PROTOCOL TITLE:

Assessing the impacts of an upper esophageal sphincter assist device on laryngeal symptoms and salivary pepsin: A Pilot Study

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Determining the role of pH-impedance and salivary pepsin level testing in predicting PPI-responsiveness in patients suspected to have reflux associated laryngeal symptoms

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1.0 Objectives

1. To determine baseline salivary pepsin concentration in subjects with laryngeal symptoms
2. To assess the association between UESAD use and laryngeal symptom response
3. To assess the association between UESAD use and change in salivary pepsin concentration

2.0 Background

A cost-effective and care appropriate algorithm to streamline the diagnosis and management of patients with laryngopharyngeal reflux (LPR) has not been described. Generally, patients are empirically treated with high-dose proton pump inhibitor (PPI) therapy for 2-3 months with dose tapering if symptomatic response is achieved, however up to 50% of patients do not respond to acid suppression and there is a reported 10% placebo response. [1] Post-surgical outcomes following anti-reflux surgery have also been shown to have mixed results. The expense of managing patients with suspected extraesophageal syndromes of GERD has been estimated to cost over 5 times that of patients with typical GERD symptoms, which may amount in over $50 billion. [2]

It is postulated that the incompetence of the upper esophageal sphincter (UES) to restrict passage of esophageal refluxate is fundamental to the development of LPR. The UES Assist Device (UESAD) is a novel device that applies relatively modest external cricoid pressure, which results in a 20 to 30 mmHg intraluminal UES pressure increase. Shaker et al. studied the UESAD in 14 patients with LPR compared to 12 healthy volunteers. All subjects received a slow esophageal infusion of HCl resulting in objectively confirmed LPR events in the LPR cohort and subjective LPR in all patients. Sustained cricoid pressure resulted in significant UES pressure augmentation and during application of the UESAD, there was a significant decrease in the frequency of subjective and objective LPR events. {Shaker, 2014 #1}

A multi-center non-randomized prospective open label trial of 95 patients with LPR across 5 sites was conducted. No major adverse events were noted. 5% experienced pain, 5% described a choking sensation, 5% had a skin reaction, and 15% experienced a UESAD band related problem. The reflux symptom index (RSI) score significantly ($p < 0.0001$) decreased at 2 weeks and at 4 weeks follow-up (pre-treatement mean RSI 26, 2 week mean RSI 14.6 and four week RSI 12). The study concluded that the REZA BAND is safe and effective. (Silvers S, Vaezi MF, Vakil NB, et al 2014 DDW).

Pepsin, a proteolytic enzyme produced in the stomach, has been detected in the laryngeal epithelium of patients with reflux associated laryngeal symptoms and implicated in the pathogenesis of laryngopharyngeal reflux. Pepsin retains some of its peptic activity at pH levels as high as 6.5, thus necessitating an evaluation of both acid and nonacid LPR. Data from our pilot study demonstrated an increased concentration of pepsin for patients with laryngeal and esophageal reflux symptoms compared to healthy controls (Mean salivary pepsin of 118 ng/mL vs 32 ng/mL, $p = 0.01$), suggesting a role of pepsin quantification. A study examining salivary pepsin levels for patients pre- and post-fundoplication for LPR found that all patients with positive preoperative pepsin levels and postoperative elimination had symptom improvement, suggesting that changes in pepsin level may be reflective of surgical responsiveness.

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There is a need to develop a high quality and cost effective approach to diagnosing and managing patients with suspected LPR. The goals of our study are to explore the therapeutic role of the UESAD in patients with LPR symptoms, and measure its effectiveness by objective criteria (salivary pepsin) and symptomatic improvement.

Hypotheses:

1) Patients with LPR symptoms will demonstrate a 50% decrease in salivary pepsin concentration after 2 weeks of treatment with the UESAD.
2) Patients with LPR symptoms will demonstrate a significant decrease in RSI score after 2 weeks of treatment with the UESAD.

