in inspiratory flow.

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**Fig. 6. γE Analysis of respiratory data.** A: TE; B: Ti; C: VT; D: Dia peak. Number of swallows as defined for this analysis in Methods and Fig. 2B in the graphs for TE, Ti, and VT was 259. Number of observations for Dia peak was 194. Each value is presented as a percentage of control of the individual animal’s control value.
analysis of the $\theta_1$ curve found a slope of $-1.01 \pm 0.01$, with a $y$-intercept of $-0.004 \pm 0.001$ and a correlation coefficient ($R^2$) of 0.97, indicating that swallowing had no effect on the timing of the previous cycle regardless of the phase of onset in the respiratory cycle. In contrast, the flattening of the $\theta_{n1}$ curve between the $\phi$ values of 0.1 and 0.3 reflects a phase delay in the respiratory timing produced by increases in $T_i$ with swallows during inspiration. The slope of the $\theta_{n1}$ curve after the IE transition ($=0.4$) to a $\phi$ value of 0.7 was approximately $-1.23$. This slope was more negative than that found for the $\theta_{n1}$ curve over the same period, indicating that swallows during this period may have produced a phase advance in the respiratory rhythm. This latter finding is supported by the tendency of $T_e$ to decrease early in the $T_e$-vs.-$\gamma_E$ relationship (Fig. 6A). After $\phi$ values of 0.7, the $\theta_{n1}$ curve again flattens and runs parallel with its expected intersection with zero. This flattening of the $\theta_{n1}$ curve and its extension beyond $\phi$ values of 1.0 is a result of both an increase in $T_e$ delay in the onset of the next cycle, and a comparable decrease in the subsequent $T_i$. These later observations are also seen in the $\gamma_E$ analysis in the $T_e$ above 90% and in the generally depressed $T_i$-vs.-$\gamma_E$ relationship in the breaths with swallows (Fig. 6 and Table 3). There was a parallel shift between the $\theta_{n1}$ and $\theta_{n2}$ and $\theta_{n3}$ curves, except between $\phi$ of 0.9 and 1.2, where an upturn in $\theta_{n2}$ and $\theta_{n3}$ suggests a slight phase delay. These results clearly support a type 1 or weak resetting of the respiratory rhythm generator.

The changes in $T_i$ relative to $T_e$ during a respiratory cycle due to swallowing is shown in the graph of $T_i$/ $T_{tot}(n)$-$T_i$/ $T_{tot}(c)$, where $c$ is the control breath (Fig. 7C). In this figure, the $T_i$/ $T_{tot}(n)$-$T_i$/ $T_{tot}(c)$ curve increases above control during the inspiratory section of the phase response plot. This increase is explained by progressive increases in $T_i$, with swallows during inspiration having no effect on $T_e$ (Fig. 5). However, after the IE transition ($=0.4$), the cause of the increased $T_i$/ $T_{tot}$ is due to an overall shortening of $T_e$ relative to $T_i$, as shown in the $\gamma_E$ analysis (Fig. 6). Thereafter, the eventual return to control levels of the $T_i$/ $T_{tot}(n)$-$T_i$/ $T_{tot}(c)$ curve is due to the relative lengthening of $T_e$ compared with a general shortening of $T_i$ (Fig. 6). The effect of swallows on $T_i$/ $T_{tot}$ is limited to the $n1$ breaths, as $n2$ and $n3$ curves are observed at control levels.

In Fig. 8, the effect of swallows on $V_t$ is seen during expiration ($\phi=-0.8$ to $1.5$), where the $V_t$/ $V_{peak}(n)$-$V_t$/ $V_{peak}(c)$ curve is lowered during the inspiration after the swallow ($n2$ curve). Subsequent compensation due to a reduction in $V_t$ was not seen in the $n3$ curve. A modest decrease in $Dia_{peak}(n)/Dia_{peak}(c)$ is observed at different sections of the $n1$ and $n2$ curves. The $n1$ curve is slightly depressed near the IE transition ($\phi=0.35$), whereas the $n2$ curve is depressed in the later part of expiration ($\phi=0.8$; Fig. 8B). In contrast to the categorical data (Fig. 4) and the within-breath data (Figs. 5 and 6), these latter data show that swallowing has a limited, temporal perturbation effect on respiratory output.

