

Inhibition of Resting Lower Esophageal Sphincter Pressure by Pharyngeal Water Stimulation in Humans

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Background/Aims: Normal inhibition of lower esophageal sphincter (LES) tone occurs during swallowing and belching. However, it is known that it may occur independently of these functions. The aim of this study was to characterize the effect of pharyngeal water stimulation on resting LES pressure. **Methods:** The effect of rapid-pulse and slow continuous intrapharyngeal injection of minute increments of water on the resting tone of the upper and LES of 14 healthy young volunteers was evaluated by concurrent manometry, submental electromyography, and respirography. **Results:** At a threshold volume, pharyngeal water injection induced an isolated LES relaxation in all volunteers. The threshold volume inducing LES relaxation by rapid-pulse injection, 0.16 ± 0.01 mL, was significantly lower than that with slow continuous injection (0.5 ± 0.05 mL) ($P < 0.05$). The duration and magnitude of LES relaxation were not volume dependent. The duration of LES relaxation induced by rapid-pulse injection was significantly longer than that of swallows. **Conclusions:** Minute amounts of liquid injected into the pharynx induce LES relaxation different from that of the normal swallow. Neither the duration nor the magnitude of this relaxation is volume dependent. Whereas the contribution of this finding to the mechanism of transient LES relaxation remains to be ascertained, it may partially explain the variability of the basal LES pressure.

Normal inhibition of lower esophageal sphincter (LES) tone occurs during swallowing and belching. However, it is known that sphincter relaxation may occur independently of these functions.¹⁻⁶ During our studies to characterize swallows triggered by pharyngeal water stimulation, it was noted that subthreshold volumes for pharyngeal swallow resulted in LES relaxation without stimulation of swallowing.

Because the effect of direct stimulation of the pharynx on the resting LES tone in humans has not been systematically investigated, this study was undertaken to characterize the effect of pharyngeal water stimulation on the resting LES pressure.

Materials and Methods

We studied 14 healthy young volunteers (6 women and 8 men; age range, 20-32 years). The studies were performed with the subjects in the supine position after overnight fasting. The study protocols were approved by the Human Research Review Committee of the Medical College of Wisconsin, and the subjects gave informed written consent.

LES pressure and esophageal-body and gastric pressure phenomena were monitored by a catheter assembly that incorporated a sleeve device ($6 \times 0.5 \times 0.4$ cm) (Dentsleeve, Adelaide, Australia); four esophageal recording sites located 3, 6, 12, and 15 cm above the sleeve; and one gastric port located at the distal end of the sleeve device. A recording site at the proximal end of the sleeve was used for manometric positioning.

The upper esophageal sphincter was monitored by a second catheter assembly that incorporated an upper esophageal sphincter sleeve device ($6 \times 0.5 \times 0.3$ cm) (Dentsleeve). The sleeve assembly had recording ports at the proximal and distal ends of the sleeve for manometric positioning. It also incorporated an injection port located 2 cm proximal to the sleeve device. This manometric assembly was positioned such that the injection port faced posteriorly. The subjects were monitored for 10 minutes after positioning of the two manometric assemblies, after which pharyngeal water injections were performed by two methods: rapid-pulse and slow continuous injections. Rapid-pulse injections were started with 0.1 mL water, and the volume was increased by 0.1-mL increments until an irrepressible swallow occurred. Slow continuous infusion was performed in 10 subjects at a rate of 5.5 mL/min with a Harvard infusion pump (model N0975; Harvard Apparatus Co., Inc., Dover, MA) until an irrepressible swallow occurred. Each injection was started 5-10 seconds after the LES pressure stabilized at baseline after a swallow, and subjects withheld swallowing as long as they could. Each volume was tested three times.