Summary of study:
Diagnostic and management approaches to reflux associated laryngeal symptoms are not well defined or understood. Patients with laryngeal symptoms are often empirically treated with PPI therapy. However, PPI response rate is only 50%, which also includes a known placebo response rate. The cost of managing patients with assumed reflux associated laryngeal symptoms is high. The upper esophageal sphincter assist device (UESAD) offers a novel approach to managing laryngopharyngeal reflux (LPR) through external application of cricoid pressure which in studies has shown to increase the upper esophageal sphincter intraluminal pressure and reduce pharyngeal reflux. The aim of this study is to explore the therapeutic role of the UESAD in patients with symptoms of LPR. We plan to conduct a prospective clinical trial. Patients seen in GI clinic with laryngeal complaints will complete validated symptom questionnaires – the RSI, GerdQ and N-GSSIQ scores. Those with an RSI > 13 will be included. They will submit 3 baseline sputum samples for pepsin analysis, taken upon awaking. They will then be advised to use the UESAD nightly for 2 weeks. 3 follow-up sputum samples for pepsin analysis will be taken and symptom scores reevaluated after the 2 week period

3.0 Inclusion and Exclusion Criteria
Inclusion criteria:
1) Male or female persons age 18-90
2) Patients with LPR symptoms (RSI >13)

Exclusion criteria:
1) Pregnant patients per history on initial evaluation.
2) Adults unable to consent in English
3) Patients who are currently imprisoned
4) Patients started on PPI therapy within 4 weeks of study
5) Patients with implants or implant parts that reside in the area where the REZA BAND is applied.
6) Patients with an implanted pacemaker, implanted cardioverter defibrillator (ICD), vagus nerve stimulator, or
   other such similar devices implanted in the neck.
7) Patients diagnosed with glaucoma.
8) Patients who had a malignancy of the neck, including neck surgery.

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9) Patients that may have an altered mental status including due to the use of sedative drugs or narcotics.
10) Patients with carotid artery disease, thyroid disease, a history of cerebrovascular disease, or any disorder of connective tissues (e.g., Marfan's Syndrome or Ehlers-Danlos Syndrome).
11) Patients who use nocturnal NIV machines such as CPAP or BiPAP.

4.0 Study-Wide Number of Subjects
Goal to recruit 30 subjects and enroll 25 subjects

5.0 Study-Wide Recruitment Methods
N/A

6.0 Multi-Site Research
N/A

7.0 Study Timelines
Visit #1-day 0:

1) Screening: Subject will be given the opportunity to ask questions about the study and to provide informed consent. Once consent has been obtained, the subject will be interviewed as to their eligibility
2) Subject will complete GerdQ, RSI and N-GSSIQ questionnaires
3) Subject will be instructed on how to collect salivary samples for pepsin analysis. Salivary samples will be collected upon awakening on three consecutive days prior to initiation of UESAD use and prior to eating. In brief, the subject will be instructed to clear his or her throat and collect 1-2 mL of saliva into a provided conical tube with 0.5 mL of preservative solution. The subject will be instructed to store all samples in a refrigerator for no more than a total of 7 days until providing them to the research team for pepsin analysis.
4) Subject will be fitted, free of charge, with a UESAD (REZA BAND) per manufacturer guidelines. Briefly, the subject will have the REZA BAND fitted such that it applies between 20-30 mmHg of cricoid pressure as measured by the manufacturer-provided external manometer. Subject will be instructed on the correct positioning as well as operation of the Clasp and Comfort Dial. Subject will be instructed to begin wearing the REZA BAND night of day 3 after collecting the three initial salivary samples.

Visit #2 – days 3 through 5

1) Subject will return to GI lab on day of their choice between day 3 and 5 to drop off their initial 3 morning salivary samples.
2) Subject will be instructed to collect an additional 3 morning salivary samples on days 17 through 19, for a total of six samples altogether.

