Endoscopy

Anti-reflux mucosectomy for gastroesophageal reflux disease: efficacy and the mechanism of action

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Abstract:
Previous studies suggest that anti-reflux mucosectomy (ARMS) is effective in reducing reflux symptoms and total acid exposure, although the mechanism is unknown. Our objective was to investigate the effect of ARMS on reflux parameters and mechanism of action.

Methods: Gastroesophageal reflux (GERD) patients with insufficient symptom control despite twice daily proton pump inhibitor (PPI) underwent a piecemeal multiband mucosectomy of 50% of the circumference of the esophago-gastric-junction (EGJ), extending 2cm into the cardia. The primary endpoint was the total number of reflux episodes during 24-h pH-impedance studies.

Results: 11 patients were treated (8 men, age 37 (32-57) years), one patient is lost to follow-up after treatment. ARMS reduced the total number of reflux episodes from 74 (50-82) to 37 (28-66) p=0.008 and total acid exposure from 8.7% (6.4-12.7) to 5.3% (3.5-6.7) (p=0.008). Treatment reduced the number of transient lower esophageal sphincter relaxations (TLESRs) (from 4 (1-8) to 2 (1-4), p=0.027) during a 90-minute postprandial period. Reflux symptoms were reduced substantially (from 3.6 (3.6-3.9) to 1.6 (0.7-2.7), p=0.007). Treatment did not increase dysphagia (Brief Esophageal Dysphagia Questionnaire) of 8.2 (±7.3) to 8.5 (±6.5) (p=0.879). Impedance planimetry showed no changes in EGJ distensibility after treatment (4.4 (±2.1) mm2/mmHg to 4.3 (±2.2) mm2/mmHg), p=0.952). One delayed post-procedural bleeding (10%, (1/10)) occurred requiring repeat endoscopy, no strictures developed.

Conclusion: ARMS is an effective treatment option in PPI refractory GERD patients reducing acid exposure, reflux episodes and symptoms. While its working mechanism could not be explained by a difference in distensibility, a reduction in TLSERs might play a role.

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Thieme

Anti-reflux mucosectomy for gastroesophageal reflux disease: efficacy and the mechanism of action

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Kuipers et al.

Abbreviations: AET; acid exposure time, ARMS; anti-reflux mucosectomy, BMI; body mass index, BEDQ; Brief Esophageal Dysphagia Questionnaire, EMR; endoscopic mucosal resection, GERD; Gastroesophageal reflux disease, HRM; high-resolution manometry, PPI; proton pump inhibitor, RDQ; Reflux Disease Questionnaire, TLESRs; transient lower esophageal sphincter relaxations.

Specific author contributions: RON and AB played a role in planning of the study. RON, TK and RP had a role in conducting the study. RON and TK were involved in the acquisition of data. RON, TK and AB had a role in collecting and/or interpreting data. RON and TK played a role in drafting the manuscript. RP and AB played a role in reviewing and revising the manuscript for important intellectual content. All authors approved the final draft submitted.

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ABSTRACT

Previous studies suggest that anti-reflux mucosectomy (ARMS) is effective in reducing reflux symptoms and total acid exposure, although the mechanism is unknown. Our objective was to investigate the effect of ARMS on reflux parameters and mechanism of action.

Methods: Gastroesophageal reflux (GERD) patients with insufficient symptom control despite twice daily proton pump inhibitor (PPI) underwent a piecemeal multiband mucosectomy of 50% of the circumference of the esophago-gastric-junction (EGJ), extending 2cm into the cardia. The primary endpoint was the total number of reflux episodes during 24-h pH-impedance studies.

Results: 11 patients were treated (8 men, age 37 (32-57) years), one patient is lost to follow-up after treatment. ARMS reduced the total number of reflux episodes from 74 (50-82) to 37 (28-66) p=0.008) and total acid exposure from 8.7% (6.4-12.7) to 5.3% (3.5-6.7) (p=0.008). Treatment reduced the number of transient lower esophageal sphincter relaxations (TLESRs) (from 4 (1-8) to 2 (1-4), p=0.027) during a 90-minute postprandial period. Reflux symptoms were reduced substantially (from 3.6 (3.6-3.9) to 1.6 (0.7-2.7), p=0.007). Treatment did not increase dysphagia (Brief Esophageal Dysphagia Questionnaire)of 8.2 ($\pm$7.3) to 8.5 ($\pm$6.5) (p=0.879). Impedance planimetry showed no changes in EGJ distensibility after treatment (4.4 ($\pm$2.1) mm^2/mmHg to 4.3 ($\pm$2.2) mm^2/mmHg), p=0.952). One delayed post-procedural bleeding (10%, (1/10)) occurred requiring repeat endoscopy, no strictures developed.

Conclusion: ARMS is an effective treatment option in PPI refractory GERD patients reducing acid exposure, reflux episodes and symptoms. While its working mechanism could not be explained by a difference in distensibility, a reduction in TLSERs might play a role.

Introduction

Gastroesophageal reflux disease (GERD) is a common condition where backflow of gastric contents into the esophagus causes esophageal damage and/or bothersome symptoms such as heartburn, regurgitation and chest pain. Most reflux episodes occur after the meal, when the stomach is filled with ingested foods [1]. Gastric distention activates stretch receptors in the proximal stomach and triggers transient lower esophageal sphincter relaxations (TLESRs), which are regarded to be the predominant mechanism underlying the postprandial increase in reflux [2, 3].

GERD treatment consists of non-pharmacological (weight loss, head of bed elevation, abdominal breathing exercises) and pharmacological (antacids, H2-blockers, proton pump inhibitors) options [4, 5]. Proton pump inhibitors (PPIs) form the mainstay in the management of reflux disease. Laparoscopic fundoplication is considered an alternative therapy when pharmacological treatment fails and is proven to be highly effective [1]. However, it is an invasive procedure, and therefore not attractive to all patients with refractory symptoms [6]. Several less-invasive endoscopic anti-reflux procedures have been proposed over the years [7-9]. However, various problems with techniques, costs of equipment, implantation of foreign objects, safety issues and lack of efficacy have resulted in little enthusiasm for these endoscopic procedures and none has become widely accepted as a standard treatment for reflux disease.

