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Association between gastric myoelectric activity disturbances and dyspeptic symptoms in gastrointestinal cancer patients

Aneta L. Zygulska[a,*], Agata Furgala[b], Krzysztof Krzemieniecki[a,c,1], Beata Wlodarczyk[b], Piotr Thor[b]

[a] Department of Oncology, University Hospital in Cracow, Cracow, Poland
[b] Department of Pathophysiology, Jagiellonian University Medical College, Cracow, Poland
[c] Department of Oncology, Jagiellonian University Medical College, Cracow, Poland

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ABSTRACT

Purpose: Dyspeptic symptoms present a severe problem in gastrointestinal (GI) cancer patients. The aim of the study was to analyze an association between gastric myoelectric activity changes and dyspeptic symptoms in gastrointestinal cancer patients.

Material and Methods: The study included 80 patients (37 men and 43 women, mean age 61.2 ± 7.8 years) diagnosed with GI tract malignancies: colon (group A), rectal (group B) and gastric cancers (group C). Gastric myoelectric activity in a preprandial and postprandial state was determined by means of a 4-channel electrogastrography. Autonomic nervous system was studied based on heart rate variability analysis. The results were compared with the data from healthy asymptomatic controls.

Results: In a fasted state, GI cancer patients presented with lesser percentages of normogastria time (A:44.23 vs. B:46.5 vs. C:47.10 vs. Control:78.2%) and average percentage slow wave coupling (ACSWC) (A:47.1 vs. B:50.8 vs. C:47.2 vs. Control:74.9%), and with higher values of dominant power (A:12.8 vs. B:11.7 vs. C:12.3 vs. Control:10.9) than the controls. Patients did not show an improvement in the percentage of normogastria time, dominant power, dominant frequency and ACSWC in response to food. The severity of dyspeptic symptoms correlated with the values of electrogastrography parameters. Patients showed lower values of heart rate variability parameters than the healthy controls, that indicate abnormal autonomic nervous system activity.

Conclusion: GI cancers affect the gastric myoelectric activity, decreasing normogastria and slow wave coupling. These patients do not show adequate gastric motility response to food. Impaired gastric electric motility may result from cancer-induced autonomic disturbances.

1. Introduction

Electrogastrography (EGG) is a non-invasive reproducible method for recording gastric myoelectric activity with the electrodes placed on the abdominal skin over the stomach. EGG provides information on gastric function in both fasted and fed state [1–3]. Normal frequency of rhythmic electrical depolarizations (slow waves) approximates 3 cycles per minute (cpm) [1–3]. Slow waves control maximal frequency and direction of distal stomach motility. EGG may be a useful tool for evaluating and further monitoring of functional gastrointestinal (GI) disorders [1–5].

Gastric motility may be assessed on the basis of determining gastric emptying and recording gastric myoelectric activity. While the former technique is suitable solely for assessing postprandial motor status, the latter can accurately determine gastric motor function in both preprandial and postprandial state [6–10]. Authors of previous studies evaluated gastric emptying and myoelectric activity at the same time point, and searched for a link between gastric dysmotility and clinical presentation of patients with various disorders [4,5,9,11–14]. Delayed gastric emptying was shown to be linked to EGG abnormalities, primarily to a decrease in the percentage of normal slow gastric waves and a postprandial increase in dominant power (DP). In an experimental study, each slow gastric wave was associated with a contraction, which, however, was lost in the case of dysrhythmia. Furthermore, a relative increase in DP of EGG was shown to be related to greater contractile activity of the stomach [15]. These observations were confirmed in

* Corresponding author at: Department of Oncology, Cracow University Hospital, 10 Sniadeckich St., 31-531, Cracow, Poland.
E-mail address: zygulska@poczta.onet.pl (A.L. Zygulska).
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human studies [6,7]. An increase in the percentage of normal slow waves, dominant frequency (DF) and DP, as well as a concomitant decrease in the severity of dysrhythmia, were typically observed in healthy subjects as a gastric myoelectric response to food [16,17].

Gastric myoelectric activity has been sporadically studied in GI cancer patients [13,18]. Statistically significant positive correlations were found between the feeling of fullness in the epigastric region and the percentage of preprandial bradygastria in gastric cancer and rectal cancer patients [18–21]. On the other hand, tachygastria and reduction of gastric motility were documented after neoadjuvant chemoradiotherapy due to esophageal cancer. Individuals with this malignancy showed a decrease in DF and lower prevalence of normogastria at 3 and 6 months post-surgery, with subsequent normalization of these parameters at 12 months [18]. In another study, gastric cancer patients after total or distal gastrectomy presented with lower power amplitude and lower power content of normogastria than the healthy controls and individuals subjected to total colectomy [19]. According to literature, tachygastria, bradygastria, dysrhythmia and gastric outlet obstruction may occur in up to 88.6% of cancer patients, and abnormal EGG findings co-exist with dysmotility-like symptoms [22].

Frequency domain analysis of heart rate variability (HRV) provides information on autonomic balance and is suitable for quantification of sympathetic and parasympathetic tone. HRV monitoring can be used to non-invasively examine the cardiac autonomic innervation and vegetative modulation of the sinus node. Hence, HRV is often included in studies on various autonomic disorders. Moreover, this method seems to be appropriate for evaluating cancer-specific changes in the autonomic activity [23,24].

Both, sympathetic and parasympathetic, components of the autonomic nervous system play vital roles during development and spread of solid tumors, albeit at different stages of tumorigenesis. Likewise in leukocyte and fibroblast migration, neurotransmitters also regulate the migratory activity of cancer cells. The phenomenon refers to cancer cells migrating along nerve fibers as perineural invasion, that is associated with poorer prognosis [25,26].

The aim of this study was to analyze an association between gastric motility and dyspeptic symptoms in patients with colorectal and gastric malignancies, who additionally had performed the estimation of the autonomic nervous system activity based on HRV. To the best of our knowledge, it is the first published study analyzing changes of gastric myoelectric activity in this group of cancer patients.

2. Material and methods

The study included 80 patients (37 men and 43 women, mean age 61.2 ± 7.8 years) diagnosed with GI malignancies: colon cancer (group A, n = 30, 8 men and 22 women, mean age 64.8 ± 10.2 years), rectal cancer (group B, n = 30, 14 men and 16 women, mean age 61.2 ± 9.7 years) and gastric cancer (group C, n = 20, 15 men and 5 women, mean age 62.9 ± 10.7 years). All patients were recruited at the Department of Oncology, University Hospital in Cracow (Poland) between September 2014 and September 2016. A control group comprised of 30 healthy asymptomatic subjects (15 men and 15 women, mean age 62.2 ± 9.2 years).

The inclusion criteria of the study were as follows: 1) histological evidence of gastric or colorectal carcinoma, 2) lack of neoplastic cachexia, 3) at least 18 years of age, 4) discontinuation of all medications with potential effect on gastric motility and autonomic system activity 3 days prior to the study, 5) Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 0, and 6) written informed consent.

The exclusion criteria included cardiovascular disorders, neurological disorders, gastrointestinal disorders other than carcinoma, diabetes mellitus, obesity (Body Mass Index > 30 kg/m^2), tobacco smoking, alcohol abuse, intake of medications with an established effect on gastric myoelectric measurements, previous history of