Visit #3 – days 19 through 21:

1) Subject will follow up on day of their choice between day 21 and 24
2) Subject will complete GerdQ, RSI and N-GSSIQ questionnaires
3) Subject will drop off their second set of 3 morning salivary samples.

8.0 Study Endpoints

Primary endpoints:

1) Mean salivary pepsin concentration

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2) Symptom response to management protocol

9.0 Procedures Involved
Procedures:

[Research-related] Pepsin analysis (Expectorated saliva samples) – Saliva samples will be tested for pepsin using the Peptest assay (RD Biomed, England, described below).

REZA BAND – The UESAD used will be the REZA BAND (Somna Therapeutics, Wisconsin, described below).

Location of procedures –Patients will be fitted with the UESAD in the GI lab. They will be instructed on salivary sample collection in the GI lab. They will collect salivary samples to be used in research at their residences.

Supplies:
UESAD (REZA BAND): Will be provided free of charge by Somna Therapeutics. The REZA BAND is a device designed to apply between 20-30 mmHg pressure at the cricoid cartilage. Previous studies have demonstrated the safety of the device and it has been approved for sale and marketing by the FDA. Previous studies have also demonstrated that the REZA BAND increases the pressure of the upper esophageal sphincter and decreases pharyngeal reflux events as measured by pH and impedance monitoring in response to an infusion of HCl. Studies have also shown an improvement in LPR symptoms as measured by the RSI questionnaire with 2 and 4 weeks' use of the REZA BAND.

Pepsin analysis (Peptest): Will be purchased from RDBiomed. The Peptest is a lateral flow device used to detect pepsin in expectorated saliva samples. Pepsin is an enzyme, produced only in the stomach, which is responsible for breaking down proteins. The Peptest uses two humanized monoclonal antibodies. Previous studies have quantified the sensitivity of the Peptest as able to detect pepsin levels at or above 16ng/mL. Thus, the device, which looks similar to a pregnancy test, displays up to two bars, one as an internal control and then a second bar appears if pepsin is a present in the sample at or above the threshold.

Subjects will be asked to cough up saliva or sputum into a collection tube which has a citrated buffer to preserve the pepsin. A minimum of 1mL of saliva or sputum is needed for this test; therefore 2 mL will be collected. A total of six samples, three before REZA BAND use and three following two weeks of REZA band use, will be collected. These samples will either be tested immediately or stored at 4°C, for up to one week. Samples will be centrifuged at 4,000 rpm for 5 minutes and the supernatant removed for analysis per the manufacturer's directions.

Previous studies have reported a sensitivity and specificity of this device for pepsin at 88 and 87%. The Peptest has CE Mark approval in Europe. It has not yet been reviewed by the FDA. However, the company reports that they have partners in the US and are hoping to develop a full marketing plan soon, bringing the test to market in 2014.

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10.0 Data and Specimen Banking

Data will be stored in FSM password protected computers. Data will be accessible only by authorized research personnel who have undergone appropriate training.

Information in database 1) will include clinical variables (test results, demographics), and will exclude personal identification information (for example: name, date of birth, medical record number)

Data to be stored with specimens will include a unique subject number. No personal identification information will be stored with the specimens. Research team personnel will have access to the specimens. Specimens can be obtained from a locked refrigerator in the GI lab only. Specimen analysis will be conducted within 7 days of specimen collection.

11.0 Data and Specimen Management

Data will be analyzed using descriptive statistics.

This is a descriptive pilot study. The number of subjects was chosen with this goal. There is no need for power analysis.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Subjects will be advised to follow-up in clinic with their physician.

Subject data will be coded and password protected on secure FSM password protected computers. The data will be reviewed by the PI.

13.0 Withdrawal of Subjects*

Subjects will be withdrawn from the research if indicated for safety reasons.

The investigators may use, study, or analyze already collected data about these subjects.

The investigators will not continue to obtain data about the subject following withdrawal.