In 2014 anti-reflux mucosectomy (ARMS) that uses endoscopic mucosal resection (EMR) to resect limited parts of the gastric mucosa along the lesser curve of the cardia has been introduced. First results show that reflux symptoms resolved in the majority of patients and the mean 24-hour esophageal acid exposure time decreased from 39% to 3% [10]. Subsequently, larger case series with a longer duration of follow-up confirmed that ARMS appears to be an efficacious and feasible procedure without significant intra and postoperative morbidity [11, 12]. More recently long-term follow-up results of the ARMS procedure confirmed these result; ARMS resulted in a positive effect in 68% of the patients at the 5-year follow-up. [13]

The available studies have proven the efficacy of the ARMS procedure. However, the reason why ARMS has such a good effect on reducing both esophageal acid exposure and reflux symptoms is unknown. It has been postulated that formation of fibrosis after ARMS

constricts and tightens the esophagogastric junction [12]. Partial resection of the cardiac mucosa, as done with ARMS, may also lead to a loss in stretch receptors in the gastric wall, thereby reducing the numbers of TLESRs. However, this hypothesis has never been investigated, and the exact effect of ARMS on reflux episodes and the mechanisms through which reflux control is achieved are not yet elucidated. Therefore our aim is to further study the efficacy of ARMS in reflux patients and mainly to investigate the underlying working mechanisms though which reflux control is achieved.

Methods

Study design

We performed a single center prospective therapeutic interventional study between December 2019 and September 2023. The local Medical Ethics Committee approved the study (2019_145#B2019587) on August 22, 2019. The trial was prospectively registered at the Dutch National Trial Register under number NL8246. Written informed consent was obtained from all patients. All authors had access to the complete study data and reviewed and approved the final manuscript.

Patient selection

We included adults with uncomplicated confirmed GERD (24-h ambulatory pH-impedance study with a symptom association probability ≥95%; and esophageal acid exposure ≥4%, measured after PPIs were ceased for 7 days) and insufficient symptom control on PPI therapy. The main exclusion criteria were a hiatal hernia >2cm and presence of esophagitis Los Angeles (LA) grade C or D. A list of all in and exclusion criteria can be found in *supplemental material.*

Study protocol

A high-resolution manometry (HRM) and 24-hour pH-impedance studies were done to confirm GERD and rule out other esophageal diseases. The additional esophageal function studies were performed prior to treatment with ARMS and 3 months after treatment. An upper endoscopy was also performed 3 months after treatment, to assess healing, presence of strictures and esophagitis. An overview of the study visits can be found in *supplemental figure 1*

Medication

Anti-secretory medication were discontinued at least 7 days prior to the study investigations (esophageal function tests and ARMS procedure). Antacids (maximum of six a day) could be used as rescue medication except on the day of the investigations. PPIs were restarted on the day of the ARMS procedure and continued for one month post-ARMS, PPIs were be tapered-off gradually within one week and then discontinued. If GERD symptoms returned after discontinuing of PPI therapy, a stepwise rescue therapy was implanted, starting with antacids (maximum 6 tablets daily). If symptoms persisted, PPIs were reinstituted at the initial dose.

Kuipers et al.

Study procedures

Stationary studies

Stationary esophageal high-resolution manometry was performed according to the standardized protocol used in our center to evaluate esophageal motility in supine position. Subsequently, the pH-impedance catheter was introduced while leaving the HRM catheter in situ. Patients consumed a standardized meal (one Quarter Pounder, 200cc orange juice, total 625 Kcal) in upright position within in 30 minutes. After completion of the meal, a 90-minute postprandial period of pressure, pH and impedance recording was performed in supine position. The occurrence of complete TLESRs were analyzed during the postprandial period according to validated criteria. [14]

Ambulatory 24-h impedance-pH study

Thereafter, the manometry catheter was removed and the 24-h ambulatory pH-impedance catheter was left in the esophagus, analysis was done according to the Lyon consensus. [15]

Impedance planimetry

Prior to the stationary esophageal studies an impedance planimetry study was performed to assess the esophagogastric junction distensibility (EndoFLIP catheter, model EF-325N; Crospon Ltd., Galway, Ireland). The center of the bag was positioned at the EGJ and the bag was inflated by the following distension protocol; 20, 30, 40 and 50 mL volume. A volume of 40 mL was used to assess the EGJ distensibility and EGJ distensibility is expressed in mm2/mmHg. [16] At this volume 95% of normal subjects will have a EGJ-DI above 2 mm2/mmHg, values below are considered abnormal. [17]

ARMS procedure

ARMS was performed as described by Inoue et al. [10], in patients under deep propofol sedation. During upper endoscopy an endoscopic mucosal resection (EMR) of the EGJ-mucosa was conducted in a piecemeal fashion using Multiband Mucosectomy (Duette, Cook, Limerick, Ireland), with prior submucosal lifting using a mixture of saline, adrenaline and indigo. A forward-viewing upper endoscope (GIF HQ190; Olympus, Hamburg, Germany) was used. First, the scheduled reduction area on the mucosa was marked. Marking on the mucosa was placed along the expected margin of the EMR using an electrocautery knife

connected to the electrocautery generator (Erbe Vio 300D; Erbe Elektromedizin, Tübingen, Germany). The total mucosectomy was approximately 3 centimeters in length (1 centimeter in the esophagus and approximately 2 centimeters in the stomach). Instead of the 2/3rd as described by Inoue et al. [10] we treated only 50% of the circumference of the esophago-gastric-junction (EGJ) at the lesser curvature side, in order to reduce the risk of dysphagia. EMR was carried out repeatedly until the marked mucosal area was completely resected. A coagulating forceps (FD-410LR Coagrasper; Olympus) was used for hemostasis if needed. Patients were kept on a clear liquid diet for 12 hours. In case of absence of postoperative alarm symptoms the patients were discharged on the day of the procedure with continuation of two times daily PPI for 4 weeks.

Statistical analysis

Sample size

We based our sample size calculation on a previous study in which a similar population was studied. [18] In a group of patients with gastroesophageal reflux disease (confirmed by 24-h ambulatory pH-impedance studies) the mean total number of reflux episodes was 97.6 (± 31). A 30% decrease in reflux episodes was considered clinically relevant (68.3 episodes). Using these numbers and a paired 2-sided T-test with a significance level of 5% and a power of 80%, a sample size of 11 subjects was calculated.

Endpoint analysis

The primary outcome was a change in reflux episodes after treatment during 24-hour pH-impedance measurement. Secondary outcomes included acid exposure time (AET), number of reflux episodes (acid, weakly acid and gas), belching (gastric and supragastric); manometric features; EGJ distensibility; number of TLESRs; reflux symptoms, dysphagia symptoms, health-related quality of life*(supplemental material)* and PPI use in the preceding month (PPI use in the week prior to investigation was excluded since PPIs were stopped in this week); grade of gastroesophageal flap valve according to the Hill classification and erosive esophagitis according the LA classification assessed during endoscopy and occurrence of unwanted procedural related events including perforation, (delayed) bleeding and strictures.

