Rationale of output parameters for lower esophageal sphincter stimulator

Ungureanu S.[1], Sontea V.[2], Vidiborschii V.[2], Sipitco N.[2], Fosa D[2].
[1] University of Medicine and Pharmacy „Nicolae Testemitanu", Republic of Moldova
[2] Technical University of Moldova
e-mail: vidiborschii@yahoo.com

***Abstract*. Electrical stimulation of lower esophageal sphincters is a new method for the treatment of gastroesophageal reflux disease (GERD). Own clinical data confirmed modifications of LES functions during the stimulation and after the stimulation period depending on frequency and pulse width. Optimum output parameters of electrostimulation were registered. A prototype of implantable LES stimulator with long distance wireless charging was developed and assembled. The LES stimulator is composed of an implantable pulse generator, a wireless power transmitter (wireless charger) and an Android based application acting as controller. Implantable LES stimulator (IPG) sized only 20x12mm generates constant-current stimulation pulses. Wireless charging of prototype works at distances up to 3m at air and makes possible power transfer even to deep tissues.**

***Key words:* lower esophageal sphincter, LES, electrical stimulation, gastroesophageal reflux disease, GERD, wireless powered implantable electrostimulator, IPG.**

I. Introduction

Gastroesophageal reflux disease (GERD) - is defined as a condition in which gastric reflux causes unpleasant symptoms and / or complications [9]. In Western Europe, up to 40-50% of adults have GERD symptoms (such as heartburn) at least once every month . In the USA, heartburn once a month is experienced by 44% of adults, once a week - 20%, and 7% of respondents suffer from heartburn every day. [1]. Esophageal symptoms include heartburn, eructation of acidic contents that occur after eating, at night or when the body tilts forward, abundant salivation (salivation). Quite often, patients suffering from gastroesophageal disease complain of pain behind the sternum, giving up in the neck, lower jaw, thorax and the area between the scapulae. GERD refers to non-esophageal symptoms of cough, shortness of breath, constant dryness in the throat, painful swallowing, changes in voice, caries [1]. The tactical goals of treating patients with GERD are to reduce the severity of clinical symptoms and improve the quality of life of patients. The strategic objectives of long-term treatment are prevention of erosive damage to the esophageal mucosa and its progression, as well prevention of severe complications, like Barrett's esophagus and adenocarcinoma.

Treatment of GERD includes correction of lifestyle and diet, taking antacids, prokinetics and antisecretory drugs [3]. Currently, in clinical practice, it is generally accepted that the leading direction of pharmacotherapy for GERD should be the suppression of hydrochloric acid secretion. It was shown that for effective therapy of reflux esophagitis it is necessary to increase the pH of the stomach to 4.0. The average period of treatment of patients to achieve the optimal effect is 40-80 days. The duration of anti-relapse therapy is 6-12 months. If the patient is not assigned maintenance treatment, then the probability of recurrence of erosive esophagitis during the year is 80-90% [3].

Laparoscopic fundoplication is currently the main option for surgical treatment of GERD. However, because of concerns about the long-term effect and the side effects of surgery, only a small group of patients with GERD are referred for surgery, leaving a significant number of patients without effective treatment [3].

In recent articles could be found, that effective non-medicine treatment of GERD can be achieved by direct modulation of the tone of the lower esophageal sphincter (LES)[5]. Recently, a method of increasing the pressure of LES with the help of an implantable electric stimulator has been described [4]. Because of its relatively large size, the pulse generator itself is implanted subcutaneously into the abdominal wall and connected to electrodes attached to the esophagus during the laparoscopic procedure.

II. Materials and Methods

To find optimal output parameters for the LES electric stimulator, a literature review was conducted. Published studies on the evaluation of the effect of electrostimulation on the tone of the stomach or LES usually consider three types of stimulation modes (table 1):

Table 1. Output parameters of stimulation modes

Output parameter	**Low frequency stimulation [7]**	**High frequency (20Hz) stimulation [2][5]**	**Hugh frequency (40Hz) stimulation [11]**
Amplitude	5 мА	4 – 6 мА	6 мА
Pulse Width	375 *millisecond*	220 microseccond	300 microseccond
Pulse frequency	6 PPM	20 Hz	40 Hz
Duration of stimulation	20 min (continuously)	30 min (continuously)	30 min (2s On 3s Off)

It should be noted that the primary justification for these or those regimes is usually confirmed only by experimental models in animals, with insufficient or complete clinical study. Often, in assessing the effectiveness of a given stimulation regimen, only a one-hour or 24-hour pH meter is used, while the use of such a reliable and non-invasive method, such as high pressure manometry, is often limited.

Within the MICROLESTIM project, prof. Ungureanu and his colleagues from the Republican Clinical Hospital with the author's participation conducted a clinical study to determine the optimal parameters of electrical stimulation of LES, which can be recommended for GERD therapy [6].

The data obtained from the study (assessed using the high-resolution esophagus manometry (Solar GI HRM, MMS, Holland) using a 22-channel water-perfusion catheter) indicate that with the same current strength, a change in the frequency and width of the pulse leads to different manometric manifestations. It is noteworthy that the most pronounced changes in the tone of the LES were recorded not during stimulation, but in the post-stimulation period.

At the same time, the greatest change in tone was recorded for the following stimulation mode:

- Pulse length - 0.3 ms;
- Pulse frequency - 20 Hz;
- Current strength - 5 mA;
- Duration of stimulation - 25 min.

