Two-year results of intermittent electrical stimulation of the lower esophageal sphincter treatment of gastroesophageal reflux disease

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Background. *Lower esophageal sphincter (LES) electrical stimulation therapy (EST) has been shown to improve outcome in gastroesophageal reflux disease (GERD) patients at 1 year. The aim of this open-label extension trial (NCT01578642) was to study the 2-year safety and efficacy of LES-EST in GERD patients.*
Methods. *GERD patients responsive partially to proton pump inhibitors (PPI) with off-PPI GERD health-related quality of life (HRQL) of ≥20, 24-hour esophageal pH ≤4.0 for >5% of the time, hiatal hernia ≤3 cm, and esophagitis LA grade C or lower participated in this trial. Bipolar stitch electrodes and a pulse generator (EndoStim BV, The Hague, The Netherlands) were implanted laparoscopically. LES-EST at 20 Hz, 215 μs, 3-8 mAmp was delivered over 30-minute sessions, 6-12 sessions per day, starting on day 1 after implantation. Patients were evaluated using GERD-HRQL, symptom diaries, Short Form-12, and esophageal pH testing at regular intervals. Stimulation sessions were optimized based on residual symptoms and esophageal pH at follow-up.*
Results. *Twenty-five patients (mean age [SD] = 52 [12] years; 14 men) were implanted successfully; 23 patients participated in the 2-year extension trial, and 21 completed their 2-year evaluation. At 2 years, there was improvement in their median GERD-HRQL on LES-EST compared with both their on-PPI (9 vs 0;* P = .001*) and off-PPI (23.5 vs 0;* P < .001*) baseline scores. Median 24-hour distal esophageal acid exposure improved from 10% at baseline to 4% (per-protocol analysis;* P < .001*) at 2 years with 71% demonstrating either normalization or a ≥50% decrease in their distal esophageal acid exposure. All except 5 patients (16/21) reported complete cessation of PPI use; only 2 patients were using a PPI regularly (≥50% of days). There was significant improvement in sleep quality and daily symptoms of heartburn and regurgitation on LES-EST. At baseline, 92% of the subjects (22/24) reported that they were "unsatisfied" with their condition off-PPI and 71% (17/24) on-PPI compared with 0% (0/21) "unsatisfied" at the 24-month visits on LES-EST. There were no device- or therapy-related serious adverse events and no untoward sensation or dysphagia reported with LES-EST.*
Conclusion. *LES-EST is safe and effective for treating patients with GERD over a period of 2 years. LES-EST resulted in a significant and sustained improvement in GERD symptoms, and esophageal acid exposure and eliminated PPI use in majority of patients (16 of 21). Further, LES-EST was not associated with any gastrointestinal side effects or adverse events. (Surgery 2015;157:556-67.)*

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Gastroesophageal reflux disease (GERD) is a global public health problem. The definition of GERD by the Montreal consensus emphasizes both subjective complaints and complications of GERD, defining GERD as "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications."[1] GERD symptoms are common and affect 10–20% of adults in Western countries and ≤40% in the United States.[2,3] Proton pump inhibitors (PPI) are potent suppressors of gastric acid secretion and have improved the treatment of erosive GERD; however, a substantial number of patients remain symptomatic despite maximal dose therapy. A meta-analysis of randomized, controlled trials indicate a high prevalence of incomplete response or nonresponse of reflux symptoms to PPI therapy.[4,5] A number of mechanisms are thought to contribute to incomplete response, an important one being the continuous reflux of weakly acidic or nonacidic gastric contents while on PPIs, because PPIs target acid secretion, rather than the lower esophageal sphincter (LES) dysfunction permitting persistent and unrestrained reflux of gastric contents into the esophagus.[6]

Inadequate symptom control has been cited as one of the main reasons that drive patients and physicians to seek surgical therapies for GERD.[7] The cost of life-long pharmacologic therapy and potential risks of long-term acid suppression are also of concern to patients and physicians.[8] Surgical fundoplication is effective, but is associated with long-term failures and adverse effects[7,9] This unmet need has led to multiple attempts at developing less-invasive endoscopic and surgical therapies for the treatment of GERD.[10,11]

"A desirable surgical/endoscopic GERD treatment should render an effect that is effective, yet less disruptive, has fewer adverse effects than that of a fundoplication, and be truly reversible."[12] Electrical stimulation therapy (EST) has been used successfully in treating some gastrointestinal motility disorders, such as gastroparesis and fecal incontinence, and has the required characteristics for being that "desirable" surgical therapy for GERD sufferers that are not satisfied with their medical therapy and are not interested in traditional antireflux surgery. The EndoStim LES stimulation system (EndoStim BV, The Hague, The Netherlands) is an implantable neurostimulator developed for the treatment of GERD. We demonstrated previously that temporary LES stimulation resulted in sustained improvement in LES pressure in GERD patients without any effect on LES relaxation.[13] We reported subsequently the safety and efficacy of LES-EST using a permanent LES stimulator implant in GERD patients at their 1-year follow-up.[14] This is the 2-year report of that cohort of subjects treated with LES-EST.

METHODS

Study objectives. The objectives of this prospective, open-label, single-center, treatment-only trial were to assess the safety of chronic intermittent LES-EST and to evaluate the effect of stimulation on GERD symptoms, medication use, esophageal acid exposure, and esophageal motor function in subjects with GERD. The study was registered (NCT01578642) and approved by the local Ethics Committee *Servicio de Salud Metropolitano Oriente Comitè Ètica Cientifico*, Santiago, Chile. All subjects signed an informed consent form before participating in the study.