Respiration was monitored with a RespiTrace system (Ambulatory Monitoring, Inc., Ardsley, NY), which recorded respiration-induced rib cage movement through a coiled insulated electric wire. Swallowing was monitored by submental surface

electromyography with a surface electrode taped beneath the chin over the geniohyoid-mylohyoid muscle complex. The electromyographic signals and the respirographic tracings were recorded on the same polygraph paper on which the manometric pressure phenomena were recorded. In addition, subjects signaled swallowing with a handheld event marker. During the actual test period, the polygraph paper was run at a speed of 25 mm/s. Between the water injections, the paper speed was kept at 10 mm/s. We evaluated the nature of the LES pressure response to pharyngeal water stimulation during rapid-pulse and slow continuous injection, the onset and duration of the LES response to pharyngeal water stimulation, the magnitude of the LES pressure response to pharyngeal water stimulation, the upper esophageal sphincter pressure response to pharyngeal water stimulation, and esophageal-body activity in response to pharyngeal water stimulation.

LES relaxation induced by pharyngeal water stimulation was compared with LES relaxation induced by the preceding volitional swallow. The nadir of the relaxation was used for comparison. The LES pressure response to pharyngeal water stimulation at each volume was considered positive when it occurred during all three trials. Occurrence of swallow was determined by the presence of submental electromyographic activity, deglutitive apnea, the volunteer's signal, and the observer's marking. Statistical analysis was performed with analysis of variance with repeated measures and χ^2 when appropriate. Data in the text are presented as mean \pm SEM unless stated otherwise.

Results

Rapid-Pulse Injection

A total of 212 rapid water injections were performed. In all volunteers, rapid water injections into the pharynx resulted in a decline in the resting LES pressure, which occurred in response to 188 of 212 injections. The LES pressure decline began 2.4 ± 0.17 seconds after the completion of water injection. The smallest volume that induced a decline in resting LES pressure in all three trials, the threshold volume, averaged 0.16 ± 0.01 mL. Injection of the threshold volume resulted in complete LES relaxation in half of the trials. In the rest, the pressure decline ranged between 30% and 85% of the resting LES pressure (Figure 1).

In each subject, with each incremental increase in the injected volume, the LES relaxation continued to occur until the injected volume reached the threshold for the stimulation of pharyngeal swallows (0.8 ± 0.1 mL). These swallows occurred immediately after the completion of water injection.

In 6 subjects, injection of the threshold volume induced complete LES relaxation in all three trials. In this group, complete relaxation continued with increasing increments of injected volume until a pharyngeal swallow occurred. Among the remaining 8 subjects, 3 developed

complete LES relaxation in response to volumes larger than the threshold volume. Among the other 5 subjects, the LES relaxation in response to all volumes of pharyngeal injection remained partial in 4 but was variable in 1 subject.

In most instances, the LES relaxations were ended by spontaneous swallows. However, in a total of 70 instances (38%), LES pressure recovered spontaneously before a swallow occurred (Figure 1B and C). These trials were used to measure the duration of LES relaxation. Analysis of these instances showed that there was no direct relation between the volume of injected water and the duration of LES relaxation. However, the duration of LES relaxation induced by threshold volume (6.0 ± 1.0 seconds) was significantly longer than that induced by a primary (3.0 ± 0.3 seconds) or pharyngeal swallow (3.2 ± 0.4 seconds).

When the LES relaxation recovered spontaneously, in 33% of instances it was followed by a postrelaxation contraction (Figure 2) that resulted in an LES pressure higher than the preinjection value. In the remaining instances, the LES pressure returned to the preinjection level without a postrelaxation contraction (Figure 1B and C).

In 35 of 188 trials (19%), pharyngeal water injection was associated with minimal submental electromyographic activity. Twenty-two of these activities (12%) occurred 7.5 ± 0.7 seconds (range, 3–15 seconds) after the onset of LES relaxation. The rest (7%) occurred either simultaneously with the onset of LES relaxation or within 1 second of its occurrence (Figure 3).

In nine instances, pharyngeal water injection was associated with distal esophageal motor activity. In eight of them, simultaneous contractions extended caudally from 6 cm above the LES, and in one, the simultaneous contraction involved the entire esophagus. These contractions occurred concurrently with the onset of the recovery of LES pressure (Figure 3A).