An external pulse generator Pocket Physio Pro, New Age, Italy was used for stimulation. In parallel with stimulation *in vivo*, the resistance and amplitude of the signal were measured using the Instrustar ISDS205B oscilloscope.

The calculated impedance of tissues varied in the range of 310-415 ohms, while the voltage created was within the range of only 1.04-1.79 V.

III. Discussion

The obtained experimental data show that in order to obtain the proper clinical effect, it is sufficient to provide pulsed electrostimulation with low-intensity currents with a relatively small frequency. Given in attention small pulse width, the total amount of energy per treatment session is 45 microAmpere-hours. In this case, instead of a one-time battery with a limited life, it is possible to use a supercapacitor, which can be recharged thousands of times. A simple calculation shows that a typical supercapacitor with a capacity of 5F can provide a monthly 3-time therapy (about 90 cycles). Based on the results obtained, was developed and assembled a prototype of the implantable LES electrostimulator, charged with radio waves of centimeter range (Fig. 1).

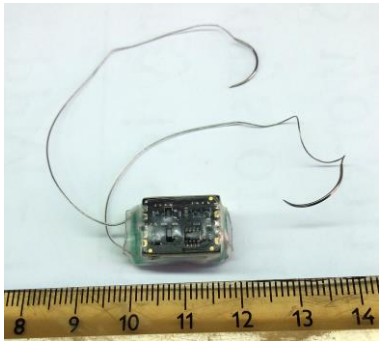

Fig.1. Assembled prototype

A small device measuring only 20x12x8mm demonstrated the possibility of wireless charging at a distance of up to 3.0 m (independent of orientation Rx and Tx parts), receiving the signal by a miniature ceramic antenna from a power RF transmitter of centimeter waves (fig.1).

The received energy was stored in a supercapacitor, while the build-in Bluetooth module allowed wireless communication and control.

Basing on the Android system with Bluetooth connectivity, a mobile application for a smartphone was developed, used to control different working mode of the device, obtaining device telemetry (signal strength, temperature, debugging information etc). Tests confirmed possibility of wireless control of the device at distance up to 10 m. Measured charging current depending of distance was from 1 to 30 mA. Next test are planned to confirm deep tissue wireless power transfer up to 50mm and more.

IV. Conclusions

Modulation of LES tone with an implantable electrostimulator is one of the newest methods of GERD therapy. Recent studies show, that this method is effective and safe [4] [5]. The transition from battery to a wireless powering could significantly reduce size of electrostimulators, improve their quality and usability. In same time the traditional limitations and risks of surgical implantation are decreased. In current article was demonstrated, that transition to the wireless powering could provide significant sizes reduction of the device with simultaneous expansion of controlling and monitoring possibilities. Device effectiveness and safety will be checked at next stage during a clinical animal test.

References

[1] Herregods, T. V. K., A. J. Bredenoord, and A. J. P. M. Smout. "Pathophysiology of gastroesophageal reflux disease: new understanding in a new era." Neurogastroenterology & Motility (2015)

[2] Hoppo T, Rodríguez L, Soffer E, Crowell MD, Jobe BA. "Long–term results of electrical stimulation of the lower esophageal sphincter for treatment of proximal GERD. Surg Endosc. 2014 Jul 22

[3] Katz, Philip O., Lauren B. Gerson, and Marcelo F. Vela. "Guidelines for the diagnosis and management of gastroesophageal reflux disease." The American journal of gastroenterology, (2013)

[4] Peter D. Siersema, Albert J. Bredenoord, José M. Conchillo et al: Electrical Stimulation Therapy (EST) of the Lower Esophageal Sphincter (LES) for Refractory Gerd and Two Year Results of an International Multicenter Trial, Gastroenterology April 2017 Volume 152, Issue 5, Supplement 1, Page S470

[5] Rodríguez L, Rodriguez P, Gómez B, Ayala JC, Oksenberg D, Perez–Castilla A, Netto MG, Soffer E, Crowell MD. Long–term results of electrical stimulation of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease. Endoscopy. 2013 Aug;45(8):595–604.

[6] S.Ungureanu, N.Sipitco, V.Vidiborschii, D.Fosa, Clinical study of the lower esophageal sphincter electrical stimulation, Global Journal For Research Analysis, Vol.7, issue 1, Jan.2018.

[7] Sanmiguel CP, Hagiike M, Mintchev MP, et al. Effect of electrical stimulation of the LES on LES pressure in a canine model. Am J Physiol Gastrointest Liver Physiol 2008;295:G389–G394.

[8] Ungureanu S.N, Lepadatu K.I., Sipitco N.I., Vidiborschi V.L., Gladun N.V., Balica I.M.: Influence of electrical stimulation on the function of lower esophageal sphincter in patients with gastroesophageal reflux disease. Experimental and Clinical Gastroenterology, 2016,128(4),p.51–55.

[9] Vakil, Nimish, et al. "The Montreal definition and classification of gastroesophageal reflux disease: a global evidence–based consensus." The American journal of gastroenterology 101.8 (2006): 1900–1920..

[10] Vidiborschii V., Wireless charged lower esophageal sphincter stimulator . Archives of 3rd International Conference Health Technology Management ICTHM–2016, October 6–7, 2016, Chisinau, Republic of Moldova

[11] Xing JH, Lei Y, Chen JD. Gastric electrical stimulation (GES) with parameters for morbid obesity elevates lower esophageal sphincter (LES) pressure in conscious dogs. Obes Surg. 2005; 15: 1321–1327.