The Laryngoscope

Prevention of Esophagopharyngeal Reflux by Augmenting the Upper Esophageal Sphincter Pressure Barrier

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Objectives/Hypothesis: Incompetence of the upper esophageal sphincter (UES) is fundamental to the occurrence of esophagopharyngeal reflux (EPR), and development of supraesophageal manifestations of reflux disease (SERD). However, therapeutic approaches to SERD have not been directed to strengthening of the UES barrier function. Our aims were to demonstrate that EPR events can be experimentally induced in SERD patients and not in healthy controls, and ascertain if these events can be prevented by application of a modest external cricoid pressure.

Study Design: Individual case control study.

Methods: We studied 14 SERD patients (57 ± 13 years, 8 females) and 12 healthy controls (26 ± 3 years, 7 females) by concurrent intraesophageal slow infusion and pharyngoscopic and manometric technique without and with the application of a sustained predetermined cricoid pressure to induce, detect, and prevent EPR, respectively.

Results: Slow esophageal infusion (1 mL/s) of 60 mL of HCl resulted in a total of 16 objectively confirmed EPR events in none patients and none in healthy controls. All patients developed subjective sensation of regurgitation. Sustained cricoid pressure resulted in a significant UES pressure augmentation in all participants. During application of sustained cricoid pressure, slow intraesophageal infusion resulted in only one EPR event ($P < .01$).

Conclusions: Slow esophageal liquid infusion unmasks UES incompetence evidenced as the occurrence of EPR. Application of 20 to 30 mm Hg cricoid pressure significantly increases the UES intraluminal pressure and prevents pharyngeal reflux induced by esophageal slow liquid infusion. These techniques can be useful in diagnosis and management of UES incompetence in patients suffering from supraesophageal manifestations of reflux disease.

Key Words: Regurgitation, cricoid pressure, supraesophageal reflux disease, extraesophageal reflux disease, laryngopharyngeal reflux, gastroesophageal reflux disease.

Level of Evidence: 3b

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INTRODUCTION

Aerodigestive tract disorders attributed to reflux of gastric content into the pharynx remain a diagnostic and therapeutic challenge. These disorders include a number of pulmonary, pharyngeal, and laryngeal abnormalities ranging from aspiration pneumonia, pulmonary fibrosis, asthma, and chronic cough to benign inflammatory lesions of the larynx, pharynx, sinuses, dental erosion, and recurrent otitis media,[1–4] with an estimated prevalence of 20% to 30%.[1,5,6] The incompetence of the upper esophageal sphincter (UES) to prevent passage of esophageal refluxate into the pharynx and occurrence of esophagopharyngeal reflux (EPR) is fundamental to development of the above disorders.[7,8]

Previous studies estimate that more than half of patients with gastroesophageal reflux disease (GERD) complain of acid regurgitation.[9,10] These studies also indicate that compared to heartburn, a regurgitation symptom is not as responsive to medical therapy aimed at acid suppression.[9] Furthermore, studies also have documented that supraesophageal manifestations are reported by over half of the patients with GERD.[11,12] These are in addition to a large number of patients who complain of supraesophageal symptoms without accompanying heartburn or esophagitis. Pharyngeal reflux of gastric content constitutes the mainstay of these disorders, and entry of the gastric content into the laryngeal apparatus, aerodigestive tract, and the upper airway has been implicated in the generation of supraesophageal symptoms.[2,13,14]

Pathophysiologic mechanisms of supraesophageal manifestations of reflux disease (SERD) or laryngopharyngeal reflux remain poorly understood. Consequently, diagnostic approaches and management strategies of SERD remain mostly empiric and are indiscriminately

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directed to acid suppression with suboptimal results, poor quality of life,[15–17] and an annual cost of care estimated at $54 billion.[18] To date there has been no reliable method to document UES incompetence resulting in pharyngeal reflux, and because of this shortcoming therapeutic approaches to SERD have not been directed to the UES.

Essential to the occurrence of EPR and development of SERD is the driving pressure of the refluxate. Earlier studies of over 270 postprandial reflux events in GERD patients had shown that intraesophageal pressure increase during gastroesophageal reflux events was generally <20 mm Hg.[19] Using this information we hypothesized that application of a relatively modest cricoid pressure resulting in a 20- to 30 mm Hg intraluminal UES pressure increase would be adequate to prevent EPR episodes.

