An Animal Study of Implantation of an Esophageal Pacemaker Based on Per-Oral Endoscopic Myotomy Approach for Alleviation of Esophageal Peristalsis Disorders

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Background: To restore esophageal peristalsis of achalasia patients by sequenced electric stimulation, an appropriate method must be established to implant the electrodes and pacemaker safely and effectively. We combined POEM (per-oral endoscopic myotomy) and abdominal wall puncture in pigs in order to explore a feasible procedure for the implantation.

Material/Methods: Five healthy male pigs were used in the present study with the permission of the Ethics Committee of Tianjin Medical University General Hospital. The electrodes were implanted in esophageal submucosal tunnel by POEM with the end of the electrode deposited in the abdominal cavity using NOTES technique. A pacemaker was then positioned under the skin of the abdomen. Finally, the electrodes were connected with the pacemaker with the help of endoscopy in the abdominal cavity. Esophageal peristalsis of these pigs after implantation was monitored for esophageal intraluminal pressure changes using electronic gastroscopy and a high-resolution manometry (HRM). The observation lasted for 6 h.

Results: The procedure was effective to implant the electrode and the pacemaker using POEM and NOTES techniques. The connection of the 2 devices was also successful. Esophageal intraluminal pressure changes after electrical stimulation were recorded using HRM. Vital signs of the pigs were stable during the 6-h follow-up.

Conclusions: From this small-sample, short follow-up animal study, it was found that the implantation of esophageal electrodes and pacemaker based on POEM and NOTES is feasible, safe, and effective. Nevertheless, there is urgent need for long-term follow-up to confirm or disprove the safety of the procedure.

MeSH Keywords: Esophageal Diseases • Esophageal Motility Disorders • POEMS Syndrome • Esophageal Achalasia

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Background

Esophageal motility is crucial for peristalsis of the esophagus body and for relaxation and contraction of the lower esophageal sphincter (LES) [1, 2]. Primary achalasia and other esophageal motility disorders of peristalsis are characterized by peristalsis in the esophagus body or by contraction of the LES when swallowing [3]. Treatment for patients involves medical, endoscopic, and surgical options. In recent years, several studies have supported POEM as an initial treatment strategy for patients with achalasia and other esophageal motility disorders. This is due to their significantly higher treatment success rates compared to other therapies [4, 5]. However, these therapies only focus on the gastrointestinal tract smooth muscles but neglect the recovery of esophageal body peristalsis, which may lead to poor long-term prognosis [6, 7]. Electrical stimulation therapy of the smooth muscles has been used as a treatment for esophageal motility disorders [8]. Based on the results of our previous study using rabbit models [9], esophageal electric stimulation induced esophageal contraction temporarily at the stimulated site in vivo, and this effect was not mediated by neurotransmitters, which made it easier to stimulate the esophageal body sequentially with successive electrodes and then induce esophageal peristalsis. We hypothesized that the esophagus in patients with primary achalasia may also regain peristalsis after sequential electrical pacing with the help of an implantable pacemaker and electrodes. Using the combination of an esophageal pacemaker, electrode implantation, and POEM, esophageal peristalsis function in patients with achalasia can be restored together with an LES incision, and hence lead to a more favorable prognosis. We inserted electrodes into the esophageal body submucosal tunnel during the POEM procedure and placed a pacemaker under the abdominal wall and then connected them. This idea was inspired by the workings of cardiac pacemakers.

Material and Methods

Five male domestic pigs (castrated), weighing 20–30 kg were purchased from the teaching laboratory of China Agricultural University, Hebei, China. The pigs were housed in an indoor environment with moderate temperature, humidity, and light. The study protocol was reviewed and approved by the Ethics Committee of Tianjin Medical University General Hospital.

Electrical stimulation equipment and manometry

Baseline and post-surgical LES pressures were recorded using a water-perfused esophageal high-resolution pressure measuring manometry (22-channel, Medical Measurement Systems, Laborie, CA). A submucosal implanted electrode automatically sensing digestive tract sequential pacing therapy device (provided by Dr. Wu, patent applied, patent number CN 103143116 A, China, Fig) was used for electrical stimulation.

Surgical procedure

Experimental pigs were housed for 7 days and fasted for 3 days prior to surgery. After endotracheal intubation and venous access were established, the pigs were anesthetized using ketamine hydrochloride injection (1 mg/min during the procedure, provided by Tianjin Medical University General Hospital Anesthesiology Department). The animals were positioned in left lateral position and ventilated. Vital signs were monitored (blood pressure checked every 5 min, respiratory rate, heart rate, and oxygen saturation) using a multi-parameter monitor. Upper endoscopy was then performed using a standard endoscope 9.8 mm in diameter with a 2.8-mm working channel (GF-H260, Olympus, Tokyo, Japan). Approximately 5 cm above the esophagogastric junction (EGJ) at the 12 o’clock position, a submucosal injection consisting of a mixture of glycerol fructose, adrenaline, and methylene blue was administered. Afterwards, the mucosa was lifted and the submucosal space was expanded to facilitate safe mucosal incision. The mucosal layer was longitudinally cut using a Hook knife (KD-620LR, Olympus, Tokyo, Japan). A submucosal tunnel was then established along the submucosal layer that reached the anterior wall of the gastric body near the lesser gastric curvature (Figure 1A). Based on the NOTES (natural orifice transluminal endoscopic surgery) procedure, the muscularis propria and serosal layer was cut using a TT knife at 7–8 cm below the cardia, at the anterior wall of the gastric body near the lesser gastric curvature and entering into the abdominal cavity. During the procedure, hemostasis using clamps and ligatures was essential. A 3–5-cm longitudinal nick was then made at the abdominal wall, directly facing the above-mentioned incision in the stomach wall (Figure 1B). Subcutaneous tissue was then bluntly separated. Electrodes were inserted through this access and merged with the endoscope in the abdominal cavity. The electrodes were clamped using forceps and pulled into the submucosal tunnel (Figure 1C). After placement, the electrodes were fixed using titanium clips so that the proximal part of the electrode was 5 cm above the EGJ (Figure 1D–1F). The pacemaker was implanted subcutaneously, with the interface connected to the distal end of the electrode.