Figure 9 presents the differences in $\theta_{n1}$-$1-\theta_{ideal}$, $\theta_{n1}$-$1-\theta_{n1}$, $\theta_{n2}$-$\theta_{n1}$, and $\theta_{n3}$-$\theta_{n2}$ every 0.05 $\phi$ interval. No significant difference was found for $\theta_{n1}$-$1-\theta_{ideal}$ at any value of $\phi$ ($P<0.02$), thus supporting the observation that the timing of the previous breath was unaltered. In contrast, $\theta_{n1}$-$1$ differed significantly from the predicted difference of 1 at several points along the $\phi$ axis ($P<0.02$). The increase in $\theta_{n1}$-$1$ from 0.15 to 0.40 of $\phi$ reflects a phase delay in the $n1$ curve due solely to increases in $T_i$. Thereafter, from a $\phi$ value of 0.40 to 0.60, the $\theta_{n1}$-$1$ curve progressively decreased. Although fewer swallows were observed during this phase of ventilation, this decrease was due to the mixed and varied effects of swallows to 1) increase $T_i$ just before the swallow (phase delay) and 2) decrease $T_e$ (phase advance) in early expiration. From a $\phi$ value of 0.65 to 0.85, the difference between $\theta_{n1}$ and $\theta_{n1}$-$1$ was not significantly different either from 1 or from the expected difference if swallowing had no effect on respiration. Thereafter, $\theta_{n1}$-$1$ significantly increased because of the effect of swallows late in expiration to increase $T_e$ or phase delay the onset of the next breath ($P<0.02$). A significant decrease ($P<0.2$) in the $\theta_{n2}$-$\theta_{n1}$ curve between a $\phi$ of 0.9 and 1.1 is a result of the effect of swallows during the later part of expiration to also decrease the subsequent $T_i$ and produce a phase advance of the next respiratory cycle.

**DISCUSSION**

Our data suggest that spontaneous swallows have a phase-dependent effect on respiratory timing and output in the awake state. Changes in breathing before and after a swallow further suggest that the interaction between the respiratory and swallowing pattern generators exists beyond the apparent, immediate, all-or-nothing event of swallowing.

The interaction between swallowing and breathing. The distribution of swallows during the phases of ventilation differs among animals, infants, and adults.
swallows at various
values
effect of swallowing to cause phase delay in the respiratory rhythm, for this analysis as presented in METHODS. A total of 427 swallows meet the criteria and the phase response analysis of the effect of the onset of swallowing respiratory timing. A total of 427 swallows meet the criteria presented relative to their onset during a normalized respiratory cycle (21). In awake rabbits, swallows during inspiration significantly increased T_E and the preceding T_I, whereas during inspiration swallows significantly increased T_I and the subsequent T_E (20). These swallows did not significantly affect T_I or T_E in the breaths that followed. In unanesthetized humans, both

unanesthetized (18, 20) and anesthetized (18, 19, 20) animals, 80–95% of the spontaneous swallows occur during inspiration. In human infants, spontaneous swallows are reported to be equally distributed during expiration and inspiration (30). In unanesthetized and anesthetized adults, spontaneous swallows are primarily produced during expiration (5, 23, 24, 27). These studies suggest that swallowing may be coupled to specific phases of ventilation. In goats, a biphasic occurrence of swallows during the phases of ventilation was observed, with the least number of swallows occurring during the IE transition and early expiration. That over half of the swallows occur during inspiration suggests a well-coordinated, anatomically efficient means to minimize aspirations during a phase of ventilation that is normally at high risk, at least in human adults. In goats, the epiglottis overlaps the soft palate (10), which has been shown to allow a bolus to circumvent the glottis during an inspiratory swallow and pass into the esophagus (22). On the basis of this anatomy, Negus (22) proposed that airflow would continue during a swallow. A similar anatomic mechanism has been proposed to occur in infants during inspiratory swallows that not only minimizes aspirations but also allows for an uninterrupted airflow (6, 28). However, in goats, we observed an interruption of airflow with inspiratory swallows similar to that found in infants by Wilson et al. (30). We attribute this interruption to a decrease in diaphragm activity (observed in this study) and upper airway closure due to constrictor activity (10). Therefore, we hypothesize that in goats the overlapping of the soft palate and epiglottis allows for inspiratory swallows with a low risk for aspirations but does not allow for separate air and liquid channels.