The aim of the present study was to test the following hypotheses: 1) application of external pressure applied perpendicularly to the cricoid cartilage increases intraluminal UES pressure and does not impede physiologic functions; 2) in patients with supraesophageal manifestations of GERD and regurgitation but not in healthy controls, slow (1 mL/min) intraesophagael fluid infusion will result in leakage of infusate into the pharynx, and this leakage can be visually documented by concurrent transnasal pharyngoscopy; and 3) a sustained intraluminal UES pressure increase of 20 to 30 mm Hg by an external assist device will prevent pharyngeal leakage of esophageal infusate in these patients.

MATERIALS AND METHODS

The relationship of external cricoid pressure with intraluminal UES pressure in SERD patients with regurgitation and healthy controls, and feasibility of maintaining an effective external cricoid pressure (20–30 mm Hg) utilizing a simple handmade assist device was determined. In parallel, we tested if EPR in SERD patients could be induced by slow infusion of acid into their distal esophagus but not healthy controls. The occurrence of the EPR using nasopharyngoscopy and direct visualization of colored liquid entering the hypopharynx from the UES was confirmed objectively. At the final stage, these techniques were applied together to determine the efficacy of sustained external cricoid pressure in preventing EPR using our handmade device in SERD patients.

Study Participants

We studied 14 patients with clinically established diagnosis of SERD (57 ± 13 years, 8 females) and 12 healthy volunteers (26 ± 3 years, 7 females) without history of any gastrointestinal disorder. SERD patients were on long-term acid suppressive therapy complaining of persistent regurgitation along with supraesophageal manifestations such as burning throat, asthma, chronic cough, or hoarseness. Twelve of these patients had no history of prior gastroesophageal surgery. One patient had a remote history of total esophagectomy and colonic interposition, and another patient had a history of partial esophagectomy and gastric pull-up 2 years prior to the study. Healthy volunteers were not on any medications other than contraceptives or antihistamines. The Medical College of Wisconsin institutional review board approved the studies and all participants signed written informed consent prior to their studies.

Study Protocol

Following 6 hours of fasting, a catheter assembly consisting of a combined high-resolution manometry/impedance catheter (outer diameter 4.2 mm) and an infusion catheter (outer diameter 2.4 mm) was placed through the same nostril following topical 2% lidocaine (APP Pharmaceuticals, LLC, Schaumburg, IL) application. The manometry catheter contained 36 circumferential solid-state pressure sensors spaced 1 cm apart, and 18 impedance sensors spaced 2 cm apart measuring at a sampling rate of 40 Hz (Given Imaging, Duluth, GA). The manometry catheter was positioned such that at least five pressure sensors were in the pharynx. Intraluminal UES pressure was measured by the e-sleeve function of the Manoview software (Given Imaging, Duluth, GA). The infusion port was placed in the distal third of the esophagus (when present), and the site was confirmed by the impedance signature of rapid air injection in the distal esophagus in the upright position. For patients who had esophagectomy, the infusion port was placed 10 cm below the lower border of UES. Following placement of manometry and infusion catheters, the remainder of the study was performed in the recumbent position.

Studies were performed in two phases. Phase I consisted of studies evaluating transient manual and sustained device-assisted external cricoid pressure. Phase II consisted of an experimental model inducing EPR and evaluation of efficacy of cricoid pressure in the prevention of EPR.

Effect of Cricoid Pressure on Intraluminal UES Pressure

To monitor the pressure applied to the cricoid we used a small noncompliant inflated balloon (10 mL), which was placed on the cricoid cartilage and was connected to a sphygmometer. A single investigator held the balloon between the thumb and index finger and pressed it gently onto the cricoid cartilage while the sphygmometer measured the externally applied cricoid pressure in real time. The correlation of predetermined levels of externally applied pressure of 10, 20, 30, and 40 mm Hg and the luminal UES pressure change compared to the baseline end-expiratory pressure was evaluated. Externally applied pressure fluctuated 3 mm Hg around the target pressure with respiration of the participants and minor variation of the force of the investigator's hand.