Subject population. Key inclusion criteria included subjects 21–65 years of age with a history of heartburn, regurgitation, or both for ≥6 months prompting physician recommending continual daily use of PPI before study entry. All had a baseline GERD health-related quality of life (HRQL) score of ≥20 off PPI and a symptomatic response to a course of GERD therapy (≥2 weeks) with a GERD-HRQL score improvement (see below) of ≥10 on PPI. Included subjects exhibited excessive distal esophageal acid exposure during 24-hour pH measurement defined as a pH of ≤4 for >5% of total or >3% of supine, time off, antisecretory therapy. Subjects had a resting LES end-expiratory pressure of ≥5 mmHg on high-resolution manometry. Subjects had esophageal body contraction amplitude of ≥30 mmHg for ≥70% of swallows and ≥50% peristaltic contractions on high resolution manometry. Subjects with esophagitis grade C or lower (LA classification) on upper endoscopy performed within 6 months of enrollment were included. Subjects with Barrett's epithelium (maximal extent (M2) > 2 cm; circumferential extent (C1) > 1 cm), any grade of dysplasia, or a hiatal hernia ≥3 cm were excluded. Subjects with a body mass index of >35 kg/m^2, uncontrolled type 2 diabetes mellitus (defined as a hemoglobin A1c of >9.5 in the previous 6 months), a history of type 2 diabetes mellitus for >10 years, or those with type 1 diabetes mellitus were excluded also. Detailed inclusion criteria, exclusion criteria, and study details have been reported previously.[14]

LES stimulation system: Investigational device description. The LES stimulation system is made up of 3 components: a bipolar electrical stimulation lead, an implantable pulse generator (IPG), and an external programmer (Fig 1, *A*).

Stimulation lead. A sterile, bipolar stitch electrode stimulation lead is used in conjunction with

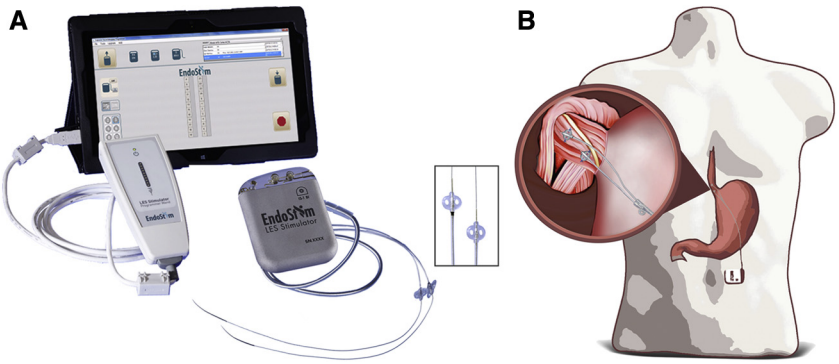

Fig 1. (*A*) EndoStim wireless programmer, implantable pulse generator and bipolar stimulation lead. Inset shows the 2 stimulation electrodes and the butterfly used for anchoring the electrode at the lower esophageal sphincter. (*B*) EndoStim System Implant in a patient. Electrode position and implantable pulse generator (IPG) implant location. Bipolar stitch electrodes are placed in the abdominal esophagus anteriorly in an inline configuration 1 cm apart. The lead is connected to the IPG that is implanted in the subcutaneous pocket in the anterior abdomen.

an implantable pulse generator (IPG) and consists of 2 platinum–iridium electrodes. The stimulation lead is 45 cm long with the 2 electrodes measuring 0.5 mm in diameter and 10 mm in length each. The 2 electrodes are implanted in the muscularis propria of the LES.

IPG. The IPG device has a casing made of titanium while containing a medical-grade lithium battery, microelectronics, communication coils, and an inclinometer for sensing the subject's posture. It is sealed hermetically to prevent damage to the device from biologic fluids. The IPG also has stainless steel contacts encapsulated in an implantable medical-grade epoxy for connection with the stimulation lead.

External programmer. The external programmer is used to interrogate and program the IPG. The programmer has 3 components: a commercially available laptop personal computer, an interface box that contains electronics, and a wand that contains communications electronics.

The LES stimulation system delivers therapy at 215-μs pulse-width at 20 Hz delivered in 30-minute sessions that can be adjusted noninvasively and customized to individual patient needs. Electrical stimulation can be optimized as follows: the stimulation parameters can be adjusted using the external programmer; additional stimulation sessions can be added or the timing of existing sessions changed; and stimulation amplitude and electrode polarity can be adjusted at follow-up to address suboptimal symptom or pH response. The device includes a sensor to detect upright and supine positions, and the stimulation algorithm can be customized based on patient position to address supine/nocturnal reflux.

LES stimulator implant procedure. After baseline evaluations, eligible subjects underwent a laparoscopic procedure to implant the EndoStim LES Stimulation System. A schematic of the EndoStim system implant is shown in Fig 1, *B* and details of the operative procedure were reported previously.[15] In brief, 4–5 trocars were typically used, with ≥1 being a 10-mm port for introduction of the lead into the abdominal cavity; the rest were 3- or 5-mm ports. For the lead implant, the anterior right aspect of the abdominal esophagus was exposed through dissection of the paraesophageal fat and pars flaccida of the hepatogastric ligament. A rectangular longitudinal area of approximately 3 × 1 cm is needed in which the electrodes are implanted. This approach minimized dissection of the phreno-esophageal attachment and damage to the anterior vagal nerve. The 2 stitch electrodes were implanted via a superficial bite into the LES muscle along the main esophageal axis with approximately 10 mm between the electrodes. Each electrode was then secured by a clip on the proximal edge of the electrode on to the nylon suture wire and also by suturing the distal anchoring "butterfly" present on the back end of the electrode. Upper gastrointestinal endoscopy was performed to verify electrode position in the LES and to confirm that no perforation of the esophageal lumen had occurred with the needle or electrode. No hiatal intervention was performed in any patient in this trial. The abdomen was desufflated, the skin incision for the pulse generator performed, and a subcutaneous pocket created by blunt dissection. After the connector was attached to the pulse generator, a functionality test was performed using the external programmer. The pulse generator was placed into its

pocket and excess lead is simultaneously pulled into the abdominal cavity and placed along the left abdominal wall away from the midline. After recovery and observation of ≥12 hours (for recording of any symptoms secondary to the device placement), the device was interrogated and lead impedance checked to ensure proper functionality.

Cardiac activity was monitored via electrocardiography while the stimulation was delivered for the first time and during the subsequent 2-hour observation period. Once the stimulation parameters of the device were programmed, subjects were discharged. The subjects were taken off acid-suppressive therapy at discharge and instructed to take per-protocol, as-needed antacid therapy. All patients were advised to follow standard GERD diet and lifestyle instructions.

