Effects of laryngeal restriction on pharyngeal peristalsis and biomechanics: Clinical implications

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Submitted 6 January 2016; accepted in final form 12 April 2016

Shaker R, Sanvanson P, Balasubramanian G, Kern M, Wuerl A, Hyngstrom A. Effects of laryngeal restriction on pharyngeal peristalsis and biomechanics: Clinical implications. Am J Physiol Gastrointest Liver Physiol 310: G1036–G1043, 2016. First published April 14, 2016; doi:10.1152/ajpgi.00010.2016.—To date, rehabilitative exercises aimed at strengthening the pharyngeal muscles have not been developed due to the inability to successfully overload and fatigue these muscles during their contraction, a necessary requirement for strength training. The purpose of this study was to test the hypothesis that applying resistance against anterosuperior movement of the hyolaryngeal complex will overload the pharyngeal muscles and by repetitive swallowing will result in their fatigue manifested by a reduction in pharyngeal peristaltic amplitude. Studies were done in two groups. In group 1 studies 15 healthy subjects (age: 42 ± 14 yr, 11 females) were studied to determine whether imposing resistance to swallowing using a handmade device can affect the swallow-induced hyolaryngeal excursion and related upper esophageal sphincter (UES) opening. In group 2, an additional 15 healthy subjects (age 56 ± 25 yr, 7 females) were studied to determine whether imposing resistance to the anterosuperior excursion of the hyolaryngeal complex induces fatigue manifested as reduction in pharyngeal contractile pressure during repeated swallowing. Analysis of the video recordings showed significant decrease in maximum deglutitive superior laryngeal excursion and related upper esophageal sphincter (UES) opening. In conclusion, repeated swallowing against anterosuperior excursion of the hyolaryngeal complex as a tool for overloading the pharyngeal musculature during swallowing will overload the pharyngeal muscles and, by repetitive swallowing, result in their neuromuscular fatigue manifested by a reduction in the pharyngeal deglutitive contractile pressure. This end point was chosen to satisfy the accepted principle of exercise physiology that, for an exercise to result in strengthening, it should overload the muscle and induce reduction in force, i.e., fatigue in the target muscle during exercise (13).

For this reason, we hypothesized that applying resistance against anterosuperior movement of the hyolaryngeal complex during swallowing will overload the pharyngeal muscles and, by repetitive swallowing, result in their neuromuscular fatigue manifested by a reduction in the pharyngeal deglutitive contractile pressure. This end point was chosen to satisfy the accepted principle of exercise physiology that, for an exercise to result in strengthening, it should overload the muscle and induce reduction in force, i.e., fatigue in the target muscle during the exercise (10, 19, 23).

The reason for choosing to use the resistance to hyolaryngeal excursion as a tool for overloading the pharyngeal musculature is based on fundamental deglutitive biomechanics wherein one of the prominent features of a normal swallow is anterior and superior movement of the hyoid and larynx that is associated with a number of important swallow events such as pharyngeal shortening and UES opening. In fact, compromised anterior and superior movement of the hyolaryngeal complex is associated with poor pharyngeal clearance in the elderly (16, 36) as well as in patients with dysphagia of varying etiology, including stroke and following cancer treatment (18, 24).

The current studies were designed to answer two questions. 1) Does the applied resistance cause restriction in any deglutitive biomechanical measures such as reduction in swallow-induced hyolaryngeal excursion as well as reduced UES opening? 2) Does imposing resistance to the anterosuperior excursion of the hyolaryngeal complex during repeated swallowing result in reduction in deglutitive contractile pressure of the pharynx indicative of fatigue of pharyngeal muscles?

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METHODS

We studied a total of 30 healthy volunteers. Studies were done in two groups and were approved by the internal review board of the Human Research Protection Program at the Medical College of Wisconsin (Milwaukee, WI). All participants gave written informed consent before the studies.

Group 1 Studies

In group 1 studies, 15 healthy subjects (age: 42 ± 14 yr, 11 females) were studied. These studies were performed to determine whether imposing resistance to the anterosuperior excursion of the hyolaryngeal complex can affect the swallow-induced hyolaryngeal excursion and its related UES opening.