To maintain the external pressure on the UES over a longer period of time for performing physiologic functions such as swallowing and belching, as well as studying the effect of cricoid pressure on the prevention of EPR during esophageal infusion, we made a simple UES assist device (UESAD) in our laboratory consisting of two components: an elastic band and a cushion. The prototype cushion was made of multiple sheets of facial tissue paper wrapped by adhesive tape and was 8-cm long, 3-cm wide, and 2.5-cm in thickness. The elastic band was 45-cm in length and 2-cm in width, and was secured around the neck using an 8-cm piece of Velcro (Fig. 1). The UESAD was placed around the participant's neck in a way that the cushion was positioned on the cricoid cartilage. With this arrangement the elastic band bridged over the carotid artery and jugular vein without coming in contact with the skin in this region landing on the sternocleidomastoid muscle. To adjust the externally applied pressure, the band was simply tightened or loosened (by a centimeter, for example) and fastened securely around the neck. Following the placement and adjustment of the UESAD to a sustained intraluminal UES pressure increase of 20 to 30 mm Hg, we allowed participants to acclimate to the device. We measured the UES basal pressure and UES nadir pressure during three repetitions of dry swallow, 10-mL water swallow,

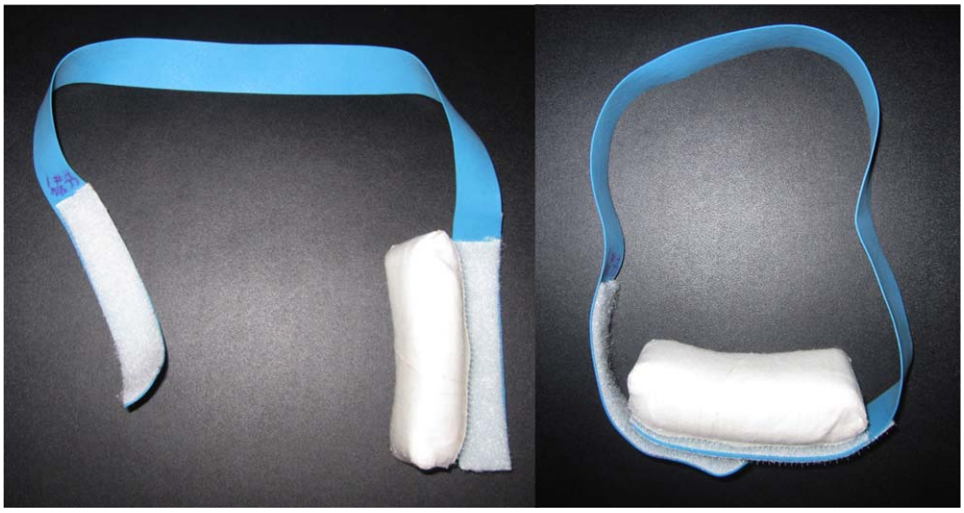

Fig. 1. Handmade upper esophageal sphincter assist device (UESAD) comprised of two components: an elastic band and a cushion. The prototype cushion was made of multiple sheets of facial tissue paper wrapped by adhesive tape and was 8-cm long, 3-cm wide, and 2.5-cm thick. The elastic band was 45-cm long and 2-cm wide, and was secured around the neck using an 8-cm piece of Velcro. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and esophageal belching at baseline without the presence of the UESAD and then measured with application of the UESAD. Esophageal belch was induced by the rapid injection of 50 mL of room air in the distal esophagus, and UES pressure was measured as the average of UES end-expiratory trough pressure over three respiratory cycles as described previously.[12] Study participants were instructed to report if they perceived difficulty swallowing or belching with the presence of the UESAD.

Inducing EPR and Effect of the UESAD

Participants were temporarily placed in the upright position to place a fiberoptic nasopharyngoscope (3.2 mm outer diameter, PENTAX FNL-10AP; PENTAX Medical, Tokyo, Japan) in the pharynx. The nasopharyngoscope was inserted though the other nasal passage, and positioned at the level of the epiglottis to visualize the UES inlet. The videoendoscopic images were synchronized with and recorded (sampling rate 15 Hz) within the high-resolution manometry system. Following the placement of the nasopharyngoscope, the remainder of protocol was performed in the recumbent position. Reflux was simulated by slow infusion of colored HCI (0.1 N) in the distal esophagus, and the hypopharynx was monitored endoscopically for occurrence of EPR. A single investigator uniformly injected 60 mL of HCI slowly over 1 minute (1 mL/s) using a 60-mL syringe. The infusate contained a green food dye (ACH Food Co., Memphis, TN) for better endoscopic visualization of EPR in the hypopharynx. The study participants were instructed to report if they perceived regurgitation throughout the recording development. Regurgitation was defined as the subjective sensation of movement of the esophageal contents into the participant's throat. We infused the esophagus three times at baseline without application of the UESAD and repeated the infusions three times after application of the UESAD with a target sustained luminal UES pressure increase of 20 to 30 mm Hg. Two observers carefully monitored videopharyngoscopic images during acid infusion and the subsequent esophageal clearance period for development of pharyngeal reflux as evidenced by unequivocal visualization of green dye in the hypopharynx.

