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## Is patient satisfaction sufficient to validate endoscopic anti-reflux treatments?

Mauro Bortolotti

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### Abstract

Endoscopic anti-reflux treatment is emerging as a new option for gastro-esophageal reflux disease (GERD) treatment in patients with the same indications as for laparoscopic fundoplication. There are many techniques, the first of which are transoral incisionless fundoplication (TIF) and nonablative radio-frequency (STRETTA) that have been tested with comparative studies and randomized controlled trials, whereas the other more recent ones still require a deeper evaluation. The purpose of the latter is to verify whether reflux is abolished or significantly reduced after intervention, whether there is a valid high pressure zone at the gastroesophageal junction, and whether esophagitis, when present, has disappeared. Unfortunately in a certain number of cases, and especially in the more recently introduced ones, the evaluation has been based almost exclusively on subjective criteria, such as improvement in the quality of life, remission of heartburn and regurgitation, and reduction or suspension of antacid and antisecretory drug consumption. However, with the most studied techniques such as TIF and STRETTA, an improvement in symptoms better than that of laparoscopic fundoplication can often be observed, whereas the number of acid episodes and acid exposure time are similar or higher, as if the acid refluxes are better tolerated by these patients. The suspicion of a local hyposensitivity taking place after anti-reflux endoscopic intervention seems confirmed by a Bernstein test at least for STRETTA. This examination should be done for all the other techniques, both old and new, to identify the ones that reassure rather than cure. In conclusion, the evaluation of the effectiveness of the endoscopic anti-reflux techniques should not be based exclusively on subjective criteria, but should also be confirmed by objective examinations, because there might be a gap between the improvement in symptoms declared by the patient and the underlying pathophysiologic alterations of GERD.

**Key Words:** Endoscopic anti-reflux treatment; Transoral incisionless fundoplication; Nonablative radio-frequency; Anti-reflux mucosectomy; Gastro-esophageal reflux disease; Laparoscopic Nissen fundoplication

**Core Tip:** Endoscopic anti-reflux treatments are being increasingly used instead of anti-reflux surgery. However, most of them have been evaluated only on the ground of subjective symptoms, without performing any objective examination. Furthermore, some also appear to be more effective than surgery in improving acid reflux symptoms, even if their acid exposure is worse, suggesting a reduced sensitivity. The Bernstein test performed after nonablative radio-frequency seems to confirm this hypothesis. Hence, to verify the effectiveness of these esophageal anti-reflux interventions, in addition to evaluating the symptoms before and after the intervention, it is necessary to perform objective examinations.

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## TO THE EDITOR

In the past few years, endoscopic anti-reflux treatments have increasingly caught the attention of many gastroenterological centers, as they offer a minimally invasive option for patients with gastroesophageal reflux disease (GERD) who show refractoriness or intolerance to proton pump inhibitors (PPI), or who refuse to take lifelong medication, but want to avoid a surgical intervention, such as the classical laparoscopic fundoplication (LF). A recent article[1] has provided an up-to-date review of the technical aspects, clinical effectiveness, and safety of the main endoscopic anti-reflux procedures including transoral incisionless fundoplication (TIF), nonablative radio-frequency (STRETTA), and Medigus ultrasonic surgical endostapler (MUSE), together with the following still experimental techniques, such as full-thickness endoscopic plication device, anti-reflux mucosectomy (ARMS), anti-reflux mucosal ablation, and band-assisted ligation techniques. However, two observations can be made after consulting the literature studies on the effectiveness of these systems.

First, in most studies the efficacy of an endoscopic anti-reflux technique has been evaluated almost exclusively considering subjective symptoms, such as the improvement in quality of life, remission of heartburn and regurgitation, and reduction or suspension of antacid and antisecretory drugs consumption, to the extent that it has been deemed a success when the patient halved the dose of PPI used prior to intervention.

Second, in most studies where these endoscopic interventions are compared with LF or PPI therapy, symptom improvement after endoscopic treatments is frequently greater than that obtained with LF, even when the 24 h pH recording shows a worse result.

This statement can be easily verified in the systematic review and network meta-analysis of Richter *et al*[2] from seven randomized controlled trials (RCTs) with a total of 1128 patients, concerning a comparison of laparoscopic Nissen fundoplication (LNF) *vs* TIF or PPI treatment. The results indicate that TIF has the highest likelihood of increasing the patient's health-related quality of life (HRQL) followed by LNF, whereas the LNF has the highest likelihood of increasing the percentage of time with distal esophageal pH > 4, followed by PPI and then by TIF, which, in addition, has a higher likelihood than LNF for persistent esophagitis.

