Research Article

Robotic Setup Promises Consistent Effects of Multilocular Gastrointestinal Electrical Stimulation: First Results of a Porcine Study

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Keywords

Gastrointestinal motility · Motility disorder · Electromyography · Robotic surgical procedure

Abstract

Background: Electrical stimulation (ES) of several gastrointestinal (GI) segments is a promising therapeutic option for multilocular GI dysmotility, but conventional surgical access by laparotomy involves a high degree of tissue trauma. We evaluated a minimally invasive surgical approach using a robotic surgical system to perform electromyographic (EMG) recordings and ES of several porcine GI segments, comparing these data to an open surgical approach by laparotomy. **Materials and Methods:** In 5 acute porcine experiments, we placed multiple electrodes on the stomach, duodenum, jejunum, ileum, and colon. Three experiments were performed with a median laparotomy and 2 others using a robotic platform. Multichannel EMGs were recorded, and ES was sequentially delivered with 4 ES parameters to the 5 target segments. We calculated pre- and poststimulatory spikes per minute (Spm) and performed a statistical Poisson analysis. **Results:** Electrode placement was achieved in all cases without complications. Increased technical and implantation time were required to achieve the robotic electrode placement, but invasiveness was markedly reduced in comparison to the conventional approach. The highest calculated (c)Spm values were found in the poststimulatory period of the small bowel with both the conventional and robotic approaches. Six of the 20 Poisson test results in the open setup reached statistical significance and 12 were significant in the robotic experiments. **Conclusions:** The robotic setup was less invasive, revealed more consistent effects of multilocular ES in several GI segments, and is a promising option for future preclinical and clinical studies of GI motility disorders.

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Introduction

The motility of the gastrointestinal (GI) tract is based on coordinated, smooth muscle contractions and relaxations, known as peristalsis. Motility irregularities can manifest throughout the entire GI tract, and they cause common, clinically relevant disorders. These disorders lead to significant impairment of the patient's quality of life [1]. Dysmotility symptoms range from dysphagia and gastroparesis to diarrhea, constipation, or even life-threatening events in patients with chronic intestinal pseudo-obstruction [2]. Although the pathophysiology of motility disorders is not fully understood, impaired GI electrical activity is frequently correlated [3–8]. Studies have shown that GI electrical activity is measurable with smooth-muscle electromyography (EMG) and that GI motility can be modified with electrical stimulation (ES) [9–14]. Thus, a multilocular ES of the GI tract may be a promising mid- or long-term therapy for medically refractory GI motility disorders. However, to date, few studies have investigated the effects of multilocular ES in multiple segments of the GI tract in animals or humans [12–14]. We recently described successful modulation of electrical activity in 5 GI segments using variable ES [15]. The conventional open surgical approach to multiple GI segments still involves a laparotomy with increased tissue trauma and may impair accuracy in the detection of modulating effects from ES. Minimally invasive surgery may allow more realistic physiologic or pathophysiologic intraoperative GI electrical recordings.

The aim of our study was to establish a modified experimental protocol for robotic placement of electrodes for EMG and variable ES in multiple segments of the GI tract and to compare the technical and electrophysiological data for this promising minimally invasive approach to the conventional open surgery setup.

Materials and Methods

Anesthesia and Surgery

We performed acute experiments with 5 healthy, overnight-fasted male pigs weighing 28–46 kg (median 36 kg) under general anesthesia and continuous monitoring. Three consecutive pigs underwent a conventional open procedure with midline laparotomy and placement of multiple monopolar hook-needle electrodes (inomed Medizintechnik GmbH, Emmendingen, Germany) in the stomach, duodenum, jejunum, ileum, and colon under general anesthesia (sodium thiopental 8–10 mg/kg body weight/h [mg/kg/h]) and piritramide (0.3–0.4 mg/kg/h) as previously described [16]. Two other pigs were subjected to a robotic-assisted procedure under general anesthesia with ketamine (5–10 mg/kg/h) and midazolam (0.25–0.5 mg/kg/h), adapted to heart rate and blood pressure. For this purpose, a periumbilical skin incision was made and a Veress needle inserted to install a capnopneumoperitoneum of 10 mm Hg. Four robotic ports (8 mm) were placed in the middle abdomen for the robotic surgical system (da Vinci Xi, Intuitive Surgical, Sunnyvale, CA, USA). A suprapubic catheter was inserted through the apex of the urinary bladder under laparoscopic assistance. Docking of the robotic surgical system was completed and surgical positioning was performed with a connected operating table (TruSystem 7000 dV OR table, Trumpf Medical System GmbH und Co. KG, Saalfeld, Germany). Hook-needle electrodes were placed analogously to the open setup using a robotic needle driver and fenestrated grasper (Fig. 1). The third robotic instrument was used for retraction under control of the operating surgeon at the surgeon's console. For both the open and robotic procedures, neutral electrodes were placed into the abdominal wall.