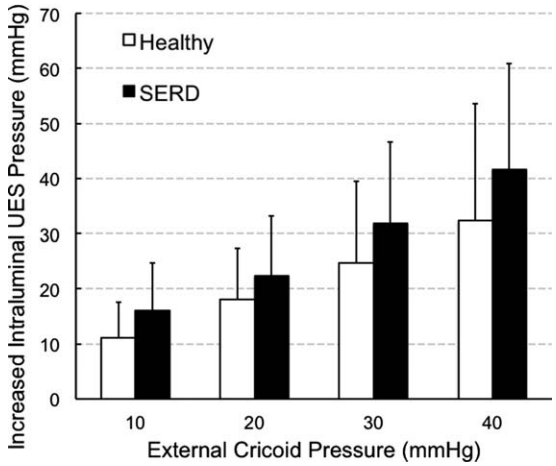

Fig. 2. Correlation of externally applied cricoid pressure with internally recorded upper esophageal sphincter (UES) pressure in healthy controls and supraesophageal reflux disease (SERD) patients. There was a direct relationship between the increase in cricoid pressure and that of UES in both healthy controls and SERD patients. In both groups, application of cricoid pressure resulted in significant increase in intraluminal UES pressure (*$P < .01$), but the magnitude of pressure augmentation between the two groups was not statistically diferent.

Statistical Analysis

Data are presented as mean and standard deviation unless otherwise noted. The effect of increasing external cricoid pressure on basal intraluminal UES pressure and on nadir UES relaxation pressure during belching and swallowing was compared using random two-way analysis of variance with unequal sample size. Frequency of the EPR and subjective regurgitation[20] between trials with and without the UESAD were compared using the Fisher's exact test.

RESULTS

All participants tolerated the studies well except one of the SERD patients, who developed severe nausea and emesis during acid infusion and her data were excluded from analysis of the second phase of the study. She fully recovered a few minutes following removal of manometry and infusion catheter.

Phase I: Effect of Cricoid Pressure on Intraluminal UES Pressure

Application of increasing amount of external cricoid pressure manually resulted in significant commensurate

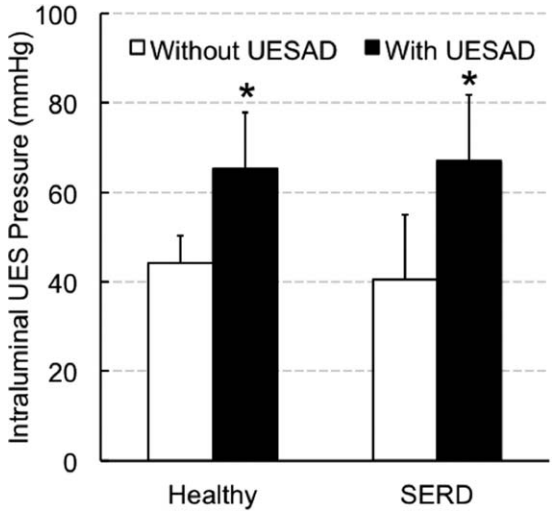

Fig. 3. Upper esophageal sphincter (UES) intraluminal pressure with and without the application of a UES assist device (UESAD) in healthy controls and patients. As seen in both groups, application of the UESAD resulted in significant increase in intraluminal UES pressure (*$P < .001$).

rise in intraluminal UES pressure ($P < .05$). The magnitude of increase in UES pressure in response to cricoid pressure in patients and healthy controls was similar, though a nonsignificant trend of higher luminal pressure augmentation in patients was observed (Fig. 2).

Application of the UESAD on cricoid cartilage was tolerated well by all study participants. By adjusting the elastic band, the device maintained a sustained increase in UES intraluminal pressure of 21 ± 9 mm Hg and 26 ± 10 mm Hg above the baseline in healthy controls and patients, respectively ($P < .001$; Fig. 3). The difference in pressure increase between healthy controls and patients was not statistically significant.