Continuous data were compared with the paired Student t-test for normal distributed data and the Wilcoxon signed rank test for non-normally distributed data. Categorical variables were evaluated using the McNemar test. Descriptive statistics were presented as percentage, mean with standard deviation (SD) or median with interquartile range (IQR). Correlations were evaluated using Pearson correlation. A p-value of <0.05 will be considered significant. SPSS statistics (version 28; SPSS) was used for statistical analysis.

Results

In total 15 patients signed the informed consent form, 11 patients were treated (8 male, 73%). Reasons for exclusion are shown in *supplementary figure 2*. One patient was lost to follow-up and therefore not included in further analysis apart from baseline criteria. Baseline criteria can be found in *table 1*. An example of endoscopy images prior to treatment, during treatment and after treatment can be found in *figure 1*.

24-hour ambulatory pH-impedance monitoring

24-hour pH-impedance monitoring revealed a significant reduction in total acid exposure time; 8.7 (6.4-12.7)% to 5.3 (3.5-6.7)%, p=0.028 as shown is *figure 2*. Also the total number of reflux episodes (74 (60-82) vs 37 (28-66), p=0.008) and the number of acid reflux episodes (65 (50-71) vs 35 (23-49), p=0.008) decreased significantly after treatment. No significant difference was seen in weakly acid reflux episodes (9 (4-16) vs 4 (3-6), p=0.051) The number of gastric belches (42 (22-56) to 43 (17-46), p=0.139) and supragastric belches (7 (2-85) to 5 (4-29), p=441) did not change significantly after treatment.

90-minute postprandial stationary measurement

During the 90-minute postprandial measurement period we found a significant decrease in complete TLESRs after intervention compared to baseline; 4 (1-8) to 2 (1-4), p=0.027. In all

patients together a total of 58 complete TLESRs were found prior to treatment compared, 27 (47%) of these were associated with reflux. After treatment we found a total of 34 complete TLESRs, 16 (47%) were associated with reflux. An overview of the total number of complete TLESRs and number of complete TLESRs associated with reflux can be found in *figure 3*. We did not see a significant difference in total number of reflux episodes (9 (3-13) vs 6 (4-12), p=0.789), acid reflux episodes (9 (2-12) vs 5 (4-10), p=0.720) or weakly acid reflux episodes (0 (0-0) vs 0 (0-1), p=0.680) during the postprandial measurement period compared to baseline. In addition, no significant difference was seen in total acid exposure time; 15.1 (5.2-7.8)% at baseline compared to 20.8 (3.2-29.1)% after treatment, p=0.799.

Esophagogastric junction

After ARMS treatment the LES-resting pressure increased significantly from 16.5 (3.3-22.5) mmHg to 18.3 (12.8-39.5) mmHg, p=0.047. IRP-4 was affected by ARMS treatment although not significantly (from 3.9 (0-10.1) mmHg to 11.5 (5.9-13.9) mmHg, p=0.093). We did not found a significant change in EGJ distensibility measured using impedance planimetry; 4.4 ($\pm$2.1) mm^2/mmHg vs 4.3 ($\pm$2.2) mm^2/mmHg, p=0.952.

Questionnaires

After treatment significantly less reflux symptoms were reported based on RDQ-GERD score (3.6 (3.6-3.9) at baseline to 1.6 (0.7-2.7), p=0.005). ARMS treatment resulted in a decrease in GERD-HRQoL score (26 (21-32) to 16 (6-24), p=0.008) indicating GERD related Quality of Life improved. We did not see a significant change in dysphagia symptoms (8.2 ($\pm$7.3) vs 8.5 ($\pm$6.5), p=0.879).

Medication

Prior to treatment all patients used PPI twice daily. After treatment 3 (30%) of 10 patients were able to cease all reflux medication, 6 (60%) of 10 were still taking PPIs. However it should be noted that two (20%) of these patients had to take PPI not because of reflux symptoms but as gastroprotection due to comedication. One patient (10%) was only using antacids on a regular basis.

Post-hoc correlations

We explored correlations between reflux episodes and pathophysiological parameters (IRP-4, LES-resting pressure, TLESRs and EGJ distensibility). After treatment we found a

correlation between the number of TLESRs in the postprandial recording period and the acid exposure time in supine position during the 24h-pH impedance measurement; $r(8) = .657$, $p=0.039$ .We also discovered a correlation between the number of TLESRs and the number of weakly acid episodes during 24h-pH impedance measurement; $r(8) = .756$, $p=0.019$. Additionally we found an inverse correlation between IRP-4 and the number of weakly acid reflux episodes measured during the postprandial period; $r(8) = -.653$, $p=0.041$.

Safety

One delayed post-procedural bleeding (10%, (1/10)) occurred requiring repeat endoscopy and re-admission for one night. During endoscopy the bleeding had already stopped and no endoscopic intervention, nor transfusion, were necessary. In one patient (10%, (1/10)) the procedure was terminated due to sedation related desaturation, which fully recovered once the patient was awake. This patient was lost to follow-up. No significant esophageal strictures were seen after treatment.

Discussion

We have evaluated the efficacy, underlying mechanisms and safety of the ARMS procedure in patients with PPI refractory reflux symptoms. We found that ARMS resulted in a significant decrease in number of compete TLSERs, a higher IRP-4 although not significant while LES resting pressure and the number of belches remained unchanged. Furthermore, we found a significant reduction of total acid exposure, total number of reflux episodes, number of acid reflux episodes and a trend was visible in healing of esophagitis. Simultaneously, the GERD-specific quality of life and reflux symptoms improved. In addition, we found a correlation between the number of TLESRs with both acid exposure time in supine position and the number of weakly acid reflux episodes, suggesting that the reduction of TLSERs after ARMS may be an important driver of the reduction of acid exposure and improved reflux symptoms.

We found a significant decrease in total acid exposure time from 8.7% to 5.3% after treatment. Acid exposure time in earlier studies that performed esophageal 24h-pH monitoring time prior to and after treatment with ARMS varied widely (20.8-3.1% prior to

treatment and 6.9-1.8% after treatment). However, all studies found a significant reduction in acid exposure time, [19-22] but comparing our results to laparoscopic fundoplication it seems evident that acid exposure time is much rigorously reduced after fundoplication (1.8-0.3%) than after ARMS (5.3%). [23]

Patients in our study reported a significant reduction of reflux symptoms based on the RDQ-GERD questionnaire (from 3.6 to 1.6 after treatment). Although most ARMS studies evaluated symptoms based on the GERDQ score (from 13.3-9.4 to 9-3.4 after treatment) the results of our trial are in line with the previously reported studies. [22] We did not find a significant change in the number of gastric belches during 24-hour pH-impedance measurement pre- and post-treatment (42 vs 43 belches) with ARMS. This is in contrast to surgical anti-reflux procedures (laparoscopic fundoplication) were a significant decrease in the number of gastric belches was seen after treatment (60 vs 12 belches). [24] Bloating and inability to belch are reported after laparoscopic fundoplication and leads to decreased satisfaction with the outcome. [24, 25] Since the number of gastric belches are not affected by the ARMS procedure it may not result in bloating and inability to belch.