Experimental tools. SWALLOW RESISTANCE EXERCISE DEVICE. To increase the load on the deglutitive muscles of the pharynx by restricting the anterosuperior excursion of the hyolaryngeal complex, we used a device constructed in our laboratory to provide an adjustable and fixed resistance to anterior and superior movement of the hyolaryngeal complex. This handmade device consists of a cotton fabric strap 63.5 cm in length and 2 cm in width. The ends of the strap are affixed with VELCRO (VELCRO brand fasteners, VELCRO is a registered trademark of Velcro Industries, Velcro USA, Manchester, NH) strips 21 cm in length to customize fitting of the device when the strap is wrapped around the neck. The middle portion of the device has an additional cotton pad 30 cm in length and 5 cm in width to provide support for the portion of the device that applies external pressure to the laryngeal cartilage when positioned on the subject. A concave flexible plastic disk is affixed to the middle of the strap assembly. This concave disk is wrapped in tape and serves as a support structure for an inflatable polyethylene bag that will act to apply an external force to the laryngeal cartilage to restrict anterior and superior movement of the larynx. The inflatable bag is connected via a flexible catheter assembly to a hand pump and pressure gauge. The inflatable pad rests in position on the thyroid cartilage fixed by closure of the VELCRO straps. A known external force may be applied to the thyroid by partially inflating the bag to a specific pressure reading on the gauge. The soft and compliant bag conforms to the surface of the skin cradling the irregular geometry of the larynx while applying a resistive force to anterior and superior distraction of the hyolaryngeal complex during swallowing.

Study technique. We used digital video fluoroscopy that recorded at 30 images/s in the sagittal view to record and subsequently analyze the deglutitive laryngeal and hyoid excursions from their resting predisglutitive position as well as the maximum deglutitive UES opening diameter at its narrowest segment. Video fluoroscopic recordings were obtained at 90 keV, using a 9-in. image intensifier and appropriate collimation. In all subjects, we recorded digital fluoroscopic movies of 0.5- and 5-ml thin liquid barium (equal parts water and E-Z EM barium sulfate powder; E-Z-EM Canada) swallows each repeated three times. Fluoroscopic sagittal images were centered on the pharyngoesophageal junction to clearly visualize the pharynx, UES, proximal esophagus, larynx, and hyoid bone. Three conditions were tested, namely: 1) no resistive device in place, 2) resistive device in place exerting zero pressure, and 3) resistive device in place exerting 40 mmHg external pressure on the thyroid cartilage.

IMAGE ANALYSIS. Digital images were measured in stop action using freely available image analysis software (29) to quantify deglutitive laryngeal and hyoid excursions from the resting predisglutitive position as well as the maximum deglutitive UES opening diameter at its narrowest segment in the sagittal view. Anterior movement was defined perpendicular to the imaginary line connecting the anterior aspect of vertebrae C4, C5, and C6 viewed in the sagittal plane while superior movement was defined parallel to that line.

Group 2 Studies

In group 2 studies, 15 additional healthy subjects (age 56 ± 25 yr, 7 females) were studied. These studies were aimed at determining whether imposing resistance to the anterosuperior excursion of the hyolaryngeal complex as described above induces reduction in force/fatigue manifested as reduction in pharyngeal contraction during repeated swallowing.

Experimental tools. PHARYNGEAL AND PROXIMAL ESOPHAGEAL MANOMETRY. Pharyngeal and proximal esophageal pressures were monitored using a high-resolution manometric catheter positioned transnasally to traverse the pharynx, UES, and proximal esophagus. The manometric probe and computerized recording and analysis system (ManoScan and ManoView Systems; Given Imaging, Duluth, GA) stores pressure data from 36 pressure sensors (1 cm sensor spacing) on the probe, displays the manometric information in topographic or line graph formats, and provides postacquisition analytic tools for parameterization of temporal and spatial pressure data.

Experimental protocol. All subjects were seated in an upright position for the duration of the study. The subjects were verbally cued to perform 40 consecutive swallows of 0.5 ml room temperature water while wearing the swallow resistance exercise device (sRED) at 40 mmHg pressure during high-resolution manometry (HRM). The most proximal sensors were intentionally positioned 2 cm proximal to the most proximal pressure-generating site in the pharynx. With this arrangement, the 36 high-resolution manometric sensors covered at minimum 12 cm area proximal to the UES, the entire UES, and 15 cm of the esophagus (covering the entire striated muscle esophagus, transition zone, and a portion of smooth muscle esophagus). Because our intent was to study the pharynx and the UES, this arrangement served our purpose. Furthermore, in additional studies (not presented in this paper), we evaluated the pharynx with HRM and fluoroscopy, further ascertaining the inclusion of all pharyngeal contractile function in our studies. The minute amount of water was used to reduce swallowing difficulty commonly seen in our laboratory when subjects swallow repetitively. There was a 20-s interval between swallows wherein the subject refrained from swallowing. The water bolus was slowly injected in the oral cavity by a syringe, and the subject was then cued to swallow the water in a single swallow. During these 40 swallows, the applied external pressure was maintained at 40 mmHg as measured by the external sRED pressure gauge. Following these swallows, the sRED was removed, and, after a 20-min rest period, another 40 swallows with 20-s intervals between swallows were recorded without the application of resistive load. During the 20-min rest period, subjects remained seated with the manometric catheter in place and were told to relax and swallow ad libitum.