The UESAD did not impede swallowing and did not result in dysphagic symptoms in either group. However, application of the UESAD minimally (<5 mm Hg) but

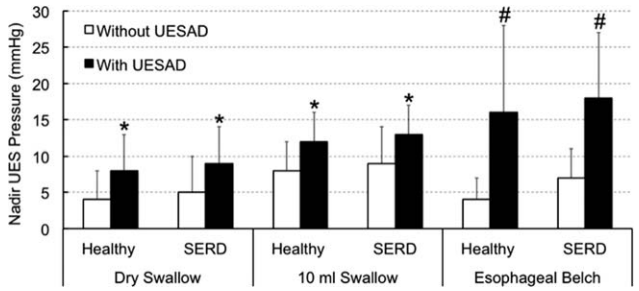

Fig. 4. Effect of the upper esophageal sphincter assist device (UESAD) on nadir relaxation pressure during swallowing and belching in supraesophageal reflux disease (SERD) patients and healthy controls. Application of the UESAD resulted in significant increase in nadir relaxation pressure during dry and 10-mL water swallow in both controls and patients (*$P < .05$). Similarly, the presence of the UESAD was accompanied by a significant increase in UES relaxation nadir pressure during esophageal belch in both groups (#$P < .001$).

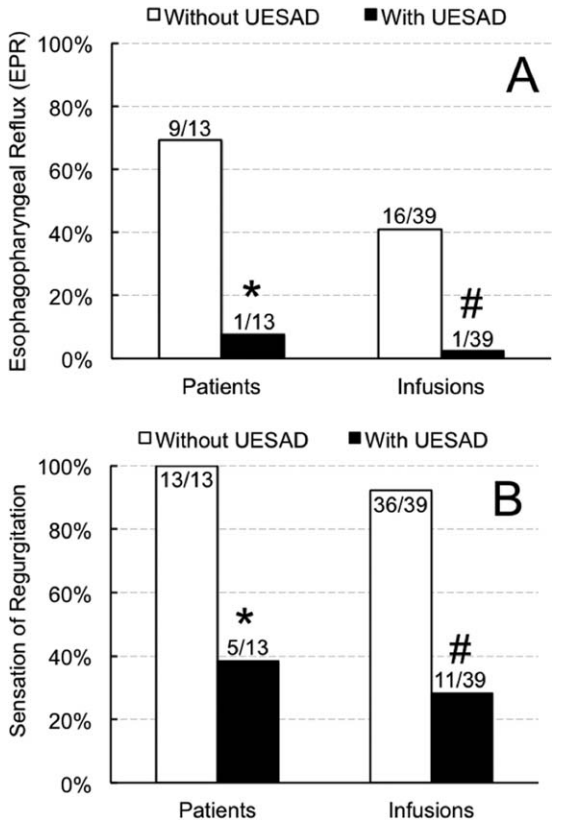

Fig. 5. Frequency of occurrence of objectively verified esophagopharyngeal reflux (EPR) (A) and subjective sensation of regurgitation (B) during esophageal slow infusions in 13 supraesophageal reflux disease patients. (A) Nine of 13 patients developed at least one EPR during their three esophageal infusions. This number was reduced to 1/13 with application of the upper esophageal sphincter assist device (UESAD) (*$P < .01$). On the other hand, 16 of 39 infusions resulted in endoscopically detected EPR without the application of the UESAD. This number decreased to 1 out of 39 with the application of the UESAD (#$P < .0001$). (B) All 13 patients developed a sensation of regurgitation during their infusions. This number was decreased to five of 13 after the application of the UESAD (*$P < .01$). Similarly, 36 of 39 infusions were accompanied by the development of sensation of regurgitation. After the application of the UESAD, the frequency occurrence of this sensation decreased to 11 of 39 infusions (#$P < .0001$).

significantly increased the UES relaxation nadir pressure during both dry and water swallows ($P < .05$). Esophageal rapid air injection resulted in a UES relaxation response and belching in both groups. Application of the UESAD resulted in a significant increase in nadir UES relaxation pressure ($P < .001$) by 12 ± 11 and 10 ± 8 mm Hg in healthy controls and patients, respectively (Fig. 4). However, none of the participants reported difficulty belching during the esophageal air injection.