Electromyography and Electrical Stimulation

Impedance measurements and differential multichannel baseline EMGs were measured with an ISIS Xpress system (inomed Medizintechnik GmbH). By measuring the impedance of all electrodes before recording the baseline EMG, we avoided short circuits or inappropriate tissue positioning. When the impedance was >10 k Ω , the electrodes were repositioned before starting the EMG recordings. A baseline multichannel smooth-muscle EMG was recorded for 3 min before stepwise application of 4 ES parameters. Gastric ES (GES), duodenal ES (DES), jejunal ES (JES), ileal ES (IES), and colonic ES (CES) were successively

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Fig. 1. Hook-needle electrodes were placed seromuscular in the ileum using robotic instruments.

applied for 30 s of 25-mA rectangular pulses. The open setup allowed pulse widths of 500 μ s (short pulse) or 1,000 μ s (long pulse), and frequencies of 30 Hz (low frequency) or 130 Hz (high frequency). The ES parameters of the robotic approach were slightly modified, at pulse widths of 500 or 800 μ s, respectively, and frequencies of 30 or 125 Hz, respectively. After each ES administration, a poststimulatory multichannel smooth-muscle EMG was recorded for 3 min. Eventually, animals were sacrificed with an intravenous injection of 20 mL of 7.45% KCl.

Computer-Assisted Counting and Statistical Analysis

The pre- and poststimulatory EMG analysis, spike detection, and statistical analysis were based on our previous study [15]. Minute-by-minute EMG spike activity was analyzed using data at 5 locations from 5 experiments ($n = 25$). For all experimental data, EMGs were 30-Hz high-pass-filtered. Spikes were detected by setting a threshold normalizing spikes under the nonstimulation condition (resting spikes) to a mean of maximally 6 spikes per minute (Spm). Spikes under the next ES condition were algorithmically detected by using the resting spike threshold. To examine the effects of ES on the poststimulatory spike activity, we used an estimation of generalized linear mixed models (glmm) with multivariate normal random effects, with a penalized quasi-likelihood (PQL) method based on a penalized mixed Poisson model with penalization for overdispersion (function glmmPQL in package MASS of R software v3.4.4; R Core Team, 2018, R Foundation for Statistical Computing, Vienna, Austria). The statistical Poisson analysis was adapted for correlation within animals and multiple electrodes at the same location. This type of model is estimated for each location, each ES parameter set, and each of the 3 poststimulatory minutes. From the pooled experimental data, the glmmPQL function delivered an algorithmically estimated pre- and poststimulatory spike count, referred to here as calculated Spm (cSpm).

Results

Surgical Procedure

During all 5 acute experiments, there were no anesthesia-associated complications. The skin openings for the primary preparation required a 10-fold-larger incision for the open technique than for the robotic approach. All recording sites could be accessed with both the conventional and minimally invasive approaches. In both surgical approaches, all hook-needle electrodes were safely placed in the stomach, duodenum, jejunum, ileum, and colon without perforation, leakage, or relevant bleeding. The overall procedure duration of the

Fig. 2. Example for baseline, pre- and poststimulatory, multichannel, 30-Hz high-pass-filtered EMG recordings of an ileum segment. Electrical stimulations were performed with all 4 technical parameter sets.

Table 1. Relevant differences between conventional open surgery and the minimally invasive robotic approach

Parameters	Open surgical approach	Robotic approach
Skin incision	approx. 400 mm	approx. 32 mm
Surrounding tissue trauma	high	low
Number of electrodes	Limited to serosal surface and electrode design	Limited to cable tangles and the number of ports
Technical effort	low	high
Technology costs	low	high
Electrode handling	straightforward	straightforward
Procedure duration	100%	130%
Dehydration of serosal surfaces	high	low

robotic setup included port placement, docking, calibration, surgical exposure, and electrode placement, and it took approximately 30% longer than the open setup with surgical access and electrode placement only. Shortly after the laparotomy, we visually observed a progressive dehydration of the serosal GI surfaces. In our minimally invasive technique, serosal moisture loss was not observed. In Table 1, we list the relevant differences between the conventional open and the minimally invasive robotic approach.

