

# Original Research Paper

Surgery

# CLINICAL STUDY OF THE LOWER ESOPHAGEAL SPHINCTER ELECTRICAL STIMULATION

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**ABSTRACT BACKGROUND:** Recently the possibility of LES tonus increasing by the means of implantable electrical stimulator was described. Although this method is already used in clinical practice, optimal parameters of LES electrical stimulation are still unknown.

AIMS: The goal of this study was obtaining of clinical data regarding effects of different types of electrical stimulation on LES tonus.

**METHODS:** LES electrical stimulation was assessed in 15 patients with GERD. These patients underwent standard laparoscopic antireflux surgery with additional insertion of 2 temporary electrodes at the level of gastroesophageal junction. Three sets of parameters were studied with high resolution esophageal manometry to assess changes in LES tonus.

**RESULTS:** Values of LES resting pressure and integrated relaxation pressure (IRP) were significantly different between prestimulation and poststimulation periods.

**CONCLUSIONS:** Modifications of LES function during the stimulation and after the stimulation period depend on frequency and pulse width.

KEYWORDS : lower esophageal sphincter, electrical stimulation, gastroesophageal reflux disease.

# INTRODUCTION

Laparoscopic fundoplication is controlling gastroesophageal reflux in 90% of patients, rest of them require reinterventions or medical treatment.

Postoperative complications among the patients with failed surgical treatment occur in 2-6% cases related to the change of JEG anatomy [1].

Therefore, there is a need for another minimally invasive method of treatment.

The stimulation of gastroesophageal junction (GEJ) with implantable device can be physiological and reversible therapeutic method, which increases the LES tone.

GEJ electrostimulation acts on smooth muscle cells through myenteric (Auerbach) plexus. The plexus contains Cajal interstitial cells, they act as digestive regional pacemaker by generating electrical slow waves.

The experiment was shown that a constant current with rectangular wave and 30-500 ms duration applied in the pacemaker node region initiates the generation of slow waves and their propagation to the antrum [2].

If the impulse rate is higher than natural, it becomes dominant and pacemaker is driven by this frequency. This phenomenon is called gastric electrical pacing, resemble to the cardiac pacing. This type of gastric stimulation induces increasing of LES tonus, by unclear mechanism [3].

Pacemaker in the pathology of digestive tract has a relatively short history.

Enterra, product of Medtronic Company, used in the treatment of gastroparesis and morbid obesity.

Similar device has been approved (EndoStim, Netherlands, 2009) for the treatment of GERD in Europe. There is multicenter study evaluating the effectiveness of LES electrostimulation in the treatment of GERD by Dr. Leonardo Rodriguez in Chile [4].

Publications related to the influence of electrostimulation on the LES tone in humans are few and contradictory [7, 8, 9].

The goal of our study was obtaining clinical data regarding effects of different types of electrical stimulation on LES tonus.

**Study design.** We present a post hoc analysis of a prospective randomized trial, realized in a single center. The efficiency of GEJ electrostimulation was appreciated by the increasing pressure of LES (primary endpoint). The second is assessment of the preservation of GEJ valve function measured by the manometric index IRP (integrated relaxation pressure).

By ethical considerations, we performed GEJ electrostimulation in patients with GERD who underwent standard laparoscopic surgery.

This study was approved by our University's and Republican Hospital's Research Ethics Committee (Minutes No. 2 of 11 May 2015).

# METHODS

LES stimulation with external pulse generator was assessed in 15 patients with severe GERD and decreased LES tonus. These patients were randomized in three groups of 5 patients by the type of electrical stimulation.

The first commercially implantable device was the neuro-stimulator

Inclusion criteria were: age > 18 years, GERD with indications for surgical treatment, duration of medical treatment > 12 weeks,

gastroesophageal reflux confirmed by 24- hours pH-metry (DeMeesterscore > 15).

There were established exclusion criteria: sliding hiatal hernia larger than 5 cm on preoperative radiological cliché, paraesophageal hiatal hernia, reflux esophagitis grade C and D (Los Angeles classification), GEJ stenosis, esophageal cancer, BMI > 35 kg/m2, severe concomitant diseases.

All patients signed informed consent form to participate in the clinical trial.

To confirm the diagnosis of GERD, preoperatively all patients underwent gastroscopy, barium radiography and 24-hours pHmetry (Orion II, MMS, Netherlands). The day before surgery, high resolution esophageal manometry (Solar GI HRM, MMS, Netherlands) was performed for all of 15 patients. The procedure was performed after 12 hours fasting in supine position (10 water swallows with a 30-sec period to assess basal pressure values). Patients enrolled in this study underwent laparoscopic intervention, which included GEJ dissection, posterior cruroraphy and fundoplication. At the end of intervention two temporal electrodes Flexon (Covidien, USA) were fixed by sero-muscular layer of the abdominal esophagus. The leads were sutured to the anterior part of esophagus at a distance of at least 2 cm from each other avoiding vague nerve involvement. The ends of electrodes were exteriorized separately on the anterior abdominal wall in the epigastric region and fastened on skin. LES pressure and other parameters of esophageal motility were registered by HRM at the 3rd postoperative day (after restoring of the digestive peristalsis).