In 90% of the trials, rapid pharyngeal water injection resulted in an increase in upper esophageal sphincter pressure by $170\% \pm 10\%$ over the preinjection values (Figures 1–3). In the remaining instances, the upper esophageal sphincter pressure did not change.

Slow Continuous Injection

Similar to rapid-pulse injection, slow continuous injection of water into the pharynx invariably resulted in LES relaxation (Figure 4). The smallest slowly injected volume that caused LES relaxation, the threshold volume, averaged 0.5 ± 0.05 mL. This volume was significantly larger than that of the rapid-pulse injection ($P < 0.05$). A comparison of the threshold volumes required to induce

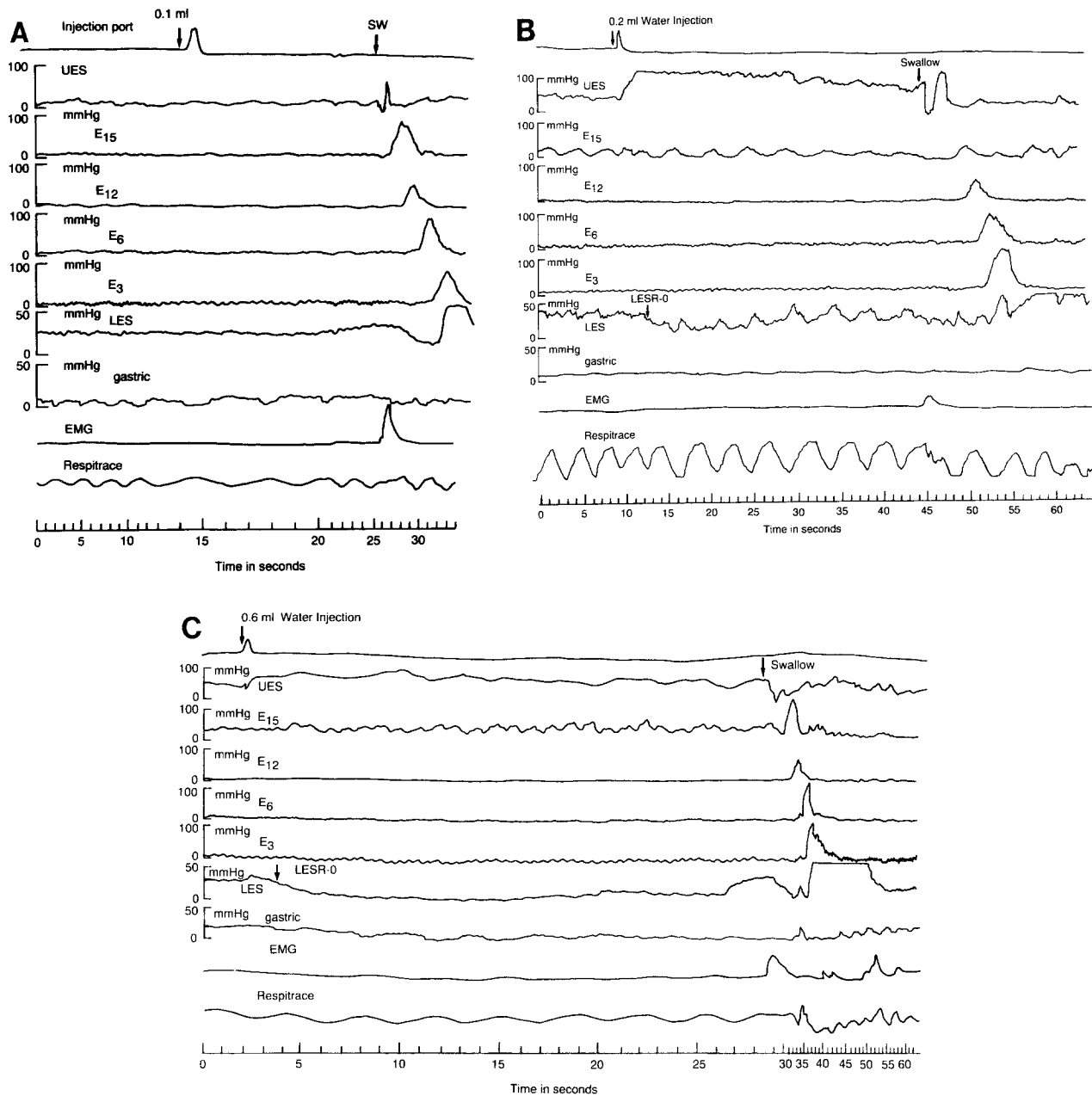


Figure 1. The effect of incremental amounts of water injected rapidly into the pharynx on LES resting pressure. (A) Subthreshold volume. Injection of 0.1 mL water directed to the posterior wall of the pharynx did not induce any change in the LES pressure. Water injection is followed by a spontaneous swallow 10 seconds later. (B) Partial LES relaxation induced by 0.2 mL water injected into the pharynx. (C) Complete LES relaxation induced by injection of 0.6 mL water into the pharynx. In these examples, the LES recovers from relaxation spontaneously. In addition, this recovery is not accompanied by a postrelaxation contraction. In B and C, there is an increase in the upper esophageal sphincter resting pressure after the injections.