Phase II: Inducing Esophagopharyngeal Reflux and Effect of the UESAD

None of the healthy controls reported sensation of regurgitation or esophageal discomfort during slow esophageal infusion. Videopharyngoscopic monitoring also did not show penetration of the infusate through

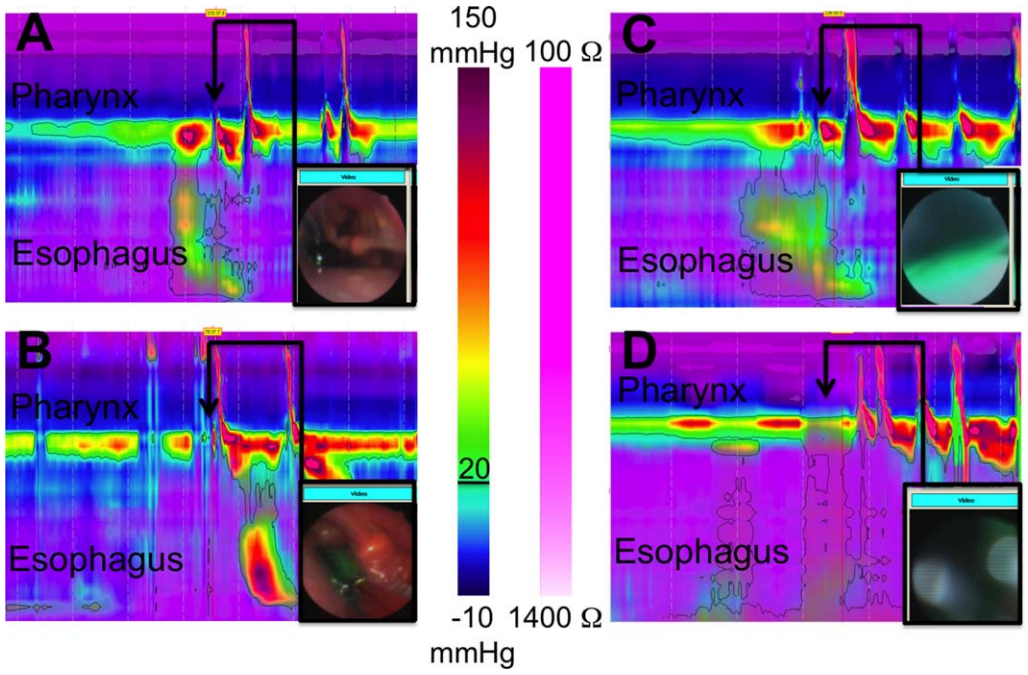

Fig. 6. Four examples of still frames of esophagopharyngeal reflux (EPR) detected by videopharyngoscopy and the color contour topographic representation of the pharyngeal, upper esophageal sphincter, and esophageal pressures (A–D). In each image, the exact time that the EPR occurred based on videopharyngoscopic image is indicated by an arrow. The corresponding endoscopic image of EPR is shown in the inset at the right lower corner of each figure. EPR events are evidenced by the presence of green-colored fluid in the hypopharynx of (A) and (B). In C and D the infusate has come in contact with the lens of the endoscope obscuring the hypopharyngeal view. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

UES into the pharynx of healthy volunteers. In contrast, esophageal slow infusion for 60 seconds universally resulted in the subjective sensation of regurgitation in all SERD patients (Fig. 5B). However, not all of the regurgitation sensation occurrences were accompanied by objective videoendoscopic documentation of EPR. We observed a total of 16 EPR events in nine patients. Four patients did not show any episode of endoscopically confirmed EPR but reported sensation of regurgitation (Fig. 5A). Three patients, including the two patients with prior esophagectomy, exhibited EPR during all three infusions. The six remaining patients exhibited between 1 and 2 EPR events during their three infusions. A swallow to clear the hypopharynx followed the overwhelming majority of EPR events, and only two patients had mild coughing presumably to clear the infusate from their upper airway. Figure 6 demonstrates several examples of concurrent high-resolution manometry and videopharyngoscopy of four different patients with objective endoscopically confirmed episodes of EPR.