During the manometry session GEJ electrical stimulation was performed with external pulse generator. Preoperative manometry data compared with postoperative prestimulation, during stimulation and poststimulation data. Three parameter sets, the most commonly used in published works for GEJ electrostimulation were applied [3,5,8,9]. These sets of parameters are presented in Table 1.

Postoperative manometry was performed in three steps: prestimulation, during stimulation (25 min), poststimulation. The duration of the procedure was not exceeded 45 minutes and the patient drank about 150 ml of water. Multiple rapid swallowed test was not performed.

Manometric indicators that reflect the tone and functionality of LES were analyzed separately:

- LES resting pressure,
- Integrated relaxation pressure with duration of 4 seconds (IRP index 4s).

Cutoff value for IRP4s was 7 mmHg in accordance to study performed by Kessing using MMS device with water perfused catheter[10].

Pre- and postoperative values of these indicators (pre-, during and poststimulation) were compared to each other within study groups and in the general group of 15 patients.

Electrical resistance and signal amplitude were recorded during GEJ electrostimulation by oscillometer ISDS205B. The electrical resistance of tissues varied within 310-415 Ohm and voltage created was 1-2V.

The electrodes were extracted at the end of the session of postoperative manometry, patients were under observation until the next day and discharged.

High resolution manometry data, which have been obtained during the postoperative period were evaluated using third version of the esophagus motility disorders Chicago classification [11].

Statistical analysis. The Wilcoxon test was used for statistical analysis for two paired samples.

## **STUDY RESULTS**

Preoperative HRM revealed esophageal peristalsis disorders in majority of patients included in the study (13 from 15 patients): in 7 patients (46.7 %) fragmented peristalsis was demonstrated, in other 6 (40 %) – ineffective esophageal motility. A normal esophageal motility was registered in 2 cases (13.3 %).

Values of LES resting pressure and of IRP (during 4 s) are presented in the tables 2 and 3 respectively.

A significant difference between preoperative and postoperative LES pressure values was established in the general group of 15 patients. As was expected, mean values of LES resting pressure and IRP become higher after the antireflux procedure (p < 0.01 for each parameter, directional test).

Comparison of mean LES resting pressure values recorded in postoperative period before the LES electrical stimulation with values of this parameter in the poststimulation period showed a significant difference with p < 0.01 for bidirectional test.

Within subgroups data analysis revealed some specific tendencies for each type (set) of LES stimulation. Stimulation set I produces only insignificant increase in LES pressure during the stimulation and at the same time influences deglutitive GEJ relaxation. It was manifested manometrically through normalizing of IRP during the stimulation in comparison with prestimulation values (directional test, p < 0.05). This parameter was elevated in majority of patients in postoperative period probably due to performed antireflux operation Figure 1 (a, b).

The second set of stimulation parameters produce moderate relaxation of LES during the stimulation and significant increase of its tone in the poststimulation period (p < 0.05). Besides the elevation of the LES tone in the poststimulation period this type of stimulation generates significant increase of IRP 4s - a manometric sign of impaired deglutitive LES relaxation (p < 0.05, in comparison with prestimulation values). The third set of parameters show similar effects as stimulation set II. In some patients from groups II and III, LES pressure reached very high values – more than 100 mm Hg (spasm) and remained at these values throughout the examination Figure 2 (a, b). In these cases patients preserved ability to swallow; some of them manifested mild and transitory dysphagia. Complications related to insertion and removals of electrodes were not registered.

# DISCUSSION

In our study model, preoperative esophageal manometry was compared with postoperative manometry in order to reveal and separate modifications due to antireflux procedure. An important characteristic of this model is continuous recording of manometric data in the poststimulation period.