When looking at the safety parameters in our study one patient (10%) was readmitted due to delayed bleeding, no perforation occurred and no stricture was seen at follow-up endoscopy. Other studies reported a percentage of patients with bleeding of from 0 to 43% with a mean of 5%. [26] The total number of patients in these studies ranged from 12 to 109. Since our study population was small (n=11), the percentage of patients with delayed bleeding can be overvalued compared to the previous studies. We did not see any esophageal strictures while other studies reported a incidence of 10.6%. [26] This might be explained by the fact that in our study only 50% of the circumference around the EGJ was treated, in comparison to 60-80% of the circumference in other studies. [10, 22]

An important objective of this study was to clarify the underlying working mechanism of ARMS. We evaluated the number of complete TLESRs after the ARMS procedure and found the number of TLESRs during the 90 minutes post-prandial measurement period was reduced by approximately 50%; from 4 (1-8) to 2 (1-4). The absolute number of complete TLESRs we found might are on the lower side compared to previous studies. Although the variability in frequency of TLESRs varies in different studies from 0 to 12 TLESRs/hour. [27, 28] Both studies included both complete and incomplete TLESRs. To our knowledge this is the first study that analyzed the number of TLESRs after ARMS. TLESRs are mainly triggered by

gastric distension trough tension receptors that are located in the subcardiac region of the stomach. [29] Since the mucosectomy is extended in the stomach for 2cm it is hypothesized the gastric stretch receptors have become less sensitive for gastric distension and the number of TLSERs is reduced. It is known that a surgical fundoplication also reduces the number of TLSERs and this reduction is thought to have an important role in reduction of reflux episodes and acid exposure time. [30] In addition, we also found a correlation between a decreased number of TLSERs and decreased number of weakly acid reflux episodes and reduced acid exposure time during ambulatory pH-impedance measurement, which indicates this might be one of the mechanisms to explain the effect of ARMS. During the postprandial period no correlation between TLESRs and acid exposure or reflux episodes was seen, but this may be explained by the small number of reflux episodes measured in the 90-minutes postprandial period. It is important to note that the sample size is small and therefore some caution is advised interpreting these correlations.

Another assumed mechanism of action of ARMS is the formation of a mechanical reflux barrier due to fibrosis at the esophagogastric junction. In this trial we did not found a significant change in EGJ-distensibility (4.4 vs 4.3 mm^2/mmHg). Therefore, we may can conclude the mechanical barrier formed by fibrosis is not one of the underlying working mechanisms of ARMS. However, it is also possible the sample size was too low to sort out any effect or the EGJ-distensibility protocol was not optimal. In this study we measured the EGJ-distensibility at a balloon volume of 40ml while other studies used different balloon volumes. [17] We do see a trend in higher IRP-4 (from 3.9 to 11.5 mmHg) after treatment with ARMS. This increase is not significant, possibly also due to the small sample size. Secondly, while the effect of the mucosectomy might not results in a change in EGJ distensibility, the fibrosis at the lesser curvature side may still be mechanical barrier for reflux.

A strength of this study is the fact we focused not only on the effect of ARMS but also on the underlying working mechanism. Furthermore, participating GERD patients were well characterized and thoroughly studied using different techniques. Some limitations have to be acknowledged. First, we only did follow-up for three months after treatment. Three months seems enough to evaluate adverse events as delayed bleeding (mean time between EMR and bleeding is 2.5 days) or the occurrence of strictures (time between EMR and first dilation due to strictures is 31 days). [31, 32] However, 3 months might be not enough to evaluate long-term effect of ARMS on symptoms, acid exposure and number of reflux episodes. Currently,

no long-term (>1 year) data of the effect of ARMS on acid exposure is available. Secondly, we did not compare ARMS treatment to the current gold standard surgical approach; Laparoscopic Fundoplication, but the outcome data suggests it is not anywhere near as effective. Probably, endoscopic techniques such as ARMS will never be an appropriate alternative for very severe GERD patients with a substantial hiatus hernia, but may play a role for the treatment of patients with the moderate GERD phenotype and absent to small hernia. Thirdly, the sample size was relatively small for a confirmatory study although it was suitable to investigate the underlying mechanism of action of ARMS.

The results of this study regarding the effect of ARMS on reflux symptoms and acid exposure are in line with the results that have been published previously. Additionally, we found the effect of ARMS could be driven by an inhibition of TLESRs than the mechanical reduction of backflow due to scar formation. This could be a point of interest for further studies on endoscopic anti-reflux treatment. We do think ARMS might has a place as treatment for GERD next to non-pharmacological (weight loss, head of bed elevation, abdominal breathing exercises), pharmacological (antacids, H2-blockers, proton pump inhibitors) and surgical treatment options.

In conclusion, ARMS is a successful treatment option in PPI refractory GERD patients reducing acid exposure, reflux episodes and symptoms. While the mechanism could not be explained by a difference in distensibility, a reduction in TLSERs might play a role.

Kuipers et al.

References

1. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2013; 108: 308-328; quiz 329. doi:10.1038/ajg.2012.444

2. Dent J, Dodds WJ, Friedman RH et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. The Journal of clinical investigation 1980; 65: 256-267. doi:10.1172/jci109667

3. Dodds WJ, Dent J, Hogan WJ et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. The New England journal of medicine 1982; 307: 1547-1552. doi:10.1056/nejm198212163072503

4. Eherer AJ, Netolitzky F, Högenauer C et al. Positive effect of abdominal breathing exercise on gastroesophageal reflux disease: a randomized, controlled study. Am J Gastroenterol 2012; 107: 372-378. doi:10.1038/ajg.2011.420

5. Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. World J Gastrointest Pharmacol Ther 2014; 5: 105-112. doi:10.4292/wjgpt.v5.i3.105

6. Garg SK, Gurusamy KS. Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. The Cochrane database of systematic reviews 2015. doi:10.1002/14651858.CD003243.pub3: Cd003243. doi:10.1002/14651858.CD003243.pub3

7. Corley DA, Katz P, Wo JM et al. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. Gastroenterology 2003; 125: 668-676. doi:10.1016/s0016-5085(03)01052-7