Although both the presence of swallows during EI transition and inspiration and the absence of pharyngolaryngeal problems suggest a benign interaction between the respiratory and swallowing functions, the lack of spontaneous swallows during the IE transition and early expiration is curious. In awake humans, Paydarfar et al. (27) observed the highest occurrence of spontaneous swallows during the IE transition and the lowest during EI transition, suggesting a very different relationship between the swallowing and respiratory pattern generators in humans, dogs, monkeys, and goats. Several studies (19, 27) have shown that stimulation of peripheral afferents during IE transition has a disruptive effect on respiratory timing, which may be the neurophysiological basis for the reduced occurrence of spontaneous swallows during transition in these animals.

Less well investigated has been the effect of spontaneous swallows on respiratory timing and total output. Studies in decerebrate cats showed that swallows increased the duration of the current and subsequent respiratory cycle (21). In awake rabbits, swallows during expiration significantly increased T_E and the preceding T_I, whereas during inspiration swallows significantly increased T_I and the subsequent T_E (20). These swallows did not significantly affect T_I or T_E in the breaths that followed. In unanesthetized humans, both

Fig. 7. Distribution of swallows throughout normalized respiration and the phase response analysis of the effect of the onset of swallowing respiratory timing. A total of 427 swallows meet the criteria for this analysis as presented in METHODS. A: swallows as a percentage of total swallows presented relative to their onset during a normalized respiratory cycle (\( \phi \)). Average transition from inspiration to expiration (IE) was \(-0.47 \pm 0.006\) of \( \phi \). B: individual values for phase response analysis of the cophase for breaths before (\( n-1 \)), during (\( n_1 \)), and 2 (\( n_2, n_3 \)) after a swallow. Solid line for \( n-1, n_1, n_2, \) and \( n_3 \) represents the best-fit curves for the nonlinear regression analysis. Formulas for the calculations of \( \phi, \theta_{n-1}, \theta_n, \theta_{n+1}, \) and \( \theta_n \) are presented in METHODS and Fig. 3A. C: changes in T_I/T_tot for swallows at various \( \phi \) and changes in breaths before (\( n-1 \)), during (\( n_1 \)), and 2 after (\( n_2 \) and \( n_3 \)) T_I/T_tot values are expressed as a fraction of control breaths (c) as defined in METHODS. Because of the effect of swallowing to cause phase delay in the respiratory rhythm, values >1.0 were observed for \( \phi \).
spontaneous and water-induced swallows during expiration increased $T_E$ and $T_{tot}$, as well as $V_T$, immediately after the swallow (23). Spontaneous swallows during inspiration reduced $T_I$, $V_T$, and the following $T_E$. In the subsequent breath, $V_T$ was increased. A similar response was found in stimulated swallows that occurred during inspiration, except that $T_{tot}$ was decreased (23). In goats, swallows during expiration also had a similar effect on $T_E$ and $T_{tot}$. However, in contrast to data in humans (23), the ensuing $T_I$, $V_T$, and $\text{Dia peak}$ were significantly reduced, suggesting that an inhibitory effect of swallowing persisted in the following inspiratory timing and output. The increase in $T_I$ with swallows during inspiration in goats was similar to that found in rabbits (20) but is in contrast to the findings in humans (23). Similarly, $V_T$ was slightly increased, which is opposite of that found in humans (23), and the findings of $\text{Dia peak}$ in goats study further support the idea that total respiratory output is unaltered whereas respiratory timing increases with swallows during inspiration.