LES relaxation and to induce a pharyngeal swallow is shown in Figure 5. In both modes of water injection, a significantly larger volume of water was required to induce a pharyngeal swallow than to induce isolated LES relaxation.

In 5 of 10 subjects, the threshold volume for slow continuous injection induced complete relaxation of the LES. Four of these subjects were among those with complete LES relaxation at the threshold volume for rapid-pulse injections. In the remaining subjects, the LES relax-

ation was partial, ranging between 40% and 80% of the preinjection level. The LES relaxation occurred 5.6 ± 0.5 seconds after the initiation of slow water injection. In cases of partial relaxation, the LES pressure did not decrease further between the onset of LES relaxation and the occurrence of pharyngeal swallow. Contrary to rapid-pulse injection, none of the volunteers with partial LES relaxation at the threshold volume developed complete LES relaxation with continued water infusion.

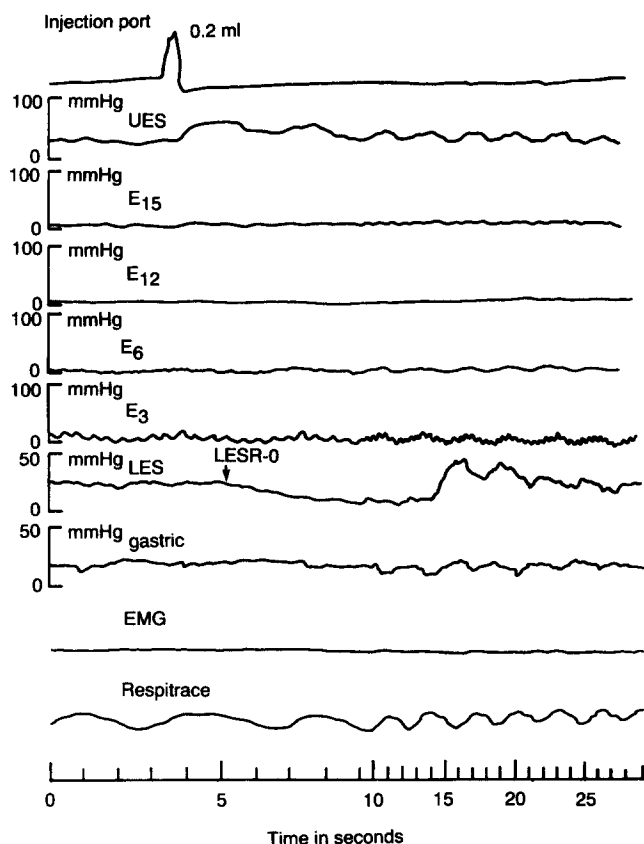


Figure 2. Postrelaxation contraction after the recovery of LES from relaxation induced by pharyngeal water injection. A 0.2-mL water injection into the pharynx induced an 80% LES pressure decline from the pre-ejection value. The total duration of this relaxation was 9 seconds. Recovery of the LES from this relaxation was accompanied by a postrelaxation contraction. This type of recovery was found in 33% of the trials.