8. Repici A, Fumagalli U, Malesci A et al. Endoluminal fundoplication (ELF) for GERD using EsophyX: a 12-month follow-up in a single-center experience. J Gastrointest Surg 2010; 14: 1-6. doi:10.1007/s11605-009-1077-2

9. Schwartz MP, Wellink H, Gooszen HG et al. Endoscopic gastroplication for the treatment of gastro-oesophageal reflux disease: a randomised, sham-controlled trial. Gut 2007; 56: 20-28. doi:10.1136/gut.2006.096842

10. Inoue H, Ito H, Ikeda H et al. Anti-reflux mucosectomy for gastroesophageal reflux disease in the absence of hiatus hernia: a pilot study. Annals of gastroenterology 2014; 27: 346-351

11. Yoo IK, Cho JY, Hong S-P. 528 Anti-reflux endoscopic surgery: endoscopic cardioplasty using endoscopic mucosal resection may effectively treat refractory gastroesophageal reflux disease. Gastrointestinal Endoscopy 2018; 87: AB89. doi:10.1016/j.gie.2018.04.102

12. Inoue H, Sumi K, Tatsuta T et al. Clinical Results of Antireflux Mucosectomy (ARMS) for Refractory GERD. Gastrointest Endosc 2017; 85

13. Sumi K, Inoue H, Ando R et al. Long-term efficacy of antireflux mucosectomy in patients with refractory gastroesophageal reflux disease. Dig Endosc 2023. doi:10.1111/den.14617. doi:10.1111/den.14617

14. Roman S, Holloway R, Keller J et al. Validation of criteria for the definition of transient lower esophageal sphincter relaxations using high-resolution manometry. Neurogastroenterol Motil 2017; 29. doi:10.1111/nmo.12920

15. Gyawali CP, Kahrilas PJ, Savarino E et al. Modern diagnosis of GERD: the Lyon Consensus. Gut 2018; 67: 1351-1362. doi:10.1136/gutjnl-2017-314722

16. Chen JW, Rubenstein JH. Esophagogastric junction distensibility assessed using the functional lumen imaging probe. World journal of gastroenterology 2017; 23: 1289-1297. doi:10.3748/wjg.v23.i7.1289

17. Bredenoord AJ, Rancati F, Lin H et al. Normative values for esophageal functional lumen imaging probe measurements: A meta-analysis. Neurogastroenterol Motil 2022; 34: e14419. doi:10.1111/nmo.14419

18. Bredenoord AJ, Weusten BL, Timmer R et al. Characteristics of gastroesophageal reflux in symptomatic patients with and without excessive esophageal acid exposure. Am J Gastroenterol 2006; 101: 2470-2475. doi:10.1111/j.1572-0241.2006.00945.x

19. Kessler WR, McNulty G, Lehman GA. A prospective, randomized study on the effect of band ligation with or without mucosectomy as a treatment for GERD: Pilot study, 12 month experience.

20. Sumi K, Inoue H, Kobayashi Y et al. Endoscopic treatment of proton pump inhibitor-refractory gastroesophageal reflux disease with anti-reflux mucosectomy: Experience of 109 cases. Dig Endosc 2021; 33: 347-354. doi:10.1111/den.13727

21. Yoo IK, Ko WJ, Kim HS et al. Anti-reflux mucosectomy using a cap-assisted endoscopic mucosal resection method for refractory gastroesophageal disease: a prospective feasibility study. Surg Endosc 2019. doi:10.1007/s00464-019-06859-y. doi:10.1007/s00464-019-06859-y

22. Garg R, Mohammed A, Singh A et al. Anti-reflux mucosectomy for refractory gastroesophageal reflux disease: a systematic review and meta-analysis. Endosc Int Open 2022; 10: E854-E864. doi:10.1055/a-1802-0220

23. Hillman L, Yadlapati R, Whitsett M et al. Review of antireflux procedures for proton pump inhibitor nonresponsive gastroesophageal reflux disease. Dis Esophagus 2017; 30: 1-14. doi:10.1093/dote/dox054

24. Kessing BF, Broeders JA, Vinke N et al. Gas-related symptoms after antireflux surgery. Surg Endosc 2013; 27: 3739-3747. doi:10.1007/s00464-013-2959-7

25. Broeders JA, Mauritz FA, Ahmed Ali U et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010; 97: 1318-1330. doi:10.1002/bjs.7174

26. Yeh JH, Lee CT, Hsu MH et al. Antireflux mucosal intervention (ARMI) procedures for refractory gastroesophageal reflux disease: a systematic review and meta-analysis. Therap Adv Gastroenterol 2022; 15: 17562848221094959. doi:10.1177/17562848221094959

27. Pandolfino JE, Zhang QG, Ghosh SK et al. Transient lower esophageal sphincter relaxations and reflux: mechanistic analysis using concurrent fluoroscopy and high-resolution manometry. Gastroenterology 2006; 131: 1725-1733. doi:10.1053/j.gastro.2006.09.009

28. Kim HI, Hong SJ, Han JP et al. Specific movement of esophagus during transient lower esophageal sphincter relaxation in gastroesophageal reflux disease. J Neurogastroenterol Motil 2013; 19: 332-337. doi:10.5056/jnm.2013.19.3.332

29. Franzi SJ, Martin CJ, Cox MR et al. Response of canine lower esophageal sphincter to gastric distension. Am J Physiol 1990; 259: G380-385. doi:10.1152/ajpgi.1990.259.3.G380

30. Kessing BF, Conchillo JM, Bredenoord AJ et al. Review article: the clinical relevance of transient lower oesophageal sphincter relaxations in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2011; 33: 650-661. doi:10.1111/j.1365-2036.2010.04565.x

31. Tomizawa Y, Iyer PG, Wong Kee Song LM et al. Safety of endoscopic mucosal resection for Barrett's esophagus. Am J Gastroenterol 2013; 108: 1440-1447; quiz 1448. doi:10.1038/ajg.2013.187

32. Abou Ali E, Belle A, Hallit R et al. Management of esophageal strictures after endoscopic resection for early neoplasia. Therap Adv Gastroenterol 2021; 14: 1756284820985298. doi:10.1177/1756284820985298

Figure legends

Kuipers et al.

Figure 1 Endoscopy images prior to treatment, during treatment and 3 months after treatment respectively

Figure 2 Pre post chart of total acid exposure and acid reflux episodes measured using 24-h pH-impedance measurement prior to and after treatment.

Figure 3 Stacked bar chart with total number of complete TLESRs in all subjects associated with and without reflux seen during the 90-minute postprandial measurement pre and post treatment.

