JOURNAL OF LAPAROENDOSCOPIC & ADVANCED SURGICAL TECHNIQUES
Volume 27, Number 9, 2017

DOI: 10.1089/lap.2017.0360

**Full Report**

# Role of Pepsin and Oropharyngeal pH-Monitoring to Assess the Postoperative Outcome of Patients with Laryngopharyngeal Reflux: Results of a Pilot Trial

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## Abstract

***Background:*** The aim of this study was to evaluate the value of salivary pepsin and oropharyngeal pH-monitoring to assess the surgical outcome of patients with laryngopharyngeal reflux (LPR).
***Materials and Methods:*** Twenty consecutive patients with LPR despite proton pump inhibitor treatment received laparoscopic antireflux surgery. Twenty-four hour esophageal pH-monitoring (multichannel intraluminal impedance monitoring [MII]-pH) and esophageal manometry (high-resolution manometry) data were documented preoperatively and at 3-month follow-up. An ears, nose and throat (ENT) examination was performed, including assessment of Belafsky Reflux Finding Score (RFS). Clinical symptoms were evaluated with the Belafsky Reflux Symptom Index (RSI) and the Gastrointestinal Quality of Life Index (GIQLI). Simultaneous to the MII-pH and collection of saliva samples, detection of oropharyngeal reflux events was performed. Treatment failure was defined as postoperative pathologic RFS or RSI score and improvement of GIQLI of <10 points, despite showing a normal DeMeester score.
***Results:*** At baseline, all patients had a pathological ENT examination, RSI score, and MII-pH data. All patients showed postoperatively a normal DeMeester score (mean $6.39 \pm 4.87$). Five patients were defined as treatment failures with a change of pepsin concentration from median 157.0 (95% confidence interval [CI]: 0–422) to 180.7 (95% CI: 0–500). In patients defined as treatment success, median pepsin value decreased from 206.3 (95% CI: 89–278) to 76.0 (95% CI: 55–205); ($P = .093$). Oropharyngeal pH-monitoring data showed no significant change in both groups.
***Conclusion:*** Salivary pepsin could be a marker for treatment success, while oropharyngeal pH-monitoring seems to be inadequate in these terms. However, larger studies are required to reach firm conclusions.

**Keywords:** GERD, pepsin in saliva, oropharyngeal pH-monitoring, laryngopharyngeal reflux

## Introduction

Gastroesophageal reflux disease (GERD) develops when the reflux of gastric contents causes troublesome symptoms and/or complications. It is a very common disease in western countries, and dysfunction of the antireflux barrier is recognized as the main cause. GERD may cause both esophageal and extraesophageal symptoms.[1–3] The most common symptoms are heartburn and regurgitation (typical symptoms). Some patients are troubled by extraesophageal symptoms, such as cough, hoarseness, frequent throat clearing, throat discomfort, or asthma-like symptoms alone or in addition to heartburn and regurgitation. These atypical symptoms can be caused or exacerbated by GERD, but other potential etiologies include postnasal drip, allergies, sinusitis, and chronic bronchitis.[4] The clinical challenge in these patients is to determine whether GERD is a causative or contributing factor for the extraesophageal (atypical) symptoms. These terms are also described at the position statement on laryngopharyngeal reflux (LPR) of the committee on speech,

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voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery.[5] Both acid suppression therapy and laparoscopic antireflux surgery (LARS) have proved to be effective in the treatment of typical symptoms of GERD.[6] However the therapeutic management of patients with atypical symptoms constitutes a significant problem, and treatment remains largely empirical. Available data regarding the effectiveness of LARS on extraesophageal symptoms of GERD are scarce and mostly controversial.[7] Encouraging outcomes have been reported in patients with extraesophageal GERD symptoms documented preoperatively by pH-impedance studies.[8] Emerging technologies and new diagnostic methods may provide a better sensitivity in diagnosing GERD symptoms and identify patient groups that would benefit the most from different management strategies.