Similar to rapid-pulse injection, upper esophageal sphincter pressure increased during slow continuous injection (Figure 4). This finding occurred in 90% of the trials. The increase averaged $138\% \pm 12\%$ over the preinjection values. In the rest, the upper esophageal sphincter pressure did not change during slow pharyngeal water injection.

Discussion

In this study, we characterized the effect of pharyngeal water stimulation on the resting LES pressure. Our study findings indicate that rapid or slow injection of minute amounts of water into the pharynx induces relaxation of the LES. This relaxation was complete in about half of the subjects. An increase in the volume of injected water resulted in complete LES relaxation in an additional 4 subjects, whereas in the remaining subjects, LES relaxation remained partial regardless of the volume of injected water. Our study findings also indicate that if the water is injected slowly, a significantly larger vol-

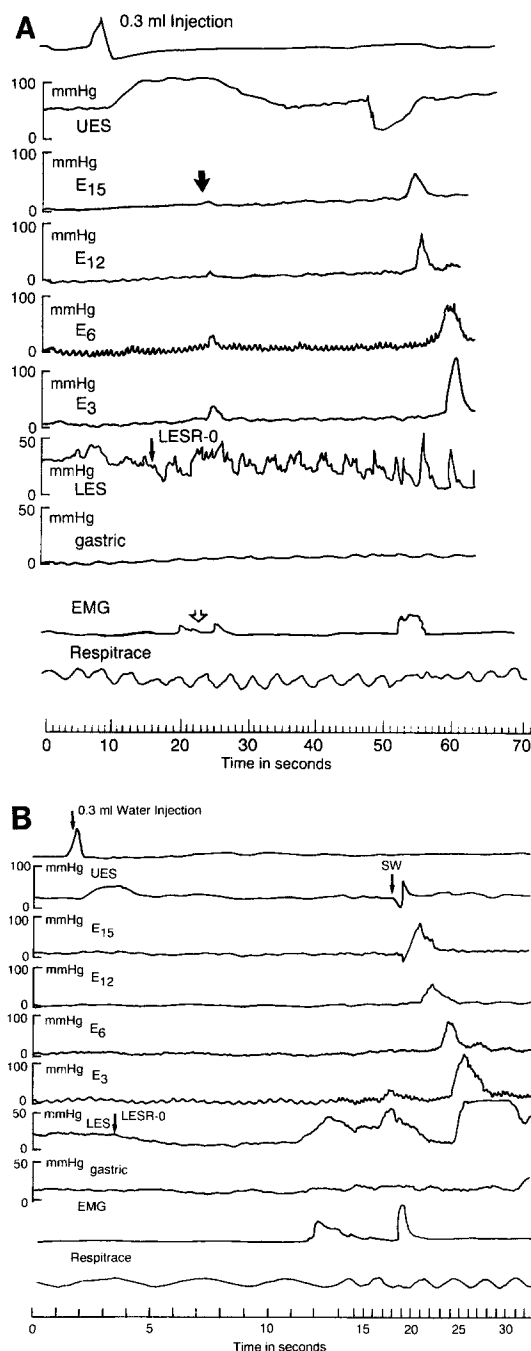


Figure 3. LES relaxations induced by pharyngeal water injection that were associated with submental electromyographic activities. (A) Injection of 0.3 mL water into the pharynx induced a partial LES relaxation. Four seconds after the onset of LES relaxation, electromyographic activity of submental muscles occurred (open arrow). This activity was accompanied by a small simultaneous contraction of the body of the esophagus (closed arrow). These events were associated with the return of LES pressure to the preinjection value. (B) Injection of 0.3 mL water into the pharynx in a different volunteer resulted in complete LES relaxation. Eight seconds after the onset of LES relaxation, a submental electromyographic signal that was temporally related to the termination of the LES relaxation developed. Contrary to the example in Figure 1A, this signal was not accompanied by an esophageal contraction. In both examples, there was a short duration of increased upper esophageal sphincter pressure after water injection.

ume is required to induce LES relaxation than during rapid-pulse injection.