Video legend

Video 1 Video of the ARMS procedure

Supplementary material

<u>Full list of in and exclusion criteria</u>

Inclusion criteria

-        Indication for surgical treatment, defined by objectively confirmed gastroesophageal reflux disease (24-h ambulatory pH-impedance study with a symptom association probability ≥95%; and esophageal acid exposure ≥4%)

-        Symptoms of heartburn, regurgitation and/or chest pain under PPI-treatment for at least 3 months at least 3 times a week.

-        Use of proton pump inhibitors at a standard dose twice a day for for a period of at least 4 weeks prior to inclusion.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

-        ASA classification of III or higher.

-        Previous (surgical or endoscopic) anti-reflux procedure

-        Previous surgery of the stomach or esophagus

-        Sliding hiatal hernia >2cm

-        Esophagitis grade C or D

-        Presence of Barrett's esophagus with dysplasia

-        Known coagulopathy

-        Unable to stop coagulants (with the exception of mono antiplatelet therapy)

-        Presence of liver cirrhosis and/or esophageal varices

-        Presence of a stricture of the esophagus

-        Presence of eosinophilic esophagitis

-        Presence of achalasia

-        Presence of connective tissue disorder

-        Absent peristalsis on high-resolution manometry

-        Pregnancy at time of treatment

Questionnaires

<u>Reflux Disease Questionnaire (RDQ)</u>

A standardized validated questionnaire will be filled in: the reflux-disease questionnaire (RDQ). (1) The RDQ is a 12-item questionnaire assessing the current severity and frequency of 3 GERD-related symptom domains (heartburn, regurgitation and epigastric pain). Each domain is assessed by four questions, all rated on a 5-point Likert scale.

Health-related quality of life for GERD (GERD-HRQL)