Manometric parameters of fatigue. Several manometric parameters were measured and analyzed for each swallow. Peak deglutitive peristaltic wave pressures were measured at positions 2, 3, 4, 5, 6, 7, and 8 cm above the upper margin of the manometrically determined upper esophageal sphincter high-pressure zone (UESHPZ). The deglutitive UES nadir pressure was also measured. Additionally, a parameter derived from the ManoView analysis software, namely the pharyngeal contractile integral (PhCI), was measured. The PhCI was calculated using the “SmartMouse” feature of the ManoView software. The contractile integral technique has been used in the distal upper esophageal sphincter to calculate “contractile vigor” (22) by multiplying the mean pressure amplitude times the contraction duration times the length of the region of interest. In the ManoView software topographic display using the computer’s mouse, the contractile integral is calculated by scrolling out an area in the topographic display delineating a space-time box and logging the displayed contractile integral value. For the purposes of our analysis, the PhCI was characterized by...
circumscribing a space-time box in the topographic ManoView display to surround the pharyngeal deglutitive pressure recording with the upper margin of the box at the most proximal probe sensor at a time before deglutition and the distal margin of the box at the predetermined upper margin of the UES high-pressure zone at the time of return of the high-pressure zone to its resting manometric profile.

Both the peak peristaltic pressures and the PhCI were used as manometric surrogates for detecting fatigue due to repeated deglutitive pharyngeal contraction against the increased load provided by the sRED. These metrics were also evaluated for the swallowing sequences without the sRED. In a second-order analysis, the linear regression slope and correlation coefficient of the peak pressures and PhCI across sequential swallows were evaluated wherein a significant negative correlation (or a negative slope statistically different from 0) was considered associated with fatigue of the deglutitive pharyngeal muscles. All parameters were analyzed via inspection of the data by study team members.

Statistical Analysis

Pearson correlation analysis was used to detect decreasing pharyngeal peak deglutitive peristaltic pressures and decreasing PhCI across consecutive water swallows. Slope values were compared for these parameters with and without the application of the resistive load by the sRED using the paired t-test. Data are presented as means ± SD unless stated otherwise.

Interrater Concordance

Fundamental to the success of this approach, automated analysis techniques notwithstanding, was the reliability and reproducibility of the measurements; therefore, selected recordings (total of 8,400 pressure signatures, 1,200 pharyngeal contractile integrals, and 1,200 intrabolus pressures) were analyzed independently by three different observers representing a spectrum of experience to measure interrater variability.

RESULTS

Group 1 Studies

The experimental procedure in this group of studies was well tolerated by all participants (Fig. 1). Healthy volunteers were recruited through advertisement, and their medical history and physical did not indicate any abnormalities related to deglutition function. In addition, these details were corroborated by a detailed questionnaire filled out by each volunteer. For all studied subjects, the video fluoroscopic findings were characterized by lack of residue, lack of aspiration, lack of penetration, lack of delay between oral and pharyngeal phase of swallowing, as well as the ability to form and hold the barium bolus without spillage or premature spill into the pharynx. Analysis of the video recordings showed significant effects of the resistive load on maximum deglutitive superior and anterior hyoid and laryngeal excursions as well as the maximum UES opening diameter (UESD) for both tested 0.5- and 5.0-ml swallowed volumes (Fig. 2, A–F). As seen, for both 0.5- and 5-ml bolus, there were significant differences in the magnitude of biomechanical metrics when comparing values without the restrictive load with those with the resistive load, i.e., sRED with 40 mmHg pressure. Additionally, there was a further significant difference comparing values when the device exerted zero external pressure compared with 40 mmHg external pressure. For both 0.5- and 5-ml bolus data, superior laryngeal excursion was significantly different when comparing values with the resistive device exerting no external pressure with values with the resistive device in place exerting 40 mmHg pressure. Also for both 0.5- and 5-ml swallows, UESD was significantly different when comparing values without the restrictive device with those with the device exerting no pressure as well as with the device on exerting 40 mmHg external pressure.