Symptom assessment and esophageal tests. Symptoms of GERD were assessed using the GERD-HRQL, a validated questionnaire.[16] The questionnaire provides a composite score as well as an assessment of individual symptoms. Quality of life was also assessed by the Short Form (SF)-12 Health Survey—Physical and Mental Component Scores.[27] Symptom assessment was carried out at baseline while the patient was on PPI therapy and after 2 weeks off PPI therapy. The variables were evaluated again at follow-up while on LES-EST.

Esophageal acid exposure was assessed using 24-hour esophageal pH-metry (AL-1 system for pH monitoring, Ver. 1.26; Alacer Biomedica, São Paolo, Brazil) and sensors positioned in the esophageal body 5 and 23 cm proximal to the manometric upper border of the LES with the patient off PPI therapy for at least 5 days. Of the 23 subjects, 22 underwent esophageal pH testing at the 12-month follow-up visit. One subject refused the 12-month pH test. Of the 21 subjects who completed the 24-month visit, 18 underwent esophageal pH testing. Three subjects refused the 24-month pH test.

Substudy to evaluate the effect of blinded turn-off of LES-EST. As part of a substudy approved by our ethics committee, 3 patients with no GERD symptoms or medication use and normal esophageal acid exposure at the 12-month time point underwent blinded turn-off of LES-EST after their 18-month follow-up. Additionally, 1 patient also with no GERD symptoms or medication use and normal 12-month esophageal pH had her therapy turned off accidentally at month 15 by inadvertent use of magnet therapy for her arthritis. These patients had their esophageal pH testing performed after cessation of LES-EST for ≥3 months to evaluate the effect of cessation of LES-EST on esophageal acid exposure.

Concomitant medications/treatments. Subjects were allowed to take antacid medications as needed per-protocol for residual GERD symptoms during the study. Those with persistent symptoms on LES-EST despite antacids were allowed PPI medications. All medication use was recorded in the daily symptoms and antacid use diary completed by the subjects.

Statistical analysis. Statistical analysis was performed by an independent statistician (JB). A sample size of 22 patients provided 90% power (2-sided alpha of 0.05) to detect a mean (SD) difference of 7 (10) on the composite GERD-HRQL score from baseline to 24 months. Allowing for 10% patient dropout, a sample size of 25 patients was chosen as the final enrollment target.

Safety evaluation was descriptive in nature and included the incidence, severity, and type of adverse effects, as well as clinically important changes or abnormalities in the physical examination, vital signs, clinical tests, and electrocardiogram.

The effect of LES stimulation on patient symptoms was measured using the GERD-HRQL. Quality of life was measured using the SF-12 Physical and Mental Component Scores (both on PPI therapy and after 2 weeks off PPI therapy). Symptoms and medication use were recorded on a daily patient symptom diary for a 2-week period before the assessment. All comparisons were made at the $P < .05$ level using paired Wilcoxon tests. Statistical and descriptive comparisons of study results were made utilizing SAS version 9.3 (Chicago, IL) and R version 2.11.1 (available from http://www.r-project.org/).

RESULTS

Patient characteristics. Seventy-five subjects were consented and enrolled in the study. Twenty-six subjects were found to be eligible and underwent a laparoscopic procedure. One subject was excluded, because a large (5-cm) hiatal hernia was identified at laparoscopy, and device implantation was not performed. Twenty-five subjects underwent implantation of the LES stimulation system. Approximately 4 weeks after the device implant, 1 subject requested and underwent removal of the IPG under local anesthesia and subsequently withdrew voluntarily from the study. Detailed subject accountability is provided in Fig 2.

The mean age (SD) of subjects implanted in the trial was 52 (12) years, and mean body mass index (SD) was 28 (3.2) kg/m^2. Based on body mass

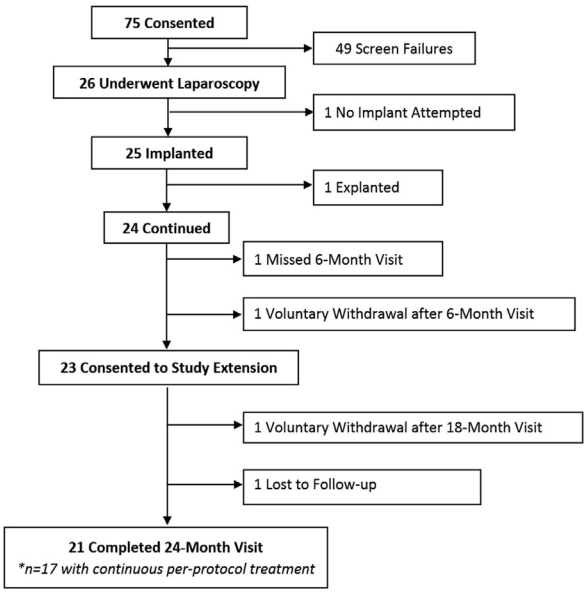

Fig 2. Subject accountability.

index, 20% of subjects were classified as being normal (<25 kg/m^2) and 80% of subjects were classified as being overweight or obese (≥25 kg/m^2). All patients were on chronic, daily PPI therapy and 6 (24%) were on twice daily PPI. The median duration of GERD diagnosis was 10.6 years with median duration of PPI use of 5.5 years before enrollment. Dissatisfaction with their control of GERD before implantation while on PPI therapy was reported by 71% of patients (17/24), and 79% (19/24) reported bothersome GERD symptoms on ≥1 of the GERD-HRQL question (score ≥ 2) while on PPI. The most important impact of GERD on quality of life while taking PPIs were persistent heartburn (46%; 11/24), effect of heartburn on diet (33%; 8/24), effect of medication on daily life (25%; 6/24), and waking up owing to heartburn (33%; 8/24). Baseline patient and disease characteristics for the 24 patients are shown in Table I.