GERD-related quality of life (QoL) will be assessed using the GERD-HRQL. (2) This questionnaire was developed to survey symptomatic outcomes and therapeutic effects in patients with GERD. The scale has 11 items, which focus on heartburn symptoms, dysphagia, medication effects and the patient's present health condition. Each item is scored on a 5-point Likert score, with a higher score indicating a better QoL.

Brief Esophageal Dysphagia Questionnaire

A standardized validated questionnaire will be used to assess dysphagia symptoms. The Brief Esophageal Dysphagia Questionnaire (BEDQ) is a 10-item questionnaire assessing both frequency and severity of dysphagia symptoms. The total score is calculated by summing the numeric value (0-5) for all items checked on the questionnaire. (3)

References

1.   Shaw MJ, Talley NJ, Beebe TJ, Rockwood T, Carlsson R, Adlis S, et al. Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. Am J Gastroenterol. 2001;96(1):52-7.
2.   Velanovich V, Vallance SR, Gusz JR, Tapia FV, Harkabus MA. Quality of life scale for gastroesophageal reflux disease. Journal of the American College of Surgeons. 1996;183(3):217-24.
3.   Taft TH, Riehl M, Sodikoff JB, Kahrilas PJ, Keefer L, Doerfler B, Pandolfino JE. Development and validation of the brief esophageal dysphagia questionnaire. Neurogastroenterol Motil. 2016;28(12):1854-60.

Table 1. Baseline characteristics (N=11)

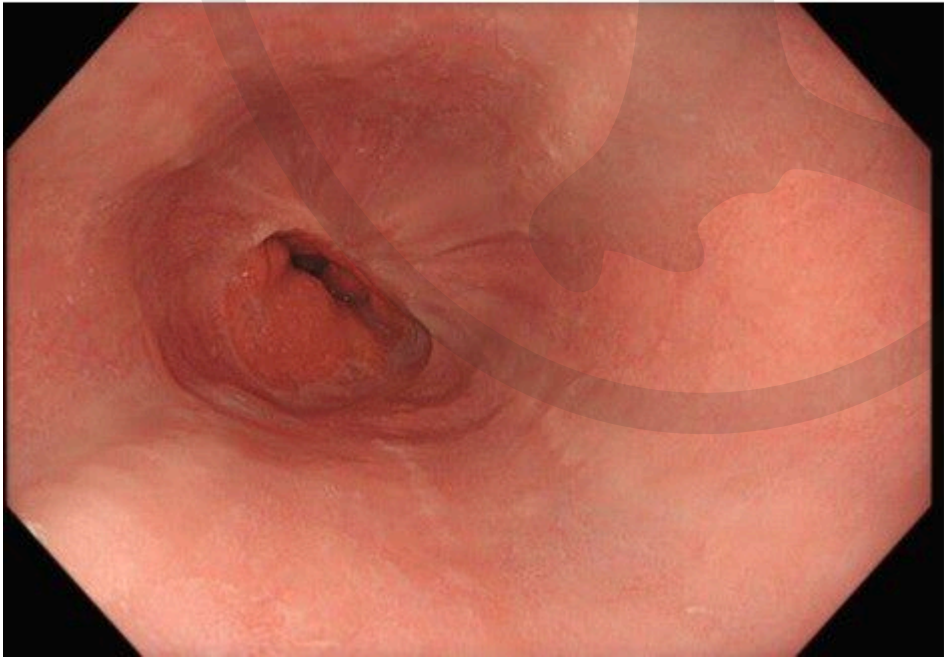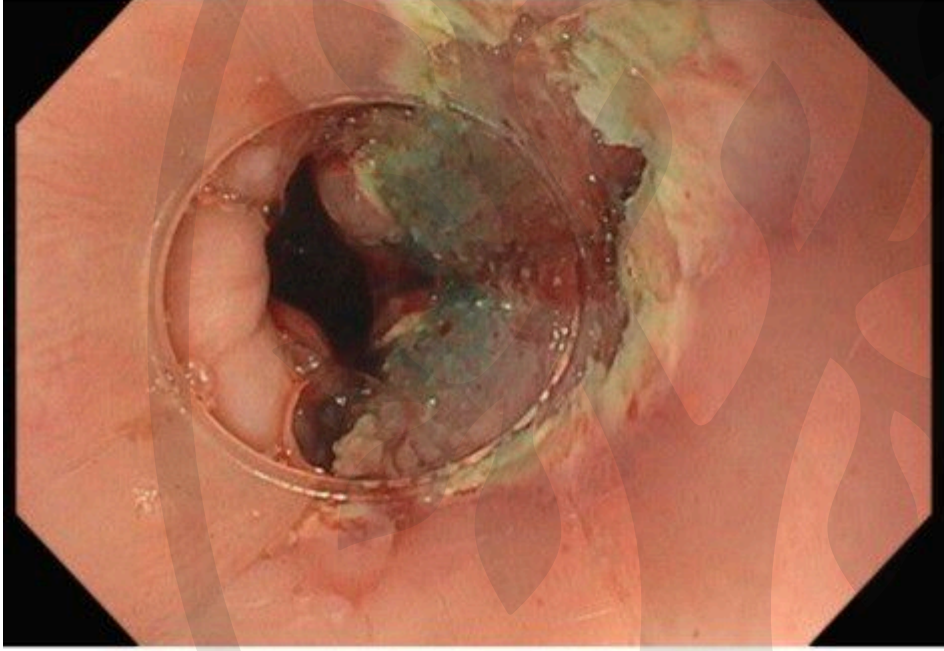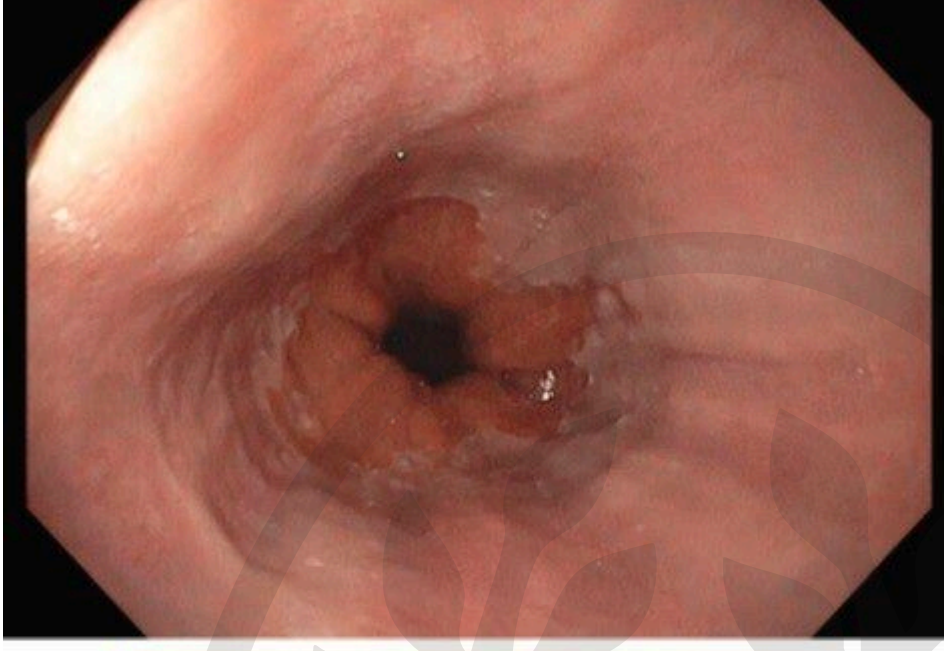|	
Age (years)	37 (32-57)
Sex	
Male	8 (73%)
Female	3 (27%)
BMI (kg/m^2)	28.4 (±3.5)
Current smoker	2 (18%)
Alcohol consumption	
No	4 (36%)
Mild (0-5U/week)	6 (55%)
Moderate (5-14U/week)	1 (9%)
Medication Use	
Use of Antacids	2 (18%)
Use of H2-receptor antagonists	1 (9%)
Use of Proton pump inhibitors	11 (100%)
HRM diagnosis	
Normal	3 (27%)
Ineffective esophageal motility	8 (73%)
Questionnaires	
RDQ GERD	3.5 (2.1-3.9)
Health-related QoL GERD	28 (21-32)
Brief dysphagia questionnaire (BEDQ)	7 (1-14)