Group 2 Studies

All subjects performed the protocol without incident. Consecutive swallows with the resistive load induced by sRED showed significant decrease in the peak pharyngeal peristaltic pressure amplitude characterized by reduced PhCI values. Correlation analysis showed a significant negative correlation between PhCI and successive swallows, suggesting neuromuscular “fatigue” of the pharyngeal muscles due to swallowing against the resistive load (P < 0.01, Fig. 3). Swallows without the application of resistive load were not associated with significant negative correlation (P > 0.05).

In further analysis, the set of 40 swallows was partitioned into 5 swallow epochs to determine the effect of resistive load across consecutive swallows. The PhCI for the five swallows were averaged in each epoch. Average PhCI was tested across epochs and across all subjects using ANOVA. Significant differences across epochs were seen for PhCI with but not without the application of the resistive load.

Epochwise tests corrected for multiple comparisons showed that, although there was a progressive decline in PhCI from epoch 1 to epoch 8, differences were driven by significant difference in epoch 2 compared with epoch 8 (P < 0.02, Fig. 4).

Because PhCI reflects the pressure phenomena across the entire pharynx, further sitewise analysis revealed that the fatigue trend significantly affected some but not all of the manometric recording sites (Table 1). As seen in Table 1, the pharyngeal sites that exhibited reduction in maximum amplitude of peristaltic pressure wave included those situated in the proximal pharynx. In the distal pharynx, i.e., sites 2, 3, 4, and 5 cm orad to the UES, where the pharyngeal pressure is influenced by the posterior tongue thrust, reduction in PhCI did not reach statistical significance.

As an example, the peak deglutitive peristaltic wave amplitudes 8 cm above the upper margin of the UESHPZ from one subject are shown in Fig. 5. As seen there is a progressive decrease in peak pressure at this location for sequential swallows with the resistive load (P < 0.05). This decrease is absent for successive swallows without the resistive load. Composite data from all subjects for the recording site 8 cm above the UESHPZ showed similar decline in peak pressure at this location with sRED. There were no decreases in force in swallow sequences without the resistive load. One-sample t-test was used to test whether correlation coefficients are significantly different from zero with the listed probability of type I error (P < 0.003) (also see Table 1).

Interrater Agreement

Intraclass correlation techniques showed significant agreement (P < 0.001) among all three observers. As seen in the Table 2, interclass correlation coefficients showed agreement among the three raters. All manometric sites showed signifi-
significant agreement among raters ($P < 0.001$), with sites $p2$ and $p3$ (2 and 3 cm, respectively, above the upper margin of the UES) having lesser agreement among the eight sites. Agreement among other swallow pressure metrics, including PhCl (0.95 with sRED, 0.94 without sRED) and UES nadir pressure (0.90 with sRED, 0.89 without sRED), showed highly significant agreement, whereas intrabolus pressure measurements ($P < 0.04$ with sRED, $P < 0.09$ without sRED) did not.

**DISCUSSION**

In this study we determined that application of a resistive load to anterior and superior laryngeal movement during repeated swallows significantly reduces the anterior and superior deglutitive excursion of the larynx as well as UES opening. Moreover, this resistive load fatigues the pharynx, as manifested by significant decrease in pharyngeal contractile integral. In addition, further analysis of the data indicated that the fatigue observed in the pharyngeal contractile integral is driven by significant reduction in force in the proximal pharynx commensurate to recording sites at 6, 7, and 8 cm orad to the upper margin of the UES. The reason for this finding merits further investigation, but it could simply be due to the masking of the inferior constrictor fatigue by the pressure contribution of posterior tongue thrust. The peristaltic pressure waves in distal pharynx are the sum effect of both contraction of pharyngeal constrictors and the posterior tongue thrust. The observed finding may mean that tongue muscles were not resistively loaded enough to induce reduction in force in posterior tongue thrust; therefore, the relatively small reduction in the pressure amplitude of the constrictors due to their fatigue could not become manifest by our current experimental technique.
Therapeutic options directly aimed at improving the contractile function of pharyngeal peristalsis are currently limited (5, 21). These options may be necessary following muscle-weakening events like stroke, radiation therapy, and surgical interventions. Compromised contractile function can result in post-deglutitive residue, aspiration, and dysphagia. Various exercises have been shown to strengthen components of the oropharyngeal deglutitive apparatus such as the suprahyoid UES opening muscles (30) and the tongue musculature (27). It is known that, for a muscle to strengthen by exercise, neuromuscular fatigue must occur during the exercise. The finding of the present study indicates that repetitive swallowing against an increased load will result in neuromuscular fatigue evidenced by a decrease in the peak amplitude of pharyngeal peristaltic pressure waves. This finding paves the way for future studies to directly evaluate the potential improvement in pharyngeal muscle strength and increase in pharyngeal contractile pressure by this approach. The therapeutic relevance of these potential improvements in swallowing strength includes enhancement of pharyngeal clearance in patients with incomplete swallow, abnormal hypopharyngeal residue, and aspiration.