Analysis of the manometric values for the entire group of 15 patients have been demonstrated, that LES electrical stimulation modifies LES pressure and produces changes in LES valve function at current of 5 mA. Published paper by P.W. Weijenborg tries to establish normal manometric values for patients after surgical GERD treatment [12]. Data obtained in our study in general correspond to these norms. Results of the study and observed tendencies in the groups of patients indicate that effects of LES electrical stimulation in humans depend upon parameters of stimulation. In our study the same current and pulse form were used. The most pronounced modifications of LES tone were registered not during the stimulation, interestingly, in the poststimulation period. In order to obtain more precise data a larger number of observations is necessary (10 or more patients in each group). In spite of postoperative modifications reflected by HRM, statistically significant differences were discovered in our study between LES

pressure values, before and after electrical stimulation. It was also important to understand, that rising of LES tone obtained by the means of LES electrical stimulation can be associated with the impaired relaxation of sphincter after swallowing, which can be clinically manifested as dysphagia and even induce structural anatomical changes in case of long-term electrical stimulation. In this study the stimulation set I favorably influenced the deglutitive relaxation of LES, although elevation of LES tone was not statistically proved in this group of patients. Our data correlates with preliminary conclusions of the multicentric study led by L. Rodrigues, which analyzed long-term treatment of GERD patients with implantable device (EndoStim®) [4]. Taking into consideration our results we can suppose, that using of alternative parameters for therapeutical LES electrical stimulation could help increase the treatment efficiency and improve patients' quality of life. Therefore, a new clinical study is needed to complete these findings.

# CONCLUSIONS

- 1. Electrical stimulation modifies LES tone.
- 2. Modifications in LES function and tone during the electrical stimulation and in the period immediate after stimulation depend upon the pulse frequency and length.
- 3. Stimulation set I favorably influences GEJ relaxation during the swallow without affecting of the LES valve function.
- 4. Stimulation sets II and III produce significant increase of LES tone especially in poststimulation period.

Parameters sets	pulse Jength	Frequen	Ampera	Nr.
1 Low-frequency long pulse	375 mc	6 pulso/	5 mA	5
1. Low-frequency, long pulse	2721112	min	JIIA	5
2. High-frequency 20 Hz	0.3 ms	20 Hz	5 mA	5
3. High-frequency 40 Hz	0.3 ms	40 Hz	5 mA	5

# Table 1 Sets of parameters used for GEJ electrostimulation

## Table 2 Mean LES resting pressure (mmHg)

Stimul	Nr.	Preoperative	Postoperati	Postoperati	Postoperati		
ation	patient		ve	ve	ve		
set			before	during	Poststimula		
			stimulation	stimulation	tion		
I	1	12.9	28.0	30.8	34.2		
	2	5.9	32.7	38.2	35.0		
	3	21.2	24.3	25.0	22.4		
	4	9.0	28.5	27.6	38.0		
	5	6.9	22.0	28.0	23.0		
II	1	14.2	38.5	30.4	118.5		
	2	11.2	29.3	27.7	58.9		
	3	8.9	34.5	33.0	47.2		
	4	6.2	34.3	38.7	84.5		
	5	4.2	33.8	37.3	57.8		
	p < 0.05						
Ш	1	13.6	31.0	30.2	85.4		
	2	14.6	25.5	24.2	39.0		
	3	22.6	38.3	32.4	47.3		
	4	15.2	53.1	46.8	88.4		
	5	5.7	33.5	50.2	72.3		
	p < 0.05						

# Table 3 Mean values of IRP 4s (mmHg)

Stimul	Nr.	Preoperativ	Postoperati	Postoperati	Postoperati
ation	patient	e	ve	ve	ve
set			before	during	Poststimula
			stimulation	stimulation	tion
I	1	5.7	14.6	12.2	13.0
	2	5.3	19.1	14.9	17.6
	3	3.4	7.7	6.7	6.8
	4	8.1	18.8	12.3	13.2
	5	4.4	8.2	6.7	6.8
	p < 0.05				

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II	1	6.8	14.5	13.3	50.1		
	2	4.5	12.7	11.4	31.4		
	3	2.3	13.8	11.2	34.5		
	4	5.6	18.3	19.5	24.2		
	5	3.5	6.3	8.6	22.4		
	p < 0.0	p < 0.05					
III	1	4.6	10.5	18.5	46.2		
	2	6.4	12.1	13.1	17.4		
	3	10.1	16.7	14.8	21.4		
	4	6.5	19.0	25.8	44.1		
	5	3.3	20.1	26.3	34.4		
	p < 0.0	p < 0.05					





(b)

Figure 1 a, b. Esophageal manometry in the postoperative period before electrical stimulation of LES (a) and during the stimulation (b) (stimulation set I). Figure 1a – absence of LES deglutitive relaxation. Figure 1b – LES deglutitive relaxation appears with maintaining of elevated pressure after EGJ closing. Additional pressure "shadow" also appears on the level of gastric fundoplication.





Figure 2 a, b. Manometric images in the postoperative before stimulation (a) and in the poststimiulation period (b). Stimulation set II. Significant increase of LES pressure with spastic contractions (> 100 mm Hg) as well as elevated pressure on the level of fundoplication are observed in the poststimulation period.

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