Recently Worrell et al. reported that pharyngeal pH-monitoring better predicts a successful outcome for extraesophageal reflux symptoms after antireflux surgery than esophageal pH-monitoring.[9] Pepsin detection in saliva has previously been proposed as a method for the diagnosis of GERD. Pepsin is a proteolytic enzyme whose precursor pepsinogen is released solely by gastric chief cells. Its presence in the esophagus or more proximally (pharynx or airways) suggests gastroesophageal reflux. To date, pepsin has been detected in saliva and secretion samples from trachea, lung, sinus, middle ear, and exhaled breath condensate.[10–14] Recently Hayat et al. showed the value of pepsin in saliva to discriminate patients with reflux related symptoms. The authors speculate that this noninvasive test could be used to improve diagnosis of GERD in patients refractory to medical or surgical treatment and in patients with extraesophageal symptoms attributed to GERD.[15]

The aim of this pilot study was to evaluate the value of pepsin concentration in the saliva and pharyngeal pH-monitoring as tests to predict surgical outcome of patients with LPR.

## Materials and Methods

### *Study population*

Adult patients who underwent laparoscopic fundoplication at the Surgical Department of the Sisters of Charity Hospital, Linz, Austria, between October 2014 and May 2016 due to chronic GERD with primary extraesophageal symptoms were included in the study.

The patients underwent a preoperative series of diagnostic studies, including gastroscopy, barium esophagography, esophageal manometry, esophageal 24 hours-multichannel intraluminal impedance monitoring (MII), oropharyngeal pH-monitoring, and measurement of pepsin concentration in the saliva. Patient inclusion criteria were as follows: primary atypical reflux symptoms despite treatment with a proton-pump inhibitor (PPI) for at least 6 months and pathologic esophageal acid exposure as documented by a reflux related DeMeester score $\geq 14.7$, or symptom correlation $\geq 50\%$, or reflux episodes >73.

Patient exclusion criteria were as follows: age less than 18 years, American Society of Anesthesiologists physical status classification >II, previous esophageal or gastric surgery, and pregnancy.

Informed consent for participation in the study was obtained from all patients. All procedures were performed by the same surgical team. Study approval was obtained by the institution's ethics committee.

### *Quality of life evaluation*

Quality of life was evaluated by means of the German Gastrointestinal Quality of Life Index (GIQLI).[16] This questionnaire has been validated in the German language and it is recommended by the European Study Group for Antireflux Surgery.[17] Including 36 items, the general response to the GIQLI is graded from 0 to 144 points. The GIQLI is divided into five subdimensions as follows: gastrointestinal symptoms (0–76 points), emotional status (0–20 points), physical functions (0–28 points), social functions (0–16 points), and a single item for stress of medical treatment (0–4 points). Higher scores indicate a better quality of life.

### *Symptom evaluation*

Symptom and postoperative ''side effects'' evaluation was carried out in a standardized way using a written questionnaire assessing the severity and intensity of 14 symptoms in a 4-point scale. This questionnaire has been used previously.[18] In particular, it assesses the symptoms of heartburn, regurgitation, chest pain, cough, hoarseness, asthma, dysphagia, fullness, diarrhea, flatulence, constipation, belching, bloatedness, and distortion of taste. The above symptoms were graded as none (0), once per week (1), several times per week (2), daily (3), and constantly (4). Intensity of the symptoms was graded as none (0), mild (1), moderate (2), severe (3), and extremely severe (4). To obtain the ultimate result, the frequency of each symptom is multiplied by its degree, resulting in scores from 0 to 16 for each symptom, with a total maximum score of 224 and a minimum score of 0. In addition, four different scores were extracted to assess symptoms specific for reflux (heartburn, regurgitation, and chest pain), gas-bloat (fullness and bloatedness), bowel dysfunction (diarrhea, constipation, and flatulence), and atypical reflux symptoms (cough, hoarseness, asthma, and distortion of taste).