LES-EST treatment parameters. EST was initiated within 24 hours of the implant procedure with 215 μs pulse at 20 Hz delivered for 30 minutes at median of 4 sessions per day (interquartile range [IQR], 3–5) and at median amplitude of 3.5 mA (IQR, 3.2–4.1). The details of parameter changes between baseline and 12 months have been reported previously.[14] The median number of sessions at month 12 were 12 sessions per day (IQR, 8–12). The median stimulation current at month 12 was 5.1 mA (IQR, 4.1–5.8). The median increase in the stimulation current from baseline to month 12 was 1.8 mA (IQR, 1.2–2.2). All patients were programmed with a fixed stimulation protocol of 215 μs pulse width, 5 mA amplitude, 30-minute sessions delivered 12 times per day at or after their 12-month visit. These parameters were continued for the remainder of their follow-up, except for 3 patients who underwent the blinded turn off after their 18-month follow-up visit.

Table I. Baseline patient characteristics and relevant medical history

Characteristics	*Value*
Age, mean (SD), y	52.0 (12)
BMI, mean (SD)	27.7 (3.2)
Normal (<25), *n*	5
Overweight (≥25–<30), *n*	13
Obese (≥30), *n*	7
Sex, *n*	
Male	14
Female	11
Patients using daily PPI, *n/N* (%)	24/24 (100)
Duration of GERD symptoms (y), mean (SD)	11.0 (7.9)
Median (IQR)	10.0 (7–11)
Duration of PPI use (y), mean (SD)	5.6 (3.4)
Median (IQR)	5.0 (3–10)
GERD-HRQL score	
Total score on PPI therapy, mean (SD)	9.8 (6.2)
Median (IQR)	9.0 (6–10)
Not satisfied, *n/N* (%)	17/24 (71)
Total score off PPI therapy, mean (SD)	23.7 (3.5)
Median (IQR)	23.5 (21–25.3)
Not satisfied, *n/N* (%)	22/24 (92)
Heartburn, frequency/week off PPI (%), mean (SD)	86 (15)
Median (IQR)	92 (85, 93)
Regurgitation, frequency/week off PPI (%), mean (SD)	57 (37)
Median (IQR)	65.5 (16.2–92.3)
Nocturnal heartburn, frequency/week off PPI (%), mean (SD)	59 (35)
Median (IQR)	71 (36–85)
Nocturnal regurgitation, frequency/week (off PPI; %), mean (SD)	39 (38)
Median (IQR)	31 (0–74.5)
Total proportion of 24-hour period with pH < 4 (%), mean (SD)	11.4 (5.8)
Median (IQR)	10.1 (7.8–13.0)
Hiatal hernia, *n/N* (%)	
None	22/25 (88)
<2 cm	2/25 (8)
>2 cm	1/25 (4)

BMI, Body mass index; *GERD*, gastroesophageal reflux disease; *HRQL*, health-related quality of life; *IQR*, interquartile range; *PPI*, proton pump inhibitor; *SD*, standard deviation.

Safety. A total of 65 events occurring in 19 subjects were reported. Two serious adverse events were reported in 2 subjects (2/25 [8%]), and both were adjudicated as not related to the procedure, device, or therapy by an independent data safety monitoring board. One subject reported an episode of acute, retrosternal chest pain occurring 2 months after the implant procedure and underwent a negative cardiac evaluation and was diagnosed with noncardiac chest pain. The subject reported experiencing similar events before enrollment in the study and continued with LES-EST without recurrence of chest pain. The other subject was hospitalized for an elective thyroidectomy 3 months after the implant.

Of the remaining 63 nonserious adverse events, 12 were adjudicated to be possibly or probably related to the device or procedure. Six events in 6 subjects were related to the procedure; nausea or vomiting was noted in 3 subjects occurring on or the day after the procedure and resolving in ≤1 day; pain or discomfort in the shoulder and a "hypertensive episode" occurring the day after the procedure and lasting for 1 day were reported in 2 patients. A superficial skin infection at the pocket site was reported in 1 patient. Six events in 5 subjects were reported as pain or discomfort in the abdomen possibly or probably related to the device. One subject had 2 events, 1 reported as a "psychotic disturbance," and a second event reported as a "nervous breakdown" adjudicated as possibly related to the device and/or procedure.

Fifty-one adverse events were adjudicated as not related to device or procedure. Among unrelated adverse events, events involving the respiratory system were the most common with 19 in 13 subjects reported. Of these, the event type "cold" was reported in 17 of the 19 patients.

No patient reported gastrointestinal side effects of new-onset dysphagia, bloating, inability to belch, or diarrhea associated with LES stimulation.

GERD-HRQL and daily symptom diaries. GERD symptoms improved immediately on initiating LES stimulation and cessation of daily PPI in most patients, and the remaining patient symptoms improved over the next 3 months with optimization of LES stimulation. A significant (>50%) improvement in GERD-HRQL scores compared with baseline off-PPI scores was reported in 18 of 24 patients (75%; median GERD-HRQL, 4; IQR, 1.3–9.5) at 1 month and 24 of 24 patients (100%; median GERD-HRQL, 2; IQR, 0–4) at the 3-month follow-up.

Baseline median composite GERD-HRQL scores were 9 on-PPIs and 23.5 off-PPIs. At the 6-, 12, 18-, and 24-month visits, median GERD-HRQL scores were 2, 2, 0, and 0, respectively ($P < 0$; Table II). Improvement in median GERD-HRQL at 6, 12, 18, and 24 months were statistically better ($P \leq .002$) than both median baseline on-PPI and off-PPI scores.

At baseline, 92% of subjects (22/24) reported that they were "unsatisfied" with their condition off PPI and 71% (17/24) on PPI compared with 0% (0/21) "unsatisfied" at the 24-month visits on LES-EST. The subjects' satisfaction with their condition was better than both on-PPI and off-PPI baseline satisfaction ($P < .001$).

At baseline, 38% of subjects (9/24) on PPI and 71% of subjects (17/24) off PPI reported symptoms (individual GERD-HRQL scores ≥ 1) of difficulty swallowing, respectively, versus 5% of subjects (1/21) at the 24-month follow-up visit (Fig 3). A total of 21% (5/24) and 83% (20/24) of subjects reported odynophagia at baseline on PPI and off PPI, respectively, versus 10% (2/21) of subjects at the 24-month follow-up visit (Fig 3). There were no new-onset dysphagia or odynophagia reported with LES-EST during the 2 years of follow-up.