With application of the UESAD, only one of the SERD patients developed a single episode of EPR. This patient had three EPR episodes without the UESAD. Three out of four SERD patients without objective evidence of EPR (the same patients who did not exhibit EPR during infusions without the application of the UESAD) continued to complain of sensation of regurgitation with the presence of the UESAD during nine out of nine infusions (Fig. 5B). The frequency of subjective regurgitation and objective EPR were both highly statistically reduced in the presence of the UESAD ($P < .01$). All together, the frequency of objective EPR decreased from 16 to one and that of sensation of regurgitation from 39 to 11 during the 39 total esophageal infusions ($P < .0001$).

DISCUSSION

In SERD patients and healthy controls, perpendicularly applied external pressure on the cricoid cartilage is proportionally transmitted onto the UES high-pressure zone resulting in predictable luminal pressure augmentation. The incompetent UES in SERD patients is unable to prevent pharyngeal reflux of the esophageal content, demonstrated by slow intraesophageal infusion of 0.1 N HCl and concurrent observation of the UES inlet by transnasal pharyngoscopy documenting the entry of the infused liquid into the pharynx. Applying a laboratory handmade device designed to exert external pressure on the cricoid cartilage induced a sustained increase in intraluminal UES pressure between 20 and 30 mm Hg and prevented EPR.

Perceived pharyngeal reflux (regurgitation) is one of the cardinal symptoms of GERD. Recent reports[9,10] suggest that regurgitation can indicate either true EPR or simply "an unpleasant movement of material upward from the stomach," potentially reaching the subsphincteric proximal esophagus and distal border of the UES. These notions were experimentally confirmed in the present study by showing that, in addition to actual pharyngeal reflux of esophageal content, patients

complained of regurgitation during acid infusion without reflux of acid into their pharynx. Earlier studies had shown that in these cases, acid infusate had reached the cervical esophagus just distal to the UES.[21]

The UES high-pressure zone is the main barrier against pharyngeal reflux of gastroesophageal contents,[22–25] and the refluxate has to overcome the UES pressure barrier to reach the pharynx. A gold standard technique that can reliably detect EPR does not currently exist, and as such, studying the potential therapeutic measures that could prevent occurrence of EPR episodes is quite challenging. We hypothesized that continuous slow infusion of acid in the esophagus in the supine position will challenge the protective mechanisms of UES and induce EPR, providing an experimental model to evaluate patients with suspected esophagopharyngeal reflux. Furthermore, we utilized nasopharyngoscopy[26] to objectively and unequivocally identify these events.

Unlike the smooth-muscle lower esophageal sphincter that is embedded within the diaphragm in the thoracic and abdominal cavities and is inaccessible to noninvasive manipulations, the striated-muscle UES is positioned behind the cricoid cartilage and in front of the vertebrae in the neck and is amendable to external influence. For example, the Mendelsohn maneuver can prolong the duration of UES opening during swallow,[27] and by the Shaker exercises the UES opening diameter during swallowing can be significantly increased.[28,29] Because cricopharyngeal muscle, one of the main components of the UES, is anatomically positioned between the vertebrae posteriorly and the cricoid cartilage anteriorly, its intraluminal pressure can be enhanced by external pressure applied perpendicularly to the cricoid cartilage.[30,31] The utility of cricoid pressure has been previously recognized in several other settings; for example, cricoid pressure has been used in acute life-threatening situations to prevent aspiration of gastric content, and during ventilatory assistance of cardiopulmonary resuscitation to prevent air-induced gastric distention.[30–32] Application of a firm cricoid force has been universally adopted to prevent potential aspiration in the period between the induction of anesthesia and tracheal intubation commonly described in anesthesiology literature as Sellick's maneuver.[31] Studies have shown that trained anesthesiology staff apply a wide range of 10 to 120 newtons of force during cricoid pressure.[33] The needed applied cricoid force based on a small study was found to be 44 newtons, resulting in 55 mm Hg luminal pressure to prevent regurgitation of gastric contents during induction of anesthesia.[34] Findings of the present study show a direct relationship between applied cricoid pressure and intraluminal UES pressure increase similar to those studies, but the magnitude of pressure increase that prevents the pharyngeal reflux in the present study is lower than that used for Sellick's maneuver.

CONCLUSION

The application of cricoid pressure commensurately augments the UES pressure barrier. Slow intraesophageal 0.1 N HCl infusion can be useful for uncovering the UES incompetence in preventing pharyngeal reflux. An increase of 20 to 30 mm Hg in intraluminal UES pressure by applying sustained cricoid pressure prevents pharyngeal reflux and significantly reduces the subjective sensation of regurgitation.

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