Although the information in the literature on the effect of swallows on the present and subsequent breaths reveals general trends in the interaction between respiratory and swallowing centers, it does not investigate or eliminate a within-breath and/or multi-breath interaction. Most studies (20, 23) utilized the breath(s) before the swallows as controls. This latter point assumes that stimulated and spontaneous swallows only have an effect on breathing during and after the swallows. Although our results support these findings, they also show that both timing and the output to the diaphragm are altered before a swallow. The neural substrate for this interaction is unknown. However, it is presumed that a build-up of secretions in the upper airway activates receptors that travel to the nucleus tractus solitarius via the superior laryngeal nerve (15). Jean (12–14) reported that some neurons in the nucleus tractus solitarius exhibit a "preswallowing activity" that may act as trigger neurons for swallowing whose activity is increased with stimulation of the superior laryngeal nerve. Dick et al. (7) also observed that stimulation of the superior laryngeal nerve below the threshold for eliciting a swallow resulted in a prolongation of $T_E$. Together, these results suggest a peripheral feedback mechanism to the medullary neurons that may elicit changes before a swallow and function to prepare the animal for a swallow.

The within-breath analysis of the effects of swallowing on the pattern of breathing provides an insight into the moment-to-moment relationship between the swallowing and respiratory centers. In infants, there is a linear relationship between the duration of inspiration
and the Ti at the onset of airway closure due to a swallow (30). The earlier the swallow occurred (within the first half of a breath), the shorter the Ti. Therefore, swallows produced a longer period of inspiration. Swallows during expiration also had the greatest effect in increasing Ttot. This relationship produced a negative correlation between Ttot and the occurrence of swallow during expiration. This finding is in contrast to the observation in anesthetized and unanesthetized adult humans, in whom spontaneous swallows occurred primarily during expiration, producing a positive relationship between Te and the occurrence of swallows during expiration, thereby increasing Ttot (23, 24). However, in anesthetized adult humans, swallows during inspiration abruptly interrupted inspiration and were followed by a short expiratory period, thereby producing a significant positive correlation between Ti and the onset time of the swallows (24).

Similarly, there is a positive correlation between VT and the onset of swallows during inspiration in anesthetized and unanesthetized adults (23, 24). In contrast, an abrupt cessation of inspiration followed by expiration was not observed in goats. Instead, swallows progressively lengthened Ti the later they occurred in inspiration (Table 2, Fig. 5B). In addition, although swallows at the very beginning of inspiration were related to a reduced VT, thereafter a positive correlation (above control) was observed for VT and the onset of the swallow during inspiration. In contrast, no change in Diapeak was observed. These observations suggest that not only did swallowing insert a pause into the inspiratory period while not widening the swallow complex and increasing the interruption in flow, it also had a mild progressive inhibition on ventilation (decreasing) while not altering total activity of the diaphragm.

During expiration in goats, the relationships between the onset of a swallow and the values of Te, Ti, and VT are considerably different from previously reported data. In contrast to those for humans, our data show that the earlier the onset of a swallow during expiration, the shorter the Te observed, until ~75% ykrs, at which point swallowing increased Te above control. This temporal effect of swallowing during expiration is also seen in the negative slope of n − 1 Tt data, whereas a generalized overall inhibitory effect of swallowing was found in the relationship of the Ti vs. ykrs for the n breaths. Also consistent with this latter finding was the significant effect of expiratory swallows on the subsequent VT, whereas Diapeak was not altered. These findings suggest that output to the diaphragm is not reduced during inspiration after a swallow; only the timing and the subsequent VT are reduced.