14.0 Risks to Subjects*

Risks associated with completion of questionnaires: There exists a small risk of emotional upset when filling out questionnaires. Subjects may experience some anxiety as they are asked to answer personal questions or are reminded of unpleasant thoughts or experiences during the questionnaire process. The subject, as always, has the right to refuse to answer any question they are asked. However the study team shall determine if the extent of refusal may warrant the removal of the subject from the research study so as to ensure complete and accurate data collection.

REZA BAND:
The safety of the REZA BAND has been assessed in previous studies. Adverse events that were reported during these studies were generally mild, short in duration, and the majority of

these events were not related to the device. Those events that were related to the device were also generally mild and short in duration. Device-related adverse events did not result in reduced outcomes in relation to the change of the RSI score from baseline to the score measured after 4 weeks of use. There were no deaths in these studies and there were no unexpected adverse events, and none of the subjects withdrew from the studies due to an adverse event. These studies also showed that there was no effect on heart rate, blood pressure, cardiac rhythm, or intraocular pressure when the REZA BAND was worn as intended as well as when it was intentionally displaced laterally, as compared to the baseline. This device has been approved for sale and marketing by the FDA.

Pepsin analysis:
The Peptest requires non-invasive (subject induced) collection of saliva. There is no diagnostic or therapeutic procedure performed. There may be a small amount of discomfort when the subject is bringing up saliva for collection. There is also a risk that the Peptest result will be incorrect (false negative or false positive). However, no decisions regarding management of a patient's disease will be made based on the results of this test.

Finally, there is a risk that confidentiality of subject information will be breached. However, all subject data will be kept confidential, following HIPAA regulations. Subject data will be stored on encrypted files.

15.0 Potential Benefits to Subjects
The subjects in this study will be symptomatic volunteers. The knowledge will help in the diagnosis and management of subjects with symptoms of LPR, and will offer a potential therapeutic option for their symptoms

16.0 Vulnerable Populations
N/A

17.0 Community-Based Participatory Research

N/A

18.0 Sharing of Results with Subjects

Results of symptom scores will be shared with subjects at scheduled follow-up in GI clinic.

19.0 Setting
Subjects will be recruited from GI and ENT clinics at NMG. Subjects who have participated in prior studies who meet inclusion criteria will also be contacted through mailings and subsequent telephone calls. Research procedures will occur in the GI motility lab.

20.0 Resources Available
Qualifications: The principal investigator is a board-certified gastroenterologist who specializes in esophageal disorders. The co-investigators are internal medicine/gastroenterology trainees with significant experience in the execution of clinical GI research. The study staff has significant experience in the execution of clinical GI research.

We will not specify study personnel by name to fulfill particular roles. However all study personnel will be listed on the IRB application and approved for participation in this study by the IRB

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Resources available to conduct research:

- It is feasible to recruit 30 subjects with the goal of enrolling 25 subjects meeting inclusion criteria through the ENT and GI clinic and through mailings and telephone calls. Laryngeal complaints are a predominant symptom presentation in the ENT clinic, and over a 12-month period we have access to a potential of > 240 subjects. We will need to recruit < 15%.
- Time to conduct and complete the research will be at least 12-months, and if needed this will be extended to continue enrollment.
- Facilities: GI lab - REZA BAND will be fitted in a private room in the GI lab. They will be instructed on how to collect salivary samples in a private room in the GI lab.
- REZA BANDs will be provided free of charge from Somna Therapeutics.

Medical resources will be available to the subjects at their follow-up appointments with GI and ENT clinics.

All research personnel will be provided the final research protocol and procedures electronically. Regular team meetings will be held to discuss duties, functions and progress.

21.0 Prior Approvals

No prior approvals are needed

22.0 Recruitment Methods

The subjects will be recruited from patients already attending ENT and GI clinic at NMG. Potential subjects will be identified by chart review. As above, subjects who have participated in prior studies who meet inclusion criteria will also be contacted through mailings and subsequent telephone calls. All subjects will receive a UESAD (REZA BAND), valued at $298, free of charge for participating.