Sleep quality, assessed by questionnaire evaluating the effect of heartburn on sleep, improved from a baseline median of 1 on PPI and 2.5 off PPI to a median of 0 at their 6-, 12-, and 24-month follow-up visits. Seventy-one percent (17/24) and 96% (23/24) of subjects reported symptoms affecting sleep at baseline on PPI and off PPI, respectively, versus 10% (2/21) of subjects at the 24-month follow-up visit (Fig 3).

Subject daily diary symptoms. Symptoms of heartburn and regurgitation were evaluated using a 14-day symptom diary. Eighteen subjects were available for pairwise analysis of diary data at their 2 year follow-up. At the baseline visit, subjects reported a median 92% of days with heartburn off PPIs, which decreased declined to 14% at 6 months, 13% at 12 months, and 7% at both 18 and 24 months ($P < .001$; Fig 4). Similarly, subjects reported 71% of nights with heartburn at baseline off PPIs, which decreased to a median of 0% at the 6-, 12-, and 24-month follow-up visits ($P < .001$ for all times; Fig 4).

At the baseline visit, subjects reported a median 66% of days with regurgitation off PPIs. This decreased to a median of 0% at the 6-, 12-, and 24-month visits ($P < .001$). Similarly, subjects reported a median 31% of nights with regurgitation at baseline off PPIs, which declined to a median of 0% at the 6-, 12-, and 24-month follow-up visits ($P < .01$ at all time points vs baseline off PPI).

Table II. Baseline and 24-month post-therapy results

Characteristic	*Baseline*			*24 Months*			P *value*
	Median	*IQR*	n	*Median*	*IQR*	n	
GERD–HRQL							
On PPI	9	6–10	24	0	0–3	21	.002
Off PPI	23.5	21–25.3	24	—	—		<.0001
SF-12 mental health							
On PPI	43	40.5–53	22	56	44–62	21	.058
Off PPI	49	39.2–54.2	24	—	—	—	.082
SF-12 physical health							
On PPI	47	42.5–51.5	22	55	53–57	21	.0007
Off PPI	46.5	41.2–49	24	—	—	—	.0001
% 24-hour distal esophageal pH < 4.0 (intent-to-treat analysis)*							
Total	10.1	7.8–13.0	24	4.8	3.4–7.0	18	.001
Upright	10.4	8.5–14.9	24	5.3	2.1–7.1	18	
Supine	6	2–13.2	24	0.8	0.3–11	18	.66
DeMeester score	36.6	29.6–50.2	24	16.1	12.2–29.1	18	.002
Patients with abnormal distal esophageal pH* (<4 for >4%), *n/N* (%)	23/24 (96%)	—	—	11/18 (61%)	—	—	—
% 24-hour proximal esophageal pH < 4.0							
Total	0.4	0.1–1.3	21	0	0–0.1	18	.001
Upright	0.6	0.2–1.9	21	0	0–0.1	18	<.001
Supine	0	0–0.1	21	0	0–0	18	.03
Patients with abnormal proximal esophageal pH* (<4 for >1.1%), *n/N* (%)	7/21 (33%)	—	—	0/18 (0%)	—	—	—

*Four patients with normal esophageal pH at their 12 months follow-up had LES stimulation turned off for at least 3 month prior to their 24 month follow-up; all had abnormal esophageal pH at 24 month. Their results are included in this ITT analysis.
BMI, Body mass index; *GERD*, gastroesophageal reflux disease; *HRQL*, health-related quality of life; *IQR*, interquartile range; *PPI*, proton pump inhibitor.

In the patient daily diary, subjects also recorded symptom severity as none, mild, moderate, or severe for heartburn and regurgitation independently. The medians across subjects of percentage days with each severity category demonstrated a clinically meaningful decrease in heartburn and regurgitation symptom severity at all time points on LES-EST (Fig 5). Subjects reported none or mild heartburn symptoms for a median 17% of diary days at baseline off PPI, which increased to 93% after 24 months of treatment. Subjects reported none or mild regurgitation symptoms for a median 18% of diary days at baseline off PPI, which increased to 100% after 6 months of treatment and stayed at 100% through 24 months of treatment.

Global quality of life (SF-12): Mental component score and physical component score. At the baseline visit, the median SF-12 mental component score was 43 on PPI and 49 off PPI. The median SF-12 mental component score improved to 54 at the 6-month visit over both baseline on- and off-PPI scores ($P = .002$). Mental component scores remained constant at the 12- and 24-month follow-up visits (Table II).

At the baseline visit, the median SF-12 physical component score was 47 on PPI and 46.5 off PPI. Median SF-12 physical component scores improved to 54 at the 6-month visit and were better than baseline off-PPI scores through the 24-month visit at which time the scores were 55 ($P < .05$ vs baseline; Table II).

Esophageal acid exposure. At the baseline visit for 20 patients treated with per-protocol continuous therapy through their 24-month follow-up, median % 24-hour esophageal pH < 4.0 was 10.8% (Fig 6). Median % 24-hour esophageal pH < 4.0 was 3.7% ($n = 18$; $P < .001$) at 12 months, and 4.1% at 24 months ($P = .001$; $n = 14$; per-protocol continuous therapy), respectively. Seventy-one percent of subjects demonstrated either normalization (pH of <4 for <4% of 24-hour recording) or ≥50% decrease in their distal esophageal acid exposure. Fifty percent of subjects demonstrated a normalized pH, and an additional 21% demonstrated a pH that was improved by >50%, although not normalized. At the baseline visit, median % 24-hour supine acid exposure was 6% and decreased to 0.4% and 0.8% at the 12- and 24-month visits, respectively (intent-to-treat analysis).