Displayed as n(%), mean ± SD or median with IQR. HRM; high resolution manometry

Table 2. Treatment effect of ARMS (N=10)

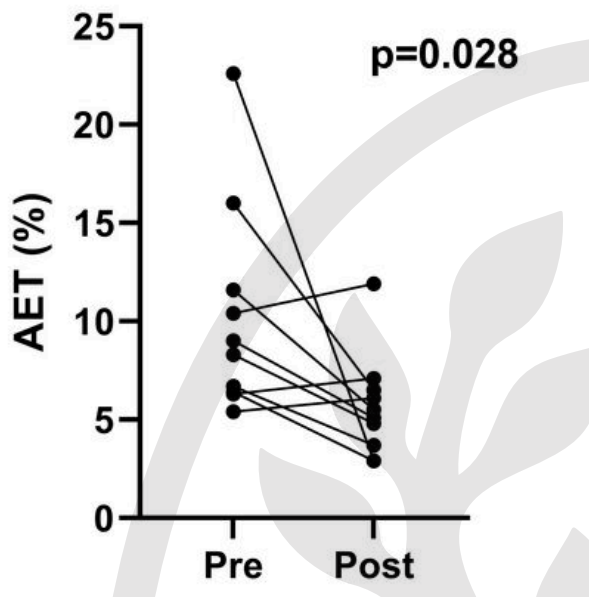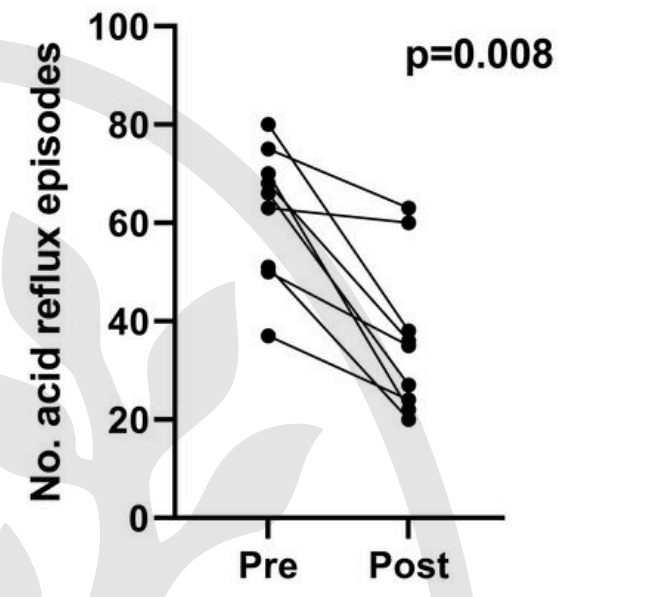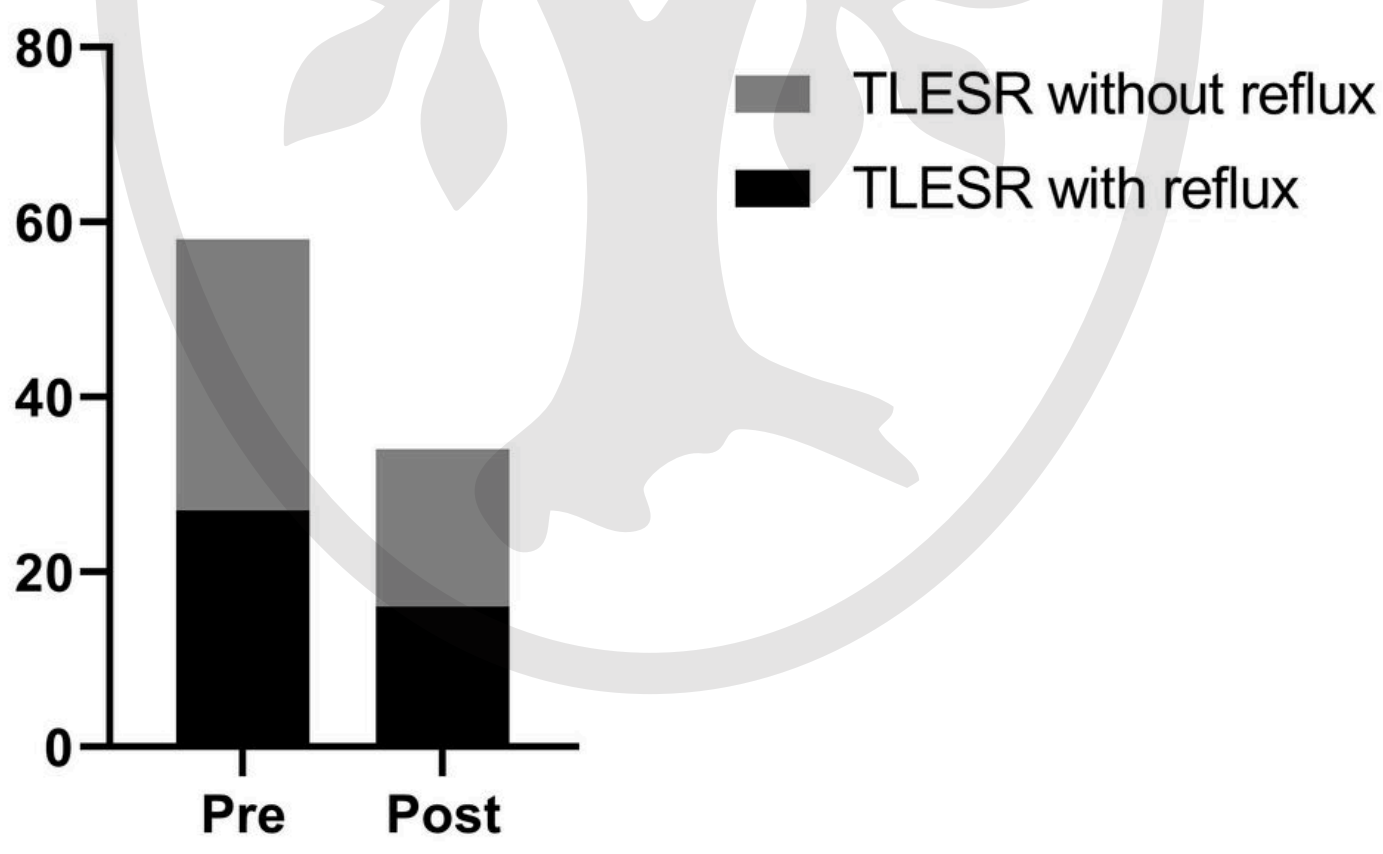|	Prior to treatment	3 months after treatment	P-value
<u>24-hour ambulatory pH-impedance monitoring</u>			
Total No. of reflux episodes, median (IQR)	74 (60-82)	37 (28-66)	**0.008**
Acidic reflux episodes, median (IQR)	65 (50-71)	35 (23-49)	**0.008**
Weakly acidic reflux episodes, median (IQR)	9 (4-16)	4 (3-6)	0.051
Total acid exposure time (%), median (IQR)	8.7 (6.4-12.7)	5.3 (3.5-6.7)	**0.028**
HRM			
IRP-4 (mmHg), median (IQR)	3.9 (0-10.1)	11.5 (5.9-13.9)	0.093
LES-resting pressure (mmHg), median (IQR)	16.5 (3.3-22.5)	18.3 (12.8-39.5)	**0.047**
<u>90-minute postprandial manometry and pH-impedance</u>			
Transient lower esophageal sphincter relaxations (TLESRs), median (IQR)	4 (1-8)	2 (1-4)	**0.027**
Total No. of reflux episodes, median (IQR)	9 (3-13)	6 (4-12)	0.798
Acidic reflux episodes, median (IQR)	9 (2-12)	5 (4-10)	0.720
Weakly acidic reflux episodes, median (IQR)	0 (0-0)	0 (0-1)	0.680
Total acid exposure time (%), median (IQR)	15.1(5.2-7.8)	20.8 (3.2-29.1)	0.799
<u>Endoflip</u>			
Distensibility index (DI) at 40ml, mm2/mmHg, mean (SD)	4.4 (±2.1)	4.3 (±2.2)	0.952
<u>Endoscopy</u>			
Esophagitis present on endoscopy, n (%)	9 (90)	5 (50)	0.125
Grade A/Grade B	4 (40) / 5 (50)	1 (10) / 4 (40)	
Hill classification during endoscopy, n (%)			0.257
Hill 1	5 (50)	6 (60)	
Hill 2	3 (30)	4 (40)	
Hill 3	2 (20)	-	
<u>Symptoms</u>			
Reflux Disease Questionnaire (RDQ-GERD), median (IQR)	3.6 (3.6-3.9)	1.6 (0.7-2.7)	**0.005**
GERD-Health Related Quality of Life, median (IQR)	26 (21-32)	16 (6-24)	**0.008**
Brief Esophageal Dysphagia Questionnaire, mean (SD)	8.2 (±7.3)	8.5 (±6.5)	0.879

Total acid exposure time

p=0.028

AET (%)

Acid reflux episodes 24h-pH

p=0.008

No. acid reflux episodes

TLESRs

TLESR without reflux
TLESR with reflux

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Baseline investigations		*ARMS procedure*	*Investigations at 3 months follow-up*	
- Informed consent - Medical history - Questionnaires - Esophageal function studies	Removal pH-impedance catheter	Upper endoscopy with ARMS	- Upper endoscopy - Questionnaires - Esophageal function studies	Removal pH-impedance catheter

Signed informed consent (n=15)

Exclusion (n=4)
- Withdrawn informed consent (n=2)
- Hiatal hernia >2cm (n=1)
- Not able to reach adequate sedation during endoscopy (n=1)

Treated (n=11)

Lost to follow-up (n=1)

Follow-up 3 months (n=10)