### *High-resolution esophageal manometry*

All patients were studied after an overnight fast in the supine position. To evaluate patients for esophageal motility disorders, a high-resolution manometry using the Sierra system (Given Imaging, Inc., Duluth, GA) was performed. A structurally defective lower esophageal sphincter (LES) was defined as an overall length below 2.4 cm, an intra-abdominal length below 0.9 cm, and/or the presence of a hiatal hernia. Pressure levels <29.8 or >180.2 mmHg of the esophageal body were rated as abnormal, and detected motility disorders were classified according to the Chicago Classification.[19]

### *Twenty-four hours ambulatory MII*

All patients had discontinued antisecretory therapy at least 1 week before examination and were encouraged to maintain their normal activities and mealtimes and to remain upright during the day except one short nap allowed. We used an ambulatory Sleuth® multichannel intraluminal impedance pH-monitoring system (Sandhill® Scientific, Inc., Highlands Ranch, CO). A 2.1 mm nasogastric probe was inserted with two antimony pH-electrodes located 5 cm above the manometrically located LES and 15 cm distally below the LES and

eight impedance electrodes, allowing to measure intraluminal impedance in six segments at 3, 5, 7, 9, 15, and 17 cm above LES. Further technical details have been published previously.[18]

We used the Symptom Index (SI), which is the number of symptoms associated with reflux events based on a 5-minute time window divided by the total number of symptoms. SI was declared positive if it was more than 50%.[20]

GERD was diagnosed if the total number of reflux events in 24 hours exceeded 73,[21,22] if an abnormal esophageal acid exposition was found, when the reflux related composite pH-score according to DeMeester exceeded 14.7, or if SI was positive for symptoms reported at least thrice.

### *Belafsky Reflux Finding Score*

An ears, nose and throat (ENT) examination, including transnasal fiber-optic laryngoscopy with photograph documentation and determination of the Belafsky reflux finding score (RFS), was performed by an otolaryngologist at baseline and at 3-month follow-up. RFS ranges from a lowest possible score of 0 (normal larynx) to a worst possible score of 26. A score greater than 7 is defined as pathological.[23–25]

### *Belafsky Reflux Symptom Index*

Evaluation of extraesophageal symptoms was carried out, using the standardized Belafsky Reflux Symptom Index (RSI) questionnaire. RSI is a nine-item self-administered outcome questionnaire. Each item is scored between 0 (no problem) and 5 (severe problem), with a maximum total score of 45. An RSI of greater than 13 is considered to indicate reflux.[23–25]

### *Salivary pepsin*

Subjects collected saliva on waking, 1 hour after finishing lunch, and 1 hour after finishing dinner during the 24-hour ambulatory MII-pH monitoring period. Saliva was collected into tubes containing 0.5 mL of 0.01 M citric acid. Subjects returned the samples together with the reflux monitoring system, and the samples were sent to the laboratory. Measurement of pepsin values was performed in a standardized procedure using Peptest (Peptest; RD Biomed™), as has been previously described.[15]

The lowest limit for accurate detection of pepsin (as determined by the manufacturer) was set at 16 ng/mL. We used the mean value out of the three samples to perform correlation analysis.

### *Oropharyngeal pH-monitoring*

Simultaneously to 24 hours ambulatory impedance/pH-monitoring, a pH-monitoring probe was placed in the oropharynx above the upper esophageal sphincter. The pharyngeal pH-monitoring was performed using a Restech Dx-pH probe (Restech Dx-pH; Restech, San Diego, CA) in a standardized procedure, as recommended by the provider. Normal values and discriminating pH thresholds have been validated, and a score (Ryan score) combining the number of reflux episodes, the duration of the longest reflux episode, and the percentage of time below the respective threshold has been developed.[26] Criteria for pathological results are Ryan score >9.4 in an upright position (pH <5.5) or >6.8 in a supine position (pH <5.0).[26]