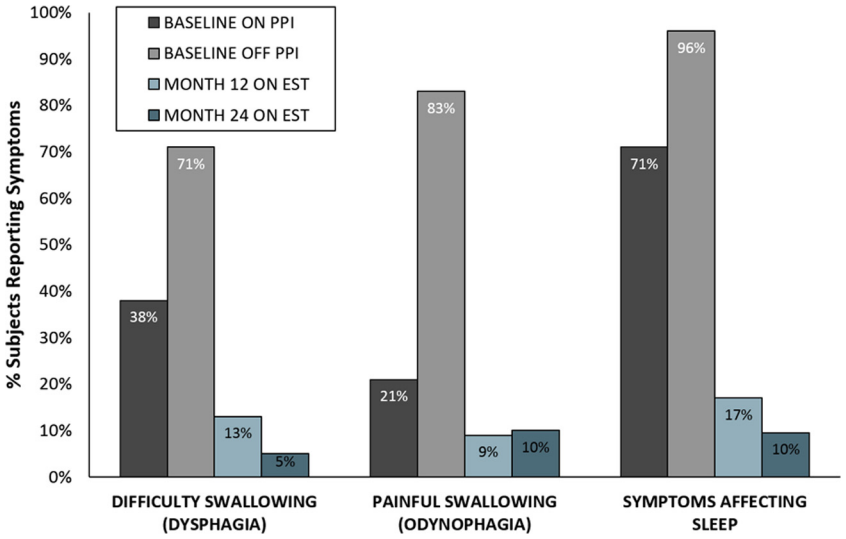

Fig 3. Percent subjects reporting gastroesophageal reflux disease (GERD) affecting their swallowing and sleep on GERD health-related quality of life questionnaires. No new-onset difficulty swallowing or painful swallowing reported. *EST*, Electrical stimulation therapy; *PPI*, proton pump inhibitor.

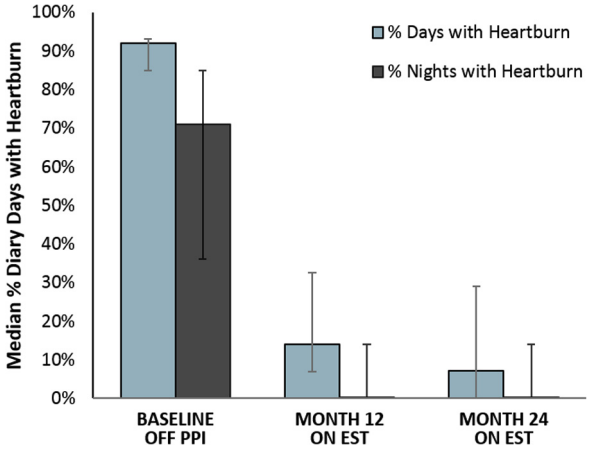

Fig 4. Subject daily diary symptoms frequency at baseline off and on proton pump inhibitor (PPI) and on lower esophageal sphincter electrical stimulation therapy (EST) at 12 and 24 months. Results are shown as median values with interquartile range.

Three subjects refused objective pH testing at their 24-month follow-up. Of these 3 subjects, 2 demonstrated improvement of ≥50% compared with both on-PPI and off-PPI GERD-HRQL scores; 1 subject demonstrated suboptimal (<50%) symptom improvement. One of these 3 subjects used PPIs occasionally at their 2-year follow-up, whereas the other 2 were using PPIs regularly (≥50% of diary days).

The median DeMeester score at baseline was 37.5 (n = 20) and improved to 17.7 (n = 18) and 14.6 (n = 14) at the 12- and 24-month visits, respectively, indicating a reduction in distal esophageal acid exposure in patients treated with per-protocol continuous therapy.

Effect of blinded turn off of LES-EST. Three patients underwent blinded turn off LES-EST after their 18-month follow-up and 1 patient had her therapy accidentally turned off by inadvertent use of magnet therapy for her arthritis at month 15. Of these 4 patients, only 1 reported recurrence of GERD symptoms at their 3-month visit after blinded turn off. On esophageal pH testing, all 4 patients demonstrated worsening in their distal esophageal acid exposure compared with their on-therapy 12-month acid exposure that, even after >3 months of cessation of LES-EST, still had not returned to their baseline esophageal acid exposure (Fig 6).

PPI medication use. At baseline, all subjects were taking daily PPI medications and 6 subjects (25%) were taking twice-daily PPI medications. PPI use on <50% of the daily diary days was defined as "occasional use" and PPI use on ≥50% of the daily diary days was defined as "regular use." Twenty-one subjects completed daily diary entries at the 12- and 24-month visits. At the 12-month visit, 20 of 21 subjects (95%) were not taking any PPI, 1 of 21 subjects (5%) reported occasional PPI use, and no subjects reported regular PPI use. At the 24-month visit, 16 of 21 subjects (76%) were not taking any PPI, 3 of 21 subjects (14%) reported occasional use, and 10% reported regular use of PPI. Median