Earlier studies have shown that pharyngeal water injection at a threshold volume during both rapid-pulse and slow continuous injection results in an irrepressible swallow (pharyngeal, or secondary, swallow).⁷ The findings of this study indicate that a significantly smaller volume of water is required to induce LES relaxation than to induce a pharyngeal swallow.

The mechanism of LES relaxation induced by pharyngeal water stimulation remains to be elucidated. However, previous studies of pharyngeal mechanical stimulation in opossums² suggest that isolated LES relaxation may occur as part of the stimulation of the swallowing pathway. The fact that our subjects were instructed to resist swallowing may have eliminated swallows that would have occurred otherwise and may have isolated LES relaxation from the rest of the swallowing complex.

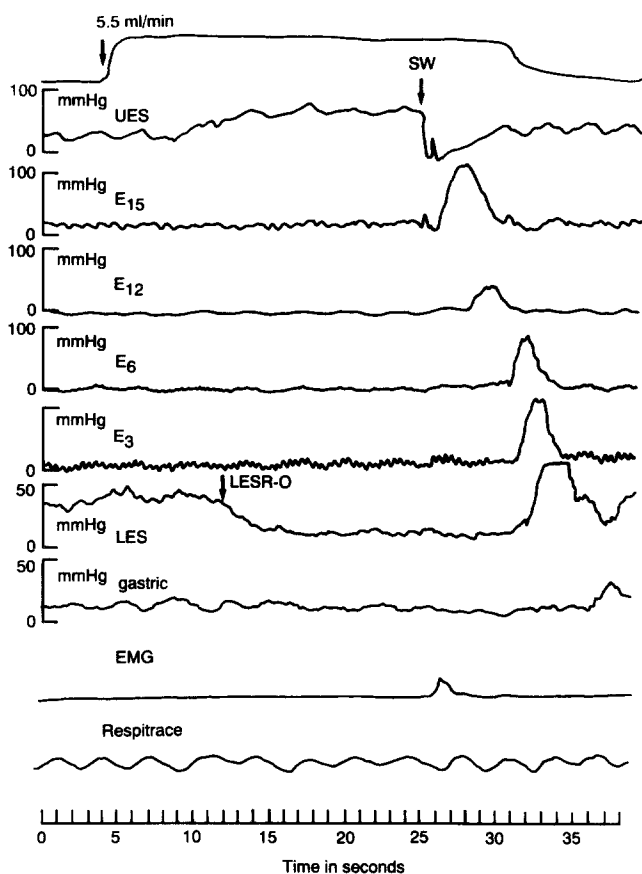


Figure 4. LES relaxation induced by intrapharyngeal slow continuous water injection. Injection of water at the rate of 5.5 mL/min resulted in complete LES relaxation (arrow) after 8 seconds. This relaxation was not accompanied by either electromyographic or esophageal contractile activities. Similar to rapid-pulse injection, this mode of injection also resulted in an increase in the upper esophageal sphincter resting pressure. Twelve seconds later, pharyngeal water infusion reached the threshold for a pharyngeal swallow, marked by SW. This threshold is heralded by a submental electromyographic signal.

Swallowing results in deglutitive inhibition in the esophagus and LES, followed by excitation. Previous studies have shown that the threshold for activation of the deglutitive inhibition is lower than that of the deglutitive excitation.⁸ Our finding that a significantly smaller volume is needed to induce LES relaxation than to initiate an irrepressible swallow corroborates these earlier findings.