One form of strength training is resistance exercise. In resistance exercise training, each effort is performed against a predetermined force generated by the resistance (10, 19). To apply this principle to swallowing and induced resistance to deglutitive contraction of pharyngeal muscles, we developed a device that was designed to hinder superior and anterior movement of the hyolaryngeal complex during swallowing as described in METHODS. We used a task-specific strength-training approach (35) by creating a predetermined amount of resistance to hyolaryngeal excursion during swallowing and

Fig. 2. Effect of resistive swallow load on biomechanical event during swallowing of 0.5 and 5 ml liquid barium. As seen, resistive load induced significant restriction on all measured aspects of deglutitive biomechanics, including laryngeal and hyoid superior and anterior excursions as well as the upper esophageal sphincter (UES) opening (P < 0.05). A: anterior and superior hyoid excursion 0.5-ml bolus; B: anterior and superior larynx excursion 0.5-ml bolus; C: UES opening 0.5-ml bolus; D: anterior and superior hyoid excursion 5-ml bolus; E: anterior and superior larynx excursion 5-ml bolus; F: UES opening 5-ml bolus.
Pharyngeal musculature is largely comprised of two layers. The external circular layer consists of superior, middle, and inferior constrictors and an internal mostly longitudinal layer that includes two levators, namely, the stylopharyngeous and palatopharyngeous. Contraction of these muscles during swallowing results in constriction and shortening of the pharynx, and, along with posterior thrust of the tongue, generates the deglutitive pharyngeal peristaltic pressure wave.

One of the prominent features of the normal pharyngeal phase of swallowing is the shortening of the pharynx along with the oral movement of the UES due to anterosuperior movement of hyolaryngo-cricoid complex by contraction of supraharyoid pharyngeal constrictors and longitudinal muscles. These events also include the anterior/superior movement of the cricoid cartilage resulting in the opening of the UES (4, 31).

The findings of the fluoroscopic part of the present study suggest that resistance to superior and anterior movement of the cricoid cartilage restricts the hyolaryngo-cricoid complex and results in a significant reduction (P < 0.01) in pharyngeal peristaltic contractile pressure. It is noteworthy that the fatigue of the pharyngeal constrictors as evidenced by decline in the pharyngeal contractile integral (PhCI) shown in the Fig. 3 showed that the applied resistive load restricts the hyolaryngo-mechanics and 2) confirmed the hypothesis that swallowing against resistance results in fatigue of the pharyngeal constrictors as evidenced by decline in the pharyngeal peristaltic contractile pressure. It is noteworthy that the fatigue in the current study was achieved by the use of volitional activation of the muscles challenged by a load vs. using a more passive approach such as enhanced contraction as a result of direct electrical stimulation of the muscle.

The external circular layer consists of superior, middle, and inferior constrictors and an internal mostly longitudinal layer

![PhCI with sRED](image1)

![PhCI without sRED](image2)

**Fig. 3.** Effect of resistive load induced by sRED on pharyngeal contractile integral (PhCI) shown in the top. Similar reduction was not seen when participants swallowed without the resistive load shown in the bottom.

**Fig. 4.** Epochwise analysis containing five consecutive PhCI in each epoch with (top) and without (bottom) resistive load. ANOVA showed significant differences across epochs for PhCI with but not without the application of the resistive load (P < 0.01). Epochwise tests corrected for multiple comparisons showed that, although there was a progressive decline in PhCI from epoch 1 to epoch 8, differences were driven by significant difference in epoch 2 compared with epoch 8 (P < 0.02).