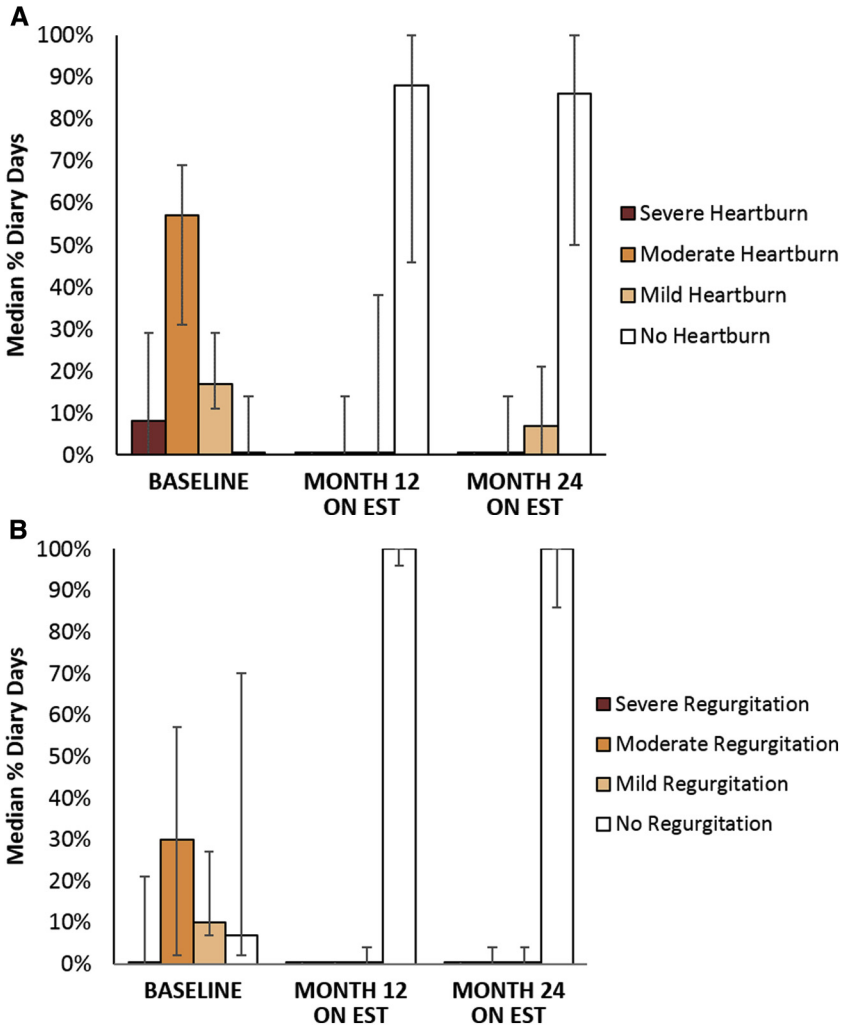

Fig 5. Subject daily diary. (*A*) Heartburn symptoms severity (median, interquartile rage [IQR]; % diary days) and (*B*) regurgitation symptoms severity (median, interquartile rage [IQR]; % diary days). *EST*, Electrical stimulation therapy.

PPI use decreased from 1 pill per day at baseline to ≤0.1 pills per day at 3, 6, 12, and 24 months follow-up ($P < .001$ by Wilcoxon paired test at each time point).

DISCUSSION

This is the first report of 2-year results of LES-EST showing a sustained improvement in GERD outcomes. Patients reported sustained improvement in GERD-HRQL and symptoms assessed by daily symptom diary, elimination of need of daily GERD medications, and improvement in their esophageal acid exposure. Our preliminary experience with temporary turn off of LES stimulation for ≥3 months suggests that the improvement in esophageal acid exposure was a result of LES-EST. Additionally, chronic LES stimulation may result in improvement in GERD that is sustained after the cessation of EST.

There is an increasing realization of incomplete response to PPI therapy among GERD patients. A meta-analysis of randomized, controlled studies in the management of GERD conducted in secondary care practices reported a partial or nonresponse of their reflux symptoms to PPI therapy in 19–44% of GERD patients.[4] Comparable rates were reported recently in a systematic review of persistent reflux symptoms in patients on PPIs evaluated in primary care and community studies.[5] In this review, the persistence of GERD symptoms was associated with decreased psychological and physical well-being. A recent observational study conducted in primary care as well as specialized settings supported these findings by reporting high prevalence of incomplete response to PPI therapy that was associated with considerable direct and indirect costs and a substantial impairment in quality of life and work

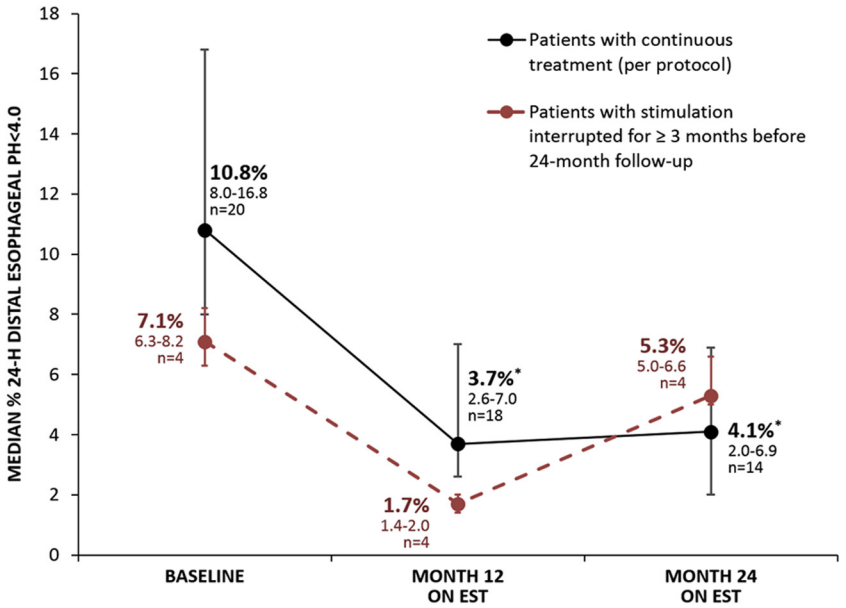

Fig 6. Change in median (interquartile range [IQR] %) 24-hour distal esophageal pH (% 24-hour pH < 4.0; median [IQR]). Four patients had therapy interrupted for ≥3 months before the 24-month follow-up. *$P < .001$ versus baseline at months 12 and 24. There was no difference between 12 and 24 months in patient treated per protocol ($P = .45$). *EST*, Electrical stimulation therapy.

productivity in GERD patients with incomplete response.[17]

PPIs are effective only in the control of heartburn, not regurgitation. In a meta-analysis, Kahrilas et al[18] reported an average therapeutic gain with PPI therapy for regurgitation of only 17% compared with placebo. Comparable gains for heartburn were >20% greater, highlighting regurgitation as an important factor in PPI failure.[19] Although almost 40% of patients continue to report bothersome GERD symptoms despite maximal medical therapy with PPI, <1% will undergo traditional antireflux surgery.[20]