Phase response analysis in the interaction of breathing and swallowing. A major advantage of the phase response analysis is the capability to characterize the relationship between pattern generators without knowing a priori the specific neuroanatomic basis of the interaction (29, 31). The phase response of stimulated and spontaneous swallows has only been investigated in humans by Paydarfar et al. (27), who found that the later a swallow occurred during inspiration, the later the onset of the subsequent breath. The peak of this response was near IE transition, after which no effect on the onset of the next cycle was seen until the swallow occurred at the very end of the respiratory cycle. This nonlinear effect of swallowing on breathing is very similar to the results of Nishino and colleagues (23, 24). In addition, Paydarfar et al. (27) demonstrated that swallows produced a “true” resetting of the respiratory rhythm. In other words, instead of an immediate, short-term shift in the bulbo-spinal output produced by swallowing, a parallel shift in the subsequent breaths occurred. In goats, resetting of the respiratory rhythm generator also occurs after swallows at different onsets within the respiratory cycle, with a parallel shift in the starting of subsequent breaths. The continuity of the calculated cophases (θ) further supports the concept of a continual oscillation of the respiratory pattern generator and true phase resetting.

However, the results from the phase response analysis in our study differ from those found in humans by Paydarfar et al. (27). The basis for this difference lies in the within-breath effects of swallows on breathing. The type of resetting observed by Paydarfar et al. was a type 0, in which the net change of the cophase was zero over a cycle of φ. Except for the phase delay and advance observed in the θn1 and θn2 curves, the net slope of the θn1, θn2, and θn3 curves in our study approximated a negative slope of −1, demonstrating a type 1 (weak) resetting effect of swallowing on breathing in goats (29, 31). This is also in contrast to a type 0 resetting observed in the breathing of anesthetized cats by different levels of superior laryngeal nerve stimulation (26).

EI and IE transitions and swallows. The transition from EI or IE has been suggested as a critical period during the respiratory cycle (7, 23, 24, 26, 27). Dick et al. (7) observed in decerebrate, unanesthetized cats that superior laryngeal nerve stimulation during EI and IE transitions consistently produced more swallows during EI transition and the least during IE transition, which is consistent with our observations of spontaneous swallows. They interpreted the occurrence of the swallows during phase transitions as points of interactions between the respiratory and swallowing pattern generators in which medullary postinspiratory neurons provide a possible neural substrate for this interaction. The definition of the IE transition period in our study extended from the observed occurrence of the thyroarytenoid activity in goats (10), which begins immediately after peak inspiratory activity. During eupnea, classifying swallows within the IE period (Fig. 1A) coincides with the abrupt depolarization of the medullary postinspiratory neurons. Too few swallows were seen during the IE transitions to interpret their effect, except to infer that the natural probability of swallows during this period is greatly reduced. The lack of swallows during the early phase of expiration also coincides with the repolarization of these medullary neurons in phase 1 of expiration. The observed values for timing and output for

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swallows during the EI transition were halfway between the observed values for swallows during expiration and inspiration. Immediately after swallows during EI transition, Ti and Vr were reduced, whereas there was no effect on Dia_peak. Similar to the findings with swallows during inspiration, Vr in the subsequent breaths was increased whereas Ti and Dia_peak were not changed. Therefore, these results support the concept that EI and IE transitions are critical periods of interaction between the respiratory and swallowing centers for timing but not respiratory output in goats. These results also suggest that the underlying neural substrate integrating superior laryngeal stimulation and swallowing and the respiratory pattern generator in goats, compared with humans and cats, is functionally different. However, to address these findings more conclusively, we believe that a combination of within- and multibreath analyses of swallowing and breathing are essential to provide an in-depth view of the nature and type of relationship between the two generators under various physiological conditions and using a wide range of whole and reduced animal preparations.

In conclusion, our study shows that swallowing produces a phase-dependent resetting of the respiratory rhythm generator in goats. Furthermore, the data suggest that the interaction between swallowing and breathing occurs before and after a swallow. We suggest that the interrelationship between the pattern generators is functionally diverse in different species and may involve not just the pattern generators directly but also a diversity of peripheral feedback mechanisms and their integration centrally.

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