LES tone is modulated by the effect of excitatory and inhibitory vagal⁹ impulses to the LES muscle. In the current study, injection of the threshold volume resulted in complete LES relaxation in approximately half of the subjects. An additional 3 subjects' response could be converted from partial to complete relaxation with an increase in the volume of injected water. However, in 4 individuals, the LES relaxation was consistently incomplete. These findings suggest that pharyngeal mechanoreceptor stimulation results in various combinations of activation of inhibitory and inhibition of excitatory pathways that control the LES tone. It also suggests the existence of intersubject variation in the threshold of activation of these pathways.

Inhibition of LES tone independent of swallowing and belching is known to occur; it is called transient LES relaxation. Although the exact mechanism of these relaxations is not known, it has been proposed that they may occur as part of subthreshold swallows,^{1,2} incomplete belch events, or both.³ Presence of a manometric catheter

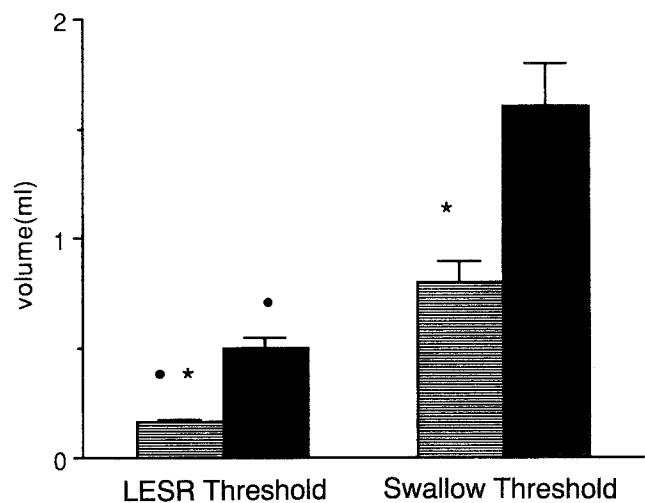


Figure 5. Comparison of the threshold volumes that induce LES relaxation (LESR Threshold) with that of pharyngeal swallow (Swallow Threshold) induced by rapid (▨) and slow (■) injection. For both modes of water injection, the threshold volume required to induce LES relaxation was significantly smaller than that for the induction of pharyngeal swallow (**P* < 0.05). In addition, for both events to occur, a significantly smaller volume was required when the water was injected rapidly than when it was injected slowly (**P* < 0.05).

in the pharynx⁴ and gastric fundal distention^{5,6} have been shown to increase the frequency of these relaxations of the LES. The present study identifies yet another factor that influences LES resting tone. Whereas the possible contribution of this finding to the mechanism of transient LES relaxation remains to be ascertained, it may explain the fluctuations of LES resting pressure observed during long-term measurements.

It is conceivable that minute amounts of fluid introduced into the pharynx through salivary production, postnasal drip, or other aerodigestive tract discharges may induce complete or partial relaxation of the LES and facilitate gastroesophageal reflux. This may also explain why elimination of a transnasal catheter did not completely abolish the occurrence of transient LES relaxation.⁴ Further studies are needed to investigate these issues.

Our findings also corroborate earlier studies, which showed that pharyngeal mechanical stimulation in cats¹⁰ and water stimulation in humans⁷ results in an increase in the resting tone of the upper esophageal sphincter, the pharyngo–upper esophageal sphincter contractile reflex. Although the physiological role of this reflex remains to be elucidated, it might be speculated that it functions as an airway-protective mechanism whereby retrograde entry of small volumes of liquid into the pharynx from the stomach results in augmentation of upper esophageal sphincter tone, reducing the chance of further regurgitation into the pharynx.

In conclusion, minute amounts of liquid injected either abruptly or slowly into the pharynx induce LES relaxation. The duration and magnitude of LES relaxation induced by pharyngeal water injection are different from those of the normal swallow. Neither the duration nor the magnitude of this relaxation is volume dependent.

The physiological contributions of this finding remain to be elucidated.

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