Afterwards, titanium clips were used to close the tunnel opening in the esophageal lumen, and the liquid perfusion high-resolution pressure measuring instrument catheter was placed into the esophagus after the electrodes and pacemaker were fixed in place (Figure 1G, 1H). The abdominal incision was then sutured (Figure 1I). Esophageal electrical stimulation was performed using a single pair of electrodes. Contraction of the esophagus was observed using an endoscope and HRM.

ANIMAL STUDY

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Post-surgical treatment

After the surgery, the animals were intravenously administered cefoxitin sodium (Yangtze River Pharmaceutical Group, China, 2 g). The pigs were resuscitated and vital signs were monitored using a multi-parameter monitor. Six hours later, the animals were euthanized using pentobarbital (0.5 g, provided by Tianjin Medical University General Hospital Anesthesiology Department). Autopsies were performed to measure bleeding of the esophagus, thoracic cavity, abdominal cavity, visceral organs, and abdominal wall.
Results

The procedure was successfully completed for all the animals and lasted about 1.5 h. After recovery from anesthesia, the experimental pigs were euthanized 6 h later. During the procedure, blood pressure and respiratory and heart rates of the pigs increased slightly but returned to pre-surgical levels after awakening. Oxygen saturation was stable based on multi-parameter monitors. Autopsies showed no obvious hemorrhage in the abdominal puncture site and abdominal cavity. The electrodes were still securely positioned in the tunnel and the junctions of the electrodes and the pacemaker were well sealed (Figure 2). Esophageal pressure changes were recorded using pressure-measuring instruments, and contraction of the esophagus was observed using an endoscope and HRM. The current mode was single-phase square wave of 8 mA, frequency 50 Hz, pulse width 3000 μs, stimulation time 1 s, and electrode sequential delay time 3 s (Figure 3). Contraction occurred immediately after stimulation.

Discussion

Esophageal motility disorders are gradually being recognized. Current therapy directly targets obstructions in the esophagus [10,11]; however, using these methods does not fully alleviate esophageal peristaltic function [12,13]. In order to restore normal physiological function of the esophagus, it is essential to develop treatment strategies to regain proper peristalsis of the esophagus.

Electrical pacing treatments for gastrointestinal tract diseases has been reported extensively and have been mostly used for gastroparesis and other motility disorders [14]. This indicates that human gastrointestinal smooth muscles can react to electrical stimulation, and, as a result, can facilitate or block food passage. Previous studies in humans and animal models have demonstrated that the esophageal smooth muscle can contract under electrical stimulation [15,16]. Our previous study demonstrated that, except for the lower esophageal sphincter, esophageal smooth muscle strips in the body of the esophagus can also contract immediately after electrical stimulation. In addition, we found that the amplitude of esophageal contraction was current- and frequency-dependent [9]. This made plausible our hypothesis, similar to cardiac electrical stimulation therapy, that the esophagus could also be induced by electrical stimulation to initiate peristalsis. The approach we took was to place an esophageal submucosal pacing electrode and connect it to the abdominal wall subcutaneous to a pacemaker. This was achieved through a submucosal tunnel to the esophagus to implant the electrode, and then to connect it to the pacemaker through the abdominal cavity. This was the most important part of the procedure, as it was necessary to connect the submucosal tunnel of the esophagus and the abdominal cavity to the exterior during the surgery. To reduce the risk of infection, every step of the surgery had to be performed rapidly without compromising sterility. To facilitate the capture of the bottom of the electrode to the nicker tethered to the abdominal cavity, we constructed a tunnel at the front wall of the gastric body. Accordingly, we demonstrated the feasibility and safety of the implantation of the esophageal pacemaker and electrode with the combination of the POEM technique and abdominal wall puncturing. We found that electrical stimulation in the esophageal
tunnel could induce esophageal contraction at the stimulation site instantaneously [17]. Similar to the multi-point stimulation procedure demonstrated by Amaris et al. [18] in the intestine serosa of a canine isolated colon, we also observed smooth muscle contraction after stimulation, which was observed using a gastroscope.

Our study demonstrated immediate contraction after stimulation. The reasons are likely dependent on different electrical stimulation parameters and electrical stimulation sites. Additional electrical stimulation parameters and esophageal body pressure changes should be evaluated in future studies.

For future studies, we aim to implant at sites at least 15 cm into the esophagus instead of the distal esophagus and to perform longer post-surgical monitoring to determine long-term safety, such as delayed bleeding and the risk of infection. Biocompatibility data for the electrodes and stimulators and the accurate effect of multi-point electrical stimulation will also have to be evaluated. Additionally, we also need to investigate the risk of electrode displacement after long-term placement and the time required for local adhesion fixation.

Conclusions

We described a novel procedural approach of esophageal electrical pacing using an esophageal submucosal pacing electrode and connecting it to a pacemaker subcutaneously. Further studies will focus on evaluating pacing parameters and long-term safety.

Conflict of interests

None.

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