### *Surgical technique*

All patients underwent laparoscopic Toupet fundoplication in a standardized manner by two experienced laparoscopic surgeons. Our technique of laparoscopic fundoplication has been previously described in detail.[27]

### *Follow-up*

Follow-up was performed 3 months after surgery. Follow-up assessment included the following: gastroscopy, esophageal manometry, esophageal 24 hours-MII simultaneous oropharyngeal pH-monitoring, and measurement of pepsin concentration in the saliva. Quality of life and symptoms were evaluated at baseline and at follow-up by questionnaires administered to all patients by an independent observer. Treatment failure was defined with postoperative pathologic RFS and/or RSI score and improvement of GIQLI of less than 10 points, despite having a normal postoperative distal acid exposure.

### *Statistical analysis*

Statistical analysis was performed using SPSS-Statistical Analysis Software (SPSS, Inc., Chicago, IL). All data were tested for normal distribution using the Kolmogorov–Smirnov

Table 1. Reflux-Specific Symptom Scores in Patients Defined as Treatment Success

| | *SCL* | | *Typical reflux* | | *Atypical reflux* | | *Bowel dysfunction* | | *Gas/bloating* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *15* | *3 months* n = *15* |
| Mean | 53.53 | 24.53 | 15.73 | 3.00 | 12.40 | 5.00 | 7.60 | 6.20 | 9.47 | 4.93 |
| SD | 27.74 | 12.71 | 11.67 | 2.36 | 7.29 | 5.10 | 5.37 | 4.30 | 7.61 | 4.13 |
| Minimum | 22.00 | 1.00 | 1.00 | 0.00 | 0.00 | 0.00 | 1.00 | 1.00 | 0.00 | 0.00 |
| Maximum | 122.00 | 46.00 | 48.00 | 7.00 | 28.00 | 15.00 | 21.00 | 15.00 | 28.00 | 13.00 |
| Percentile | | | | | | | | | | |
| 25th | 33.00 | 15.00 | 8.00 | 0.00 | 6.00 | 0.00 | 4.00 | 2.00 | 4.00 | 1.00 |
| 50th (median) | 48.00 | 24.00 | 16.00 | 4.00 | 13.00 | 3.00 | 8.00 | 6.00 | 8.00 | 5.00 |
| 75th | 63.00 | 32.00 | 20.00 | 5.00 | 17.00 | 10.00 | 9.00 | 9.00 | 13.00 | 8.00 |
| Significance | $P < .001$ ($P = .000$) | | $P < .01$ ($P = .001$) | | $P < .01$ ($P = .001$) | | $P = .169$ | | $P < .05$ ($P = .019$) | |

Comparison between scores in patients defined as treatment success at baseline versus 3-month follow-up.
SCL, summarization of typical reflux, atypical reflux, gas/bloating, bowel dysfunction scores; SD, standard deviation.

Table 2. Reflux-Specific Symptom Scores in Patients Defined as Treatment Failures

| | *SCL* | | *Typical reflux* | | *Atypical reflux* | | *Bowel dysfunction* | | *Gas/boating* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Baseline* n = *5* | *3 months* n = *5* | *Baseline* n = *5* | *3 months* n = *5* | *Baseline* n = *5* | *3 months* n = *5* | *Baseline* n = *5* | *3 months* n = *5* | *Baseline* n = *5* | *3 months* n = *5* |
| Mean | 66.00 | 47.80 | 15.40 | 8.20 | 18.20 | 11.00 | 10.20 | 12.40 | 11.00 | 8.00 |
| SD | 30.07 | 31.78 | 7.27 | 7.26 | 12.07 | 6.96 | 3.63 | 13.05 | 8.78 | 6.75 |
| Minimum | 22.00 | 10.00 | 3.00 | 0.00 | 1.00 | 4.00 | 6.00 | 1.00 | 0.00 | 2.00 |
| Maximum | 98.00 | 86.00 | 22.00 | 19.00 | 31.00 | 19.00 | 14.00 | 34.00 | 24.00 | 17.00 |
| Percentile | | | | | | | | | | |
| 25th | 36.00 | 20.00 | 9.50 | 2.00 | 7.00 | 5.50 | 7.00 | 2.50 | 4.00 | 2.00 |
| 50th (median) | 78.00 | 38.00 | 18.00 | 7.00 | 18.00 | 7.00 | 9.00 | 9.00 | 10.00 | 6.00 |
| 75th | 90.00 | 80.50 | 20.00 | 15.00 | 29.50 | 18.50 | 14.00 | 24.00 | 18.50 | 15.00 |
| Significance | $P = .186$ | | $P = .051$ | | $P = .273$ | | $P = .761$ | | $P = .463$ | |