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<tr>
<th>Sites</th>
<th>e-Scored CC</th>
<th>P value</th>
<th>e-Scored CC</th>
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<tr>
<td>P2</td>
<td>0.07 ± 0.46</td>
<td>0.74</td>
<td>0.04 ± 0.38</td>
<td>0.94</td>
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<tr>
<td>P3</td>
<td>−0.21 ± 0.39</td>
<td>0.56</td>
<td>−0.11 ± 0.28</td>
<td>0.10</td>
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<tr>
<td>P4</td>
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<td>0.04 ± 0.33</td>
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<tr>
<td>P5</td>
<td>−0.17 ± 0.53</td>
<td>0.21</td>
<td>0.15 ± 0.32</td>
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<tr>
<td>P6</td>
<td>−0.28 ± 0.58</td>
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<tr>
<td>P7</td>
<td>−0.41 ± 0.59</td>
<td>0.03*</td>
<td>0.14 ± 0.62</td>
<td>0.53</td>
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<tr>
<td>P8</td>
<td>−0.56 ± 0.34</td>
<td>0.003*</td>
<td>−0.002 ± 0.42</td>
<td>0.64</td>
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Values are means ± SD. P2–P8, positions/sites 2–8 cm, respectively, above the upper margin of the manometrically determined upper esophageal sphincter (UES) high-pressure zone; sRED, swallow resistance exercise device; CC, correlation coefficients.
The present study has also shown that applying controlled resistance to deglutitive biomechanical movements safely restricts the superior and anterior excursion of the hyolaryngeal complex and that such restriction is associated with a significant reduction in the maximum deglutitive opening of the UES. In addition to providing a means for overloading the deglutitive pharyngeal muscles and inducing their fatigue conducive to strength-training exercises for pharyngeal muscles, the other practical applications of such a restriction may include its use for modeling and simulation of various oropharyngeal disorders encountered following stroke, radiation therapy, and surgical interventions.

As a measure of pharyngeal contractile vigor, a primary metric in the present study was the pharyngeal contractile integral. A potential concern regarding this measurement could be the effect of contraction of the pharyngeal constrictors against the increased hydrodynamic resistance associated with attenuated UES opening diameter, thereby driving an increase in intrabolus pressure; however, the contribution of increased intrabolus pressure would have resulted in an increase in contractile integral. As shown in the present study, repetitive swallows against sRED resulted in a significant decrease in contractile integral, thereby suggesting no or unappreciable effects of an increase in intrabolus pressure.

Our studies, however, have several limitations. Rehabilitation of pharyngeal muscles involved in swallowing using strength-training principles has not been described before. This necessitated an empiric approach for selection of the magnitude of load and number of repetition for causing fatigue in this study. It is anticipated that, with the current proof of principle, the utilized criteria could potentially be modified in future studies and be adapted to the patient populations that can potentially include those following stroke or radiation therapy for the head and neck malignancy who develop deglutition abnormalities due to pharyngeal weakness.

In summary, swallow against an increased external load induced by restricting the anterosuperior excursion of the larynx is safe and effective for inducing fatigue in pharyngeal peristalsis and thus has the potential to strengthen the pharyngeal constrictor muscles. This finding may provide an opportunity to devise therapeutic strategies and pathophysiological models for pharyngeal-phase dysphagia observed in clinical practice.

Table 2. ICC for three independent raters of peak pressure data at manometric locations 2–8 cm above the upper margin of the UES high-pressure zone

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<thead>
<tr>
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<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
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<tr>
<td>ICC with sRED</td>
<td>0.97</td>
<td>0.98</td>
<td>0.93</td>
<td>0.98</td>
<td>0.99</td>
<td>0.99</td>
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<tr>
<td>ICC without sRED</td>
<td>0.96</td>
<td>0.94</td>
<td>0.98</td>
<td>0.97</td>
<td>0.98</td>
<td>0.99</td>
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ICC, interclass correlation coefficients.
GRANTS
This project was supported, in part, by National Institutes of Health Grants P01-DK-068051, R01-DK-025731, T32-DK-061923, and ULI-TR-001436.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
R.S., G.B., M.K.K., and A.S.H. conception and design of research; R.S., P.S., G.B., M.K.K., and A.W. performed experiments; R.S., P.S., M.K.K., and A.S.H. interpreted results of experiments; R.S. and M.K.K. drafted manuscript; R.S. and M.K.K. edited and revised manuscript; R.S. and M.K.K. approved final version of manuscript; M.K.K. analyzed data; M.K.K. prepared figures.

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