Table 2. Algorithmically calculated spikes per minute and statistical Poisson analysis of 3 pre- and post-stimulatory minutes for 5 gastrointestinal (GI) segments during conventional open and robotic porcine procedures

GI segment	ES parameter		Open approach		Robotic approach	
	pulse width	frequency	cSpm (3 min)	p value	cSpm (3 min)	p value
Stomach	at baseline		5	–	2	–
	short	low	9	0.051	68	0.201
	long	low	10	0.038	11	0.565
	short	high	10	0.028	10	0.596
	long	high	10	0.033	7	0.698
Duodenum	at baseline		5	–	4	–
	short	low	8	0.355	16	0.009
	long	low	9	0.197	16	0.011
	short	high	8	0.256	21	0.002
	long	high	5	0.854	17	0.007
Jejunum	at baseline		1	–	2	–
	short	low	111	0.081	42	<0.001
	long	low	127	0.073	38	<0.001
	short	high	100	0.089	47	<0.001
	long	high	106	0.085	32	0.001
Ileum	at baseline		3	–	1	–
	short	low	10	0.076	158	0.012
	long	low	20	0.004	165	0.011
	short	high	18	0.007	211	0.008
	long	high	17	0.008	159	0.012
Colon	at baseline		6	–	1	–
	short	low	6	0.941	104	0.053
	long	low	4	0.241	110	0.052
	short	high	5	0.412	99	0.055
	long	high	6	0.653	98	0.055

During 5 acute experiments, we applied multiple hook-needle electrodes in the stomach, duodenum, jejunum, ileum, and colon of pigs. Baseline and poststimulatory EMGs were recorded, and electrical stimulation (ES) was performed with 4 technical parameter sets with a short pulse (500 μ s), long pulse (800–1,000 μ s), low frequency (30 Hz), or high frequency (125–130 Hz). Calculated spikes per minute (cSpm) and Poisson *p* values for comparison of the 3 pre- and poststimulatory minutes were algorithmically determined (see Methods). Bold type indicates significant results (*p* < 0.05).

Different Electrical Excitabilities

Four ES parameters were successfully applied to all 5 target GI segments. In all 5 experiments, the pre- and poststimulatory multichannel EMGs were recorded (Fig. 2) and further analyzed. Table 2 shows the results of a detailed EMG analysis with cSpm and corresponding Poisson *p* values for the comparison of the baseline and post-stimulatory cSpm. The highest cSpm of the open procedures was calculated for the poststimulatory EMGs of the jejunum after JES with a long pulse width and low frequency (127 cSpm). The lowest cSpm was registered after CES with a long pulse width and low frequency in the 3 poststimulatory minutes of the colon (4 cSpm). In the open experiments, most poststimulatory reactions after GES and IES were statistically distinct, whereas the comparison of pre- and poststimulatory cSpm of the duodenum, jejunum, and colon was statistically insignificant in the Poisson analysis.

Overall, 6 of 20 test results in the open setup were statistically significant in comparison to the prestimulatory baseline.

EMG analysis of the robotic approach revealed the highest cSpm in the poststimulatory EMGs of the ileum after IES with a short pulse width and high frequency (211 cSpm). The lowest cSpm was observed after GES with a long pulse width and high frequency (21 cSpm). All cSpm responses after robotic DES, JES, and IES were statistically distinct in the Poisson analysis. The test results of the poststimulatory gastric and colonic EMG after robotic GES and CES remained insignificant in the Poisson analysis. Overall, 12 of 20 Poisson test results in the robotic setup were statistically significant.

Discussion

In this experimental study, we established a robotic setup for the placement of EMG and ES electrodes in 5 segments of the porcine GI tract, and then compared the surgical and electrophysiological results of this comfortable and minimally invasive access to our conventional surgical approach. Tremor filtering, motion scaling, and instruments with 7 df make the robotic variant appear superior to the laparoscopic one. To the best of our knowledge, no previous study has involved the assessment of a robotic approach for variable ES and EMG measurements in 5 segments of the porcine GI tract.

The robotic procedure required a more technical setup, but the skin incisions and surrounding tissue trauma were minimal in comparison to the open procedure. Robotic exposure of the target GI segment was excellent, and electrode placement with the 3 robotic instruments was easy, although the electrode cables caused some interference. The robotic procedure appeared to take longer than the open experiments because docking and calibration are mandatory, and surgical exposure is performed with the robotic instruments and the connected operating table. Nevertheless, the minimally invasive robotic approach offers the potential advantages of achieving more realistic physiologic or pathophysiologic intraoperative GI electrical recordings. Throughout the robotic procedures, serosal dehydration was negligible in comparison to the conventional setup. This difference can be explained by the porcine abdominal cavity having no continuous connection to the relatively dry and cold air of the operating theatre, and convection was regarded as being minimal.

It seems reasonable to assume that a less physiological environment alters GI electrical signals. The electrophysiological consequences of GI serosal dehydration have not previously been investigated, and published studies are few. A clinical study described delayed gastric emptying in systemically dehydrated healthy participants [17]. Other studies with healthy participants and patients with dysmotility indicated that the human GI tract significantly responds to alterations in temperature [18, 19].