Comparison between scores in patients defined as treatment failures at baseline versus 3-month follow-up.
SCL, summarization of typical reflux, atypical reflux, gas/bloating, bowel dysfunction scores; SD, standard deviation.

test. Data were compared using the paired *t*-test or the Wilcoxon signed rank test on a per subject basis. If normally distributed, they were additionally presented as mean and standard deviation. $P < .05$ was regarded as statistically significant.

## Results

Twenty patients met the inclusion criteria and were subjected to laparoscopic Toupet fundoplication. There were 14 female and 6 male patients with a mean age of $56.3 \pm 13.8$ years and a mean body mass index of $22.42 \pm 3.2\,kg/m^2$. Intraoperative complications did not occur in any of the patients. The follow-up was completed by the total study population.

### *Objective data (esophageal manometry and MII data)*

All patients had a normal distal acid exposure at follow-up. Mean composite pH-score according to DeMeester was significantly reduced from $42.12 \pm 22.07$ before surgery to $6.39 \pm 4.87$ three months after surgery ($P < .004$). The mean number of total, acid, weak acid, and nonacid reflux episodes was all reduced after the procedure.

LES-resting pressure improved from $21.8 \pm 10.9$ mmHg at baseline to $22.8 \pm 10.9$ mmHg at follow-up. The procedure had no significant influence on esophageal body motility.

### *Subjective data (quality of life, symptoms, RSI, RFS)*

The baseline mean general GIQLI was $93.7 \pm 19.1$ points. Postoperatively, the mean general GIQLI increased to $108 \pm 20.22$ points ($P < .001$).

Mean general symptom score was $56.6 \pm 28.1$ points before surgery. Postoperatively the general symptom score decreased to $30.3 \pm 20.9$ points ($P < .001$). Scores for symptoms specific to reflux, gas-bloat, bowel dysfunction, and atypical reflux symptoms in patients defined as treatment success, as well those defined as treatment failure, are shown in Tables 1 and 2, respectively.

RSI also improved from a mean score of $21.9 \pm 6.9$ to $10.1 \pm 6.6$ ($P < .001$).

After surgery, all patients had a RFS $\leq 7$ points. Mean score was significantly reduced at follow-up from $6.1 \pm 1.9$ to $2.10 \pm 1.9$ ($P < .001$).

### *Pepsin concentration in saliva and oropharyngeal pH-monitoring data*

Pepsin concentration did not change significantly. Mean scores (mean value out of three samples) decreased from $175.6 \pm 126.9$ before surgery to $120.9 \pm 115.6$ after surgery ($P = .352$). Oropharyngeal pH-monitoring data did neither