Also in the randomized controlled trial of Wittman *et al*[3] performed in 60 patients to evaluate the effectiveness of TIF in comparison with the PPI treatment, GERD symptoms after 6 mo are significantly more improved in the TIF group than in the PPI group, despite the similar improvement in distal esophageal acid exposure, whereas the pH normalization for TIF group is 50% with respect to 63% for the PPI group.

A systematic review and network meta-analysis[4] comprising 516 patients from 10 RCTs compared the anti-reflux efficacy of Stretta, TIF, and PPI. Both STRETTA and TIF are significantly superior to PPI in improving GERD-HRQL and heartburn scores, whereas PPI is better in decreasing the percentage of time with pH < 4.0 when compared with TIF.

Also in the study of He *et al*[5], the symptom score improvement was significantly higher in the STRETTA group of 26 patients compared with the PPI group of 21 patients after 6 mo, whereas both interventions improved, without significant differences, the 24 h pH parameters, including the number of acid episodes, acid exposure time, and DeMeester score.

Furthermore, the absence of correlation between the improvement in GER symptoms and the decrease in acid reflux in patients treated with STRETTA is highlighted by the following two studies.

Coron *et al*[6] in an article comparing the results in 20 patients undergoing STRETTA and 16 patients treated with PPI report that GERD-HRQL scores do not differ between groups, whereas no significant



change in esophageal acid exposure is noted between baseline and 6 mo after STRETTA treatment. So they came to the conclusion that the efficacy of the STRETTA treatment does not seem to be related to a decrease in esophageal acid exposure. In addition, the study of Arts *et al*[7] shows that 3 mo after STRETTA procedure on 11 patients, the symptom score was significantly improved, whereas no changes were observed in esophageal acid exposure.

In view of all these results, we may be led to believe that the greater improvements in GER symptoms observed after TIF and STRETTA applications as compared with LF and PPI treatments, despite the scarce improvement in GER objective parameters, likely depend on another factor, that could be identified with a decreased visceral sensitivity. The hypothesis that symptom improvement in these patients depends on a decreased esophageal acid sensitivity is confirmed, at least for STRETTA, by the study of Arts *et al*[8]. They found that 6 mo after the STRETTA procedure in 13 patients, the mean time needed to induce heartburn during esophageal acid perfusion of the Bernstein test increased from  $9.5 \pm 2.3$  (mean  $\pm$  SD) to  $18.1 \pm 4.4$  min ( $P < 0.01$ ), whereas five had become insensitive to 30 min acid perfusion, *vs* none at baseline ( $P = 0.04$ ).

Also in the case of TIF, the dissociation between symptoms and objective parameters, if compared with those of LF and PPI, suggests the post-intervention appearance of a hyposensitive condition, similar to that of STRETTA, although a Bernstein test is necessary to confirm this supposition.

The cause of this local hyposensitivity could lie in an effect of radiofrequency (RF) energy of STRETTA on the myenteric and submucosal nervous plexuses carrying sensory receptors, acetylcholine stimulatory and non-adrenergic, non-cholinergic (NANC) inhibitory neurons, as well as on the two branches of the vagus nerve, which pass in the subadventitial space at the esophagogastric junction level. RF energy inducing a thermal injury promoting submucosal fibrosis and muscularis propria hypertrophy, should also act on nervous tissues impairing the inhibitory NANC neurons with a decrease in transient LES relaxations, while increasing its yield pressures[9]. It is likely that RF energy could also act on sensitive neurons of the esophageal wall. In addition, a slight excess of RF energy or a tissue weakness may also cause damage to the vagus nerve passing below, causing delayed gastric emptying and gastroparesis reported by some authors[10-13]. With regard to the other endoscopic procedures, there are no appropriate comparative studies with LNF and PPI treatments, except for the study of Wong *et al*[14], who compared Nissen fundoplication with ARMS. But they did not perform objective measurements for reflux and only evaluated GERD-HRQL and reflux symptoms up to 2 years, without observing any difference between the two groups.

In conclusion, the evaluation of the effectiveness of any endoscopic anti-reflux technique should not be based exclusively on subjective criteria, such as a good response to PPI suspension, remission of heartburn, and GERD-HRQL improvement, but should also be established with objective examinations, such as 24 h pH monitoring, and, if possible, manometric measurement of the high pressure zone in the distal esophagus, besides endoscopy for the assessment of esophagitis. The good capacity of TIF and STRETTA to improve the reflux symptoms and the quality of life more than LF and PPI treatments, is a double-edged weapon, because a scarce prevention of acid reflux in the long term may expose the patient to the risk that more or less serious alterations will pass unnoticed. This risk could also be taken with the other more recent endoscopic techniques, which, as previously mentioned, should be compared with LF or PPI treatments and possibly examined by the Bernstein test.

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