Our electrophysiological analysis provided evidence of a strong and reliable spike alteration through the application of ES in multiple segments of the GI tract. After multilocal ES of 5 GI segments, automated EMG spike calculation within an early poststimulatory period revealed relevant cSpm changes in all investigated GI parts of the 5 experiments. In both the open and robotic experiments, several cSpm measures of the 3 poststimulatory minutes were markedly higher than the prestimulatory baseline EMG in the stomach, duodenum, jejunum, and ileum. Only the pre- and poststimulatory cSpm of the colon in the open experiments were comparably low. In contrast, EMG analysis of the colon during the robotic experiments revealed very high but statistically insignificant increases in cSpm compared to baseline. The highest spike counts were found in the small bowel of both the conventional (jejunum) and robotic (ileum) setup. This result is consistent with our previous findings [15] and other studies. Romański et al. [20] and Lammers et al. [21] reported a higher number of Spm in the

jejunum and ileum of pigs and dogs than in the human stomach and duodenum [22] and the porcine colon [23].

The statistical group analysis revealed that the effects of ES were more consistent in the robotic setup. Overall, there were twice as many statistically significant Poisson test results with the robotic approach than with the conventional setup. However, the electrophysiological data were likely influenced by the different surgical approaches and anesthesiologic regimens and energy-reduced ES parameters in the robotic approach.

The general anesthesia of the conventional experiments was maintained with thiopental and piritramide, and the robotic experiments were performed with ketamine and midazolam. Published findings on the effects of our anesthetic regimens on GI motility are mixed and controversial. Thiopental has been described as conserving a normal migrating myoelectrical complex in the small intestine of rats [24]. A canine study of conventional surgical access by laparotomy found that thiopental even triggered spike activity in the duodenum and jejunum but not in the ileum or stomach. The same study found no effects of ketamine on the GI spike activity [25]. Inhibition of the entire GI transit is induced by the administration of opioid drugs [26] like piritramide, and reduced spike activity has been described in the stomach and colon of morphinetreated rats [27]. Although midazolam shows only subtle effects in gastric, duodenal, and jejunal manometry of healthy volunteers [28], significant inhibition of GI transit has been found in mice [29].

GI electrical signals may also be influenced by the physiologic milieu. This includes blood pressure, heart rate, oxygenation, and body temperature. Under general anesthesia, these factors were kept within homeostatic ranges. Evidence of the direct influence of the surgical access on GI electrical activity is limited. Laparotomy with incision of the muscle layers and peritoneum has been described as having an inhibitory effect on GI spike activity in rats [24]. On the other hand, a faster colonic transit was found in patients after minimally invasive surgery compared to open surgery [30].

Faster recovery from postoperative intestinal paralysis was also found after laparoscopic surgery compared to conventional surgery in a canine study [31]. The electrical stimulation parameters of the robotic setup had to be slightly reduced in comparison to the open approach to achieve cross-platform compatibility of our electrotechnical setup and the robotic surgical system. During the ES in the robotic experiments, we applied pulse widths of 800 μ s instead of 1,000 μ s and frequencies of 125 Hz instead of 130 Hz. All applied ES parameters were in the range of the available literature and the pulse width was, comparably, very low [5, 9, 11–13, 15, 16, 32, 33].

In conclusion, we have demonstrated several advantages of the minimally invasive robotic setup in comparison to the more invasive open surgery approach. The robotic setup appears to be the more high-grade and promising method for clinical application; clinical realization of the open approach would likely involve disproportionately high morbidity and complications. A case report positively evaluated the robotic surgical system in the placement of a GES system for a patient with medically refractory gastroparesis [34]. Moreover, the robotic surgical system was able to easily access the stomach, duodenum, jejunum, ileum, and colon investigated in this study, but also the rectum and esophagus via small skin incisions. Although we report on an experimental study, its clinical application in patients with medically refractory GI motility disorders for electrical activity mapping of several GI segments would already be technically feasible with our minimally invasive setup. Furthermore, a first individual motility evaluation would take place in a more physiological environment. Together with recent advances in wireless GI device developments [33, 35, 36], even the scenario of robotic placement of multiple theranostic devices distributed along the GI tract appears reasonable.

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Statement of Ethics

This study complied with all relevant national regulations and institutional policies for the care and use of animals. It was approved by the Regional Board of Animal Welfare, Koblenz, Rhineland-Palatinate, Germany, under approval code G-17–1-008.

Conflict of Interest Statement

J.F.S., K.S., K.P.H., J.B., and W.K. declare no conflicts of interest. K.H.S. is an employee of inomed Medizintechnik GmbH.

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Author Contributions

W.K. and K.P.H. obtained funding. J.F.S., K.S., K.H.S.F., and W.K. were involved in the study design and experiments. J.B. handled laboratory animal issues. J.F.S. and W.K. analyzed and interpreted the data and wrote the manuscript.

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