Table 3. Results of Oropharyngeal pH-Monitoring Using Restech Dx-pH Measurement System

| | *Patients defined as treatment success* | | | | *Patients defined as treatment failures* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Ryan score in upright position* | | *Ryan score in supine position* | | *Ryan score in upright position* | | *Ryan score in supine position* | |
| | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *5* | *3 months* n = *5* | *Baseline* n = *5* | *3 months* n = *5* |
| Mean | 28.89 | 20.38 | 2.32 | 2.89 | 77.59 | 92.28 | 4.84 | 3.34 |
| SD | 38.74 | 33.33 | 0.59 | 2.60 | 97.78 | 106.97 | 5.56 | 1.04 |
| Minimum | 2.12 | 2.12 | 2.17 | 2.17 | 2.12 | 2.12 | 2.17 | 2.17 |
| Maximum | 124.10 | 112.99 | 4.47 | 12.29 | 242.00 | 234.04 | 14.76 | 4.59 |
| Percentile | | | | | | | | |
| 25th | 2.12 | 2.12 | 2.17 | 2.17 | 11.61 | 6.00 | 2.17 | 2.36 |
| 50th (median) | 13.39 | 11.56 | 2.17 | 2.17 | 31.38 | 66.49 | 2.17 | 3.30 |
| 75th | 34.13 | 26.74 | 2.17 | 2.17 | 166.69 | 204.36 | 8.84 | 4.37 |
| Significance | $P = .681$ | | $P = .428$ | | $P = .966$ | | $P = .526$ | |

Comparison between scores in patients defined as treatment success and treatment failures at baseline versus 3-month follow-up.
SD, standard deviation.

Table 4. Main Outcome Parameters of Patients Defined as Treatment Success After Antireflux Surgery

| | *GIQLI* | | *RSI* | | *RFS* | | *DeMeester score* | | *Pepsin value* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *15* | *3 months* n = *15* | *Baseline* n = *15* | *3 months* n = *15* |
| Mean | 97.00 | 113.67 | 19.93 | 7.13 | 6.33 | 2.07 | 44.85 | 6.01 | 185.93 | 106.24 |
| SD | 16.31 | 14.45 | 5.54 | 3.89 | 1.88 | 2.02 | 56.25 | 4.94 | 130.67 | 104.05 |
| Minimum | 67.00 | 82.00 | 11.00 | 0.00 | 3.00 | 0.00 | 7.80 | 0.30 | 0.00 | 0.00 |
| Maximum | 115.00 | 142.00 | 31.00 | 12.00 | 9.00 | 7.00 | 209.80 | 14.40 | 475.00 | 320.50 |
| Percentile | | | | | | | | | | |
| 25th | 80.00 | 106.00 | 17.00 | 4.00 | 5.00 | 1.00 | 14.40 | 1.80 | 77.50 | 38.00 |
| 50th (median) | 103.00 | 117.00 | 19.00 | 8.00 | 7.00 | 1.00 | 20.00 | 4.60 | 206.33 | 76.00 |
| 75th | 109.00 | 119.00 | 25.00 | 10.00 | 8.00 | 3.00 | 48.40 | 10.80 | 279.00 | 189.00 |
| Significance | $P < .001$ ($P = .000$) | | $P < .001$ ($P = .000$) | | $P < .001$ ($P = .000$) | | $P < .05$ ($P = .017$) | | $P < .1$ ($P = .093$) | |

Comparison among GIQLI, RSI, RFS, DeMeester score, and pepsin value in patients defined as treatment success at baseline versus 3-month follow-up.

GIQLI, Gastrointestinal Quality of Life Index; RFS, Belafsky Reflux Finding Score; RSI, Belafsky Reflux Symptom Index; SD, standard deviation.

change significantly, in fact Ryan score in upright position even increased from 41.1 ± 59.9 to 84.4 ± 217.8 and in supine position Ryan score increased from 2.9 ± 2.8 to 3 ± 2.3.

### *Correlation between pH-monitoring data and pepsin in saliva/oropharyngeal pH-monitoring*

Correlation analysis between pepsin in saliva data and mean DeMeester score did not demonstrate significant correlations pre- or postoperatively neither in the group defined as treatment success nor in the group defined as treatment failure.