23.0 Local Number of Subjects

Goal to recruit 30 subjects and enroll 25 subjects

24.0 Confidentiality

24.1.1 This is a single site study. Paper consent forms, questionnaires, and data collection forms will be stored in locked cabinets in the Divisional office space (Arkes 14th floor). Study data will be stored on a secure FSM password protected computer.

24.1.2 Data will be stored until 1 year after the conclusion of scholarly activity utilizing these data.

24.1.3 Only IRB-approved investigators and study staff will have access to these data.

25.0 Provisions to Protect the Privacy Interests of Subjects

Subject personal information and personal contact related to this research study will only be with the research personnel. Their personal data related to this research study will be

stored privately in a password protected file. Subjects are authorized to refuse providing information as they wish.

First, research personnel will non-intrusively ask subjects if they are interested in participating in a research study. If they decline, they will not be approached in this regard again. The research study will be explained by the research coordinator and/or co-investigators to the subject if they agree. The subject will be offered ample time, including the ability to take the information materials and consent home to discuss with family members or to further consider participation prior to signing the consent form. They will be provided with direct contact information for the research team if any questions or concerns arise. All questions will be answered completely.

The research team will access these variables about the subjects directly from the subjects on a form to be completed by the subject: Age, DOB, gender, symptoms, race/ethnicity. Subjects will also complete validated symptom questionnaires. This information will be stored in a password protected file and only accessible to research personnel.

26.0 Compensation for Research-Related Injury

No compensation for research-related injury will be provided. This study in an investigator-initiated study and Northwestern University does not plan to compensate for such injury.

27.0 Economic Burden to Subjects

Subjects will be responsible for transportation, childcare, and any other expenses related to lost work time. Parking validation will be available for subjects who park in the NMHC lots.

28.0 Consent Process

Potential subjects will be recruited in clinic by the study staff. The study will be explained to them by the study staff, they will be given the consent form to read and will be asked to sign the informed consent form prior to beginning any study procedures. Subjects will be allowed to take the consent form home to discuss with family members or to further consider participation prior to signing the consent form. We will be following the SOP: Informed Consent Process for Research (HRP-090).

Non-English Speaking Subjects

Will be excluded from the study

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

Subjects who are not yet adults (infants, children, teenagers)

N/A. Only subjects > 18 years of age will be recruited.

Cognitively Impaired Adults

The responsibility for determination whether or not an individual is capable of consent resides with the study team. This determination may rely on several factors including the individual observation of and interaction with the potential participant as well as the opinion of the medical provider or caregiver, when available. Any potential subject

whose ability to provide informed consent due to cognitive impairment will not be recruited.

Adults Unable to Consent
Will be excluded from the study

29.0 Process to Document Consent in Writing
We will be following SOP: Written Documentation of Consent (HRP-091).

30.0 Drugs or Devices
The device used in this study, UES assist device (REZA band) is a non-significant risk device. The description of the device is above (section 9). It is cleared for sale and marketing by the FDA, regulation number 21 CFR 874.5900.

The device used in this study, Peptest (RD Biomed) is a non-significant risk device without an IDE. The description of the device is above (section 9). The Peptests will be stored, as well as the tubes for sample collection, in the locked research storage space within the Division of Gastroenterology/Hepatology.

	Applicable to:		
USFDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

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1. El-Serag HB, Lee P, Buchner A, et al. Lansoprazole treatment of patients with chronic idiopathic laryngitis: a placebo-controlled trial. The American journal of gastroenterology. 2001;96(4):979-83. Epub 2001/04/24.

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2. Francis DO, Rymer JA, Slaughter JC, et al. High economic burden of caring for patients with suspected extraesophageal reflux. The American journal of gastroenterology. 2013;108(6):905-11. Epub 2013/04/03.

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