Antireflux procedures are recommended for patients who are unsatisfied with medical therapy. Estimations put that number for patients in the United States unsatisfied with medical therapy to be as great as 10 million. However, at its peak in 2000, 32,980 antireflux operations were performed, and these numbers decreased to 19,668 procedures in 2006.[21] These data suggest a substantial therapy gap in the management of GERD. The reasons for lack of more widespread use of laparoscopic, antireflux surgery despite a large patient population in need of therapy include both patient and physician fear of side effects and postoperative complications.[9] In fact, guidelines reported by the American Gastroenterological Association Institute state that "from the vantage point of risk, PPI therapy should be strongly recommended as initial therapy in view of its superior safety profile" despite superior efficacy of antireflux operations in control of symptoms of both heartburn and regurgitation.[22] Additionally, long-term failure of antireflux surgery and poorer outcomes from low-volume compared with high-volume centers remain dissuading factors.[23] Multiple endoscopic and surgical device-based therapies have been attempted to address the incomplete PPI responder patient population with mixed results.[10,11]

The lack of clinically relevant side effects, coupled with the ease of reversibility and noninvasive therapy adjustment, makes EST an attractive option for treating various diseases, including GERD. Early animal and human studies of LES stimulation showed an improvement in LES function without a negative effect on LES relaxation and esophageal body function.[13,24,25] During a follow-up of 1 year, LES-EST was found to be safe and effective for the treatment of GERD.[14] There was a significant and sustained improvement in GERD symptoms and a decrease in esophageal acid exposure with elimination of daily PPI usage without any therapy-related adverse effects.

Improvement in esophageal acid exposure has been considered the most objective and robust measure of control of GERD. At their 2-year follow-up, patients treated with per-protocol stimulation demonstrated a sustained improvement in acid

exposure of the distal esophageal. This finding suggests that LES stimulation improves the LES function in a sustained fashion over at least a long-term, 2-year duration. Similar results were also reported with sustained improvement in GERD-HRQL scores, elimination in need for daily PPI medications in most patients, and improvement in GERD symptoms of both heartburn and regurgitation. The most profound effect on symptoms was reported in regurgitation and nocturnal symptoms, both of which have been identified as the major cause of patient dissatisfaction, despite maximal medical therapy.

Prevention of progression of GERD is a desirable goal of any therapy; whether LES-EST will be able to achieve that remains to be ascertained in longer term studies. Among the small subgroup of patients ($n = 4$) who underwent a blinded turn off of the therapy, a slow deterioration in esophageal acid exposure was observed over 3 months that had not deteriorated to the baseline level at the time of the repeat pH test. This observation suggests that improvement in distal esophageal acid exposure was related to LES stimulation. Additionally, and although anecdotal ($n = 4$), chronic LES stimulation may result in prolonged improvement of LES function that persists beyond the duration of stimulation. Interestingly, of these 4 patients with temporary turn off of LES stimulation, only 1 patient reported recurrence of GERD symptoms at their 3-month, post-blinded, turn-off follow-up. After successful control of GERD for a prolonged period, a delay in the return of symptoms after cessation of therapy has been reported after PPI medications. Another possible explanation for this observation could be an improvement in LES function with chronic LES stimulation, which deteriorates slowly on cessation of stimulation, and the symptoms would recur in the due course of time. In all these patients, the esophageal acid exposure had decreased, but had not returned to baseline levels even after 3 months of cessation of therapy. It is also plausible that LES stimulation could interfere with the afferent nerve transmission and lead to loss of perception of heartburn; this possibility remains to be evaluated. Slow deterioration in esophageal acid control and improved GERD symptomatology after cessation of therapy may suggest that LES stimulation could prevent deterioration of sphincter function over long-term.

A lack of effect on esophageal body function and LES relaxation is another advantage of LES stimulation therapy. Our initial experience with LES stimulation in patients with GERD suggested that EST may be a suitable therapeutic modality in GERD patients with severe esophageal dysmotility who otherwise would be unsuitable candidates for traditional antireflux procedures; however, more experience is needed in this patient population to validate our hypothesis.

Side effects or adverse events have been the "Achilles heel" of most antireflux therapies, including the Nissen fundoplication.[9] The superior safety profile and lack of clinically relevant side effects with LES-EST will be attractive to patients seeking an alternative therapeutic option to lifelong medications. Most of the adverse events reported with LES stimulation therapy were typical of similar laparoscopic implant procedures and resolved within a few weeks postoperatively. Additionally, no new-onset dysphagia or other gastrointestinal side effects related to stimulation were reported with LES stimulation therapy. Another important aspect in considering a permanent implant for any therapy, especially one being used for a disease-associated primarily with decreased quality of life, is its compatibility with MRI machines. A formal approval for use of full-body MRI exposure with a 3T MRI machine is awaited.

Our study was an open-label, single-center trial in a small group of patients and hence suffers from the usual limitations of the open-label design. Sustained improvement in esophageal acid exposure in this group of patients over a 2-year period, however, suggests that these results are likely owing to the LES stimulation effect. Comparable positive results with LES stimulation in GERD patients are being reported from a separate, ongoing, multicenter trial.[26] The trial excluded patients with moderate and large (>3 cm) hiatal hernias, LES end-expiratory pressures <5 mmHg, and those with severe (grade D) esophagitis or long segment Barrett esophagus. These patients tend to have more severe esophageal motor dysfunction and are more likely to suffer from medically refractory GERD. Efficacy of LES-EST in these subgroups need to be established.

Although LES pressure was enhanced by EST in both animal and human trials, including the 1-year manometry results in this cohort of patients that showed improvement in LES pressures without any negative effect on LES relaxation as demonstrated by unchanged LES residual pressures, improved LES pressure alone is unlikely to be the only mechanism yielding our results.[14] Other important mechanisms may include an effect on transient LES relaxations, LES compliance, or the acid pocket. The effect of LES-EST on these important causative variables needs to be evaluated.

In conclusion, results of our long-term, open-label trial suggests that LES-EST is safe and effective in treatment of GERD and results in superior symptom control than that reported with PPI therapy at baseline. A better understanding of the mechanism of action and improvement in stimulation algorithms may improve further the outcomes of this therapy. Sham-controlled trials comparing EST with no-stimulation and comparative effectiveness trials compared with maximal medical therapy and antireflux surgery may help to better establish the role of LES stimulation in the management of GERD.

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