Correlation analysis between the evaluated Ryan scores (upright and supine) and DeMeester score showed no correlation pre- or postoperatively in either group.

### *Pepsin concentration in saliva and oropharyngeal pH-monitoring data to differentiate patients with treatment success from patients defined as treatment failure.*

According to the predefined criteria, 5 out of 20 patients (25%) were defined as treatment failures. Two out of five patients were defined as treatment failure because GIQLI did not increase more than 10 points and five out of five patients because of a pathologic RSI score. In these 5 patients, pepsin concentration in saliva increased from a mean of 154.7 ng/mL (median value: 157.0 [95% confidence interval; CI: 0–422]) to 165.1 ng/mL (median value: 180.7 [95% CI: 0–500]). In patients defined as treatment success, mean value of pepsin decreased from 186 ng/mL (median value: 206.3 [95% CI: 89–278]) to 106.2 ng/mL (median value: 76.0 [95% CI: 55–205]); ($P < .1$). Oropharyngeal pH-monitoring data showed no significant change in both groups (Table 3). Tables 4 and 5 show pre- and postoperative data of both groups in detail.

## Discussion

Previous studies have demonstrated that pepsin is correlated with extraesophageal symptoms of GERD.[28,29] Pepsin is stable up to pH 7 and regains activity after reacidification. The enzyme adheres to laryngeal cells, depletes its defenses, and causes further damage internally after its endocytosis.[30]

Pepsin as a major factor in the pathophysiology of GERD was disregarded for quite some time, but with the development of a fast and reliable test to determine its concentration in the saliva it returned into the focus of research. Hayat et al. recently highlighted the value of pepsin in the saliva in the discrimination of patients with reflux related symptoms. They reported that a positive saliva sample for pepsin (>16 ng/mL) has a sensitivity of 78.6% and a specificity of 64.9% for diagnosis of reflux-related symptoms. However, a sample with high pepsin

Table 5. Main Outcome Parameters of Patients Defined as Treatment Failures After Antireflux Surgery

| | *GIQLI* | | *RSI* | | *RFS* | | *DeMeester score* | | *Pepsin value* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Baseline* n = *5* | *3 months* n = *5* | *Baseline* n = *5* | *3 months* n = *5* | *Baseline* n = *5* | *3 months* n = *5* | *Baseline* n = *5* | *3 months* n = *5* | *Baseline* n = *5* | *3 months* n = *5* |
| Mean | 83.80 | 90.80 | 27.80 | 19.00 | 5.40 | 2.20 | 33.92 | 7.52 | 154.73 | 165.10 |
| SD | 25.12 | 26.86 | 7.66 | 4.85 | 1.82 | 1.92 | 18.41 | 5.00 | 78.27 | 149.49 |
| Minimum | 52.00 | 54.00 | 18.00 | 12.00 | 3.00 | 0.00 | 10.80 | 1.80 | 81.67 | 0.00 |
| Maximum | 110.00 | 125.00 | 38.00 | 24.00 | 7.00 | 5.00 | 51.20 | 14.60 | 280.00 | 314.00 |
| Percentile | | | | | | | | | | |
| 25th | 63.00 | 68.00 | 20.50 | 14.50 | 3.50 | 0.50 | 15.00 | 3.10 | 88.83 | 12.25 |
| 50th (median) | 74.00 | 86.00 | 29.00 | 19.00 | 6.00 | 2.00 | 37.30 | 6.70 | 157.00 | 180.67 |
| 75th | 109.50 | 116.00 | 34.50 | 23.50 | 7.00 | 4.00 | 51.15 | 12.35 | 219.50 | 310.17 |
| Significance | $P = .459$ | | $P = .111$ | | $P = .099$ | | $P < .05$ ($P = .016$) | | $P = .867$ | |

Comparison among GIQLI, RSI, RFS, DeMeester score, and pepsin value in patients defined as treatment failures at baseline versus 3-month follow-up.

GIQLI, Gastrointestinal Quality of Life Index; RFS, Belafsky Reflux Finding Score; RSI, Belafsky Reflux Symptom Index; SD, standard deviation.

concentration (>210 ng/mL) suggests that the symptoms are likely to be due to reflux with 98.2% specificity.[15]

The recommended therapy for patients with atypical symptoms of GERD consists of high dose acid suppression therapy (PPI) for up to 6 months.[31] All patients in our study had primary atypical reflux symptoms despite treatment with a PPI for at least 6 months and an objective pathologic esophageal acid exposure. We hypothesized that atypical symptoms are a result of laryngeal or pharyngeal alterations due to increased stress with pepsin. A study evaluating the concentration of pepsin in the saliva pre- and postoperatively after LARS had not been performed so far. The results of this study show that atypical symptoms could be a result of increased stress in larynx or pharynx with pepsin, since mean values in patients defined as treatment failure increased, in contrast to the significant decrease in patients defined as treatment success.

We have no conclusive explanation why pepsin values increased in the group of patients classified as treatment failures. A possible explanation could be the low power and the possibility of a type II statistical error, which is also a limitation of the present study. Nevertheless, the results underline the role of pepsin in the pathophysiology of extraesophageal symptoms and encourage performing further research.

Several studies showed promising results using oropharyngeal pH-monitoring to determine whether extraesophageal symptoms can be attributed to reflux. Yuksel et al. reported that oropharyngeal pH-monitoring appears to be more sensitive than traditional pH-monitoring in the evaluation of patients with extraesophageal reflux.[32] A retrospective review reported symptom relief after surgical antireflux procedures more often in the group with pathological pharyngeal pH levels compared to the study group with pathological esophageal pH-monitoring.[9] However, this is the first prospective observational study evaluating simultaneous pre- and postoperative oropharyngeal pH-monitoring and 24 hours esophageal pH-monitoring data. Although all patients had a normal distal acid exposure postsurgery, we could not find any significant change in oropharyngeal acid exposure in patients considered as treatment failure nor in those considered as treatment success. Remarkably, in patients defined as treatment success, Ryan scores in upright position even increased (Table 3). Based on these findings, oropharyngeal pH-monitoring may be of no value in predicting the outcome of antireflux surgery in patients with primary extraesophageal symptoms.

Correlation analysis between oropharyngeal pH-monitoring data and esophageal pH-monitoring data was neither conclusive. Several studies have reported lack of correlation between impedance/pH-monitoring and pharyngeal pH-monitoring in simulation measurements.[33–35] Differences were attributed to supposable extragastric acid production.[36] However, Becker et al. could not detect a relevant extragastric acid production in the laryngeal epithelium.[37] Willhelm et al. reported that 60% of asymptomatic gastrectomy patients had positive results in pharyngeal pH-monitoring.[38] Pharyngeal pH-monitoring may therefore be misleading in guiding diagnostic and therapeutic decisions.

The results of this study show that pepsin in saliva could be a marker for treatment success, while oropharyngeal pH-monitoring seems not to be an adequate test. However, larger studies are required to reach firm conclusions. Nevertheless, it is remarkable that 75% of the patients, who were dissatisfied under PPI therapy, had a successful surgical treatment of their symptoms 3 months after surgery.

In conclusion, a significant reduction of pepsin concentration in the saliva could be a marker of treatment success. This study suggests that pepsin plays a role in the pathophysiology of LPR and provides a scaffold for further research. Oropharyngeal pH-monitoring does not seem to be an adequate test upon which to base therapeutic decisions. However, larger studies are required to reach firm conclusions.

## Acknowledgments

The authors thank Astrid Reizner and Friedrich Radlmair from the Laboratory of the department of nuclear medicine for analyzing the saliva samples.

## Disclosure Statement

No competing financial interests exist. All authors do disclose all institutional or corporate/commercial relationships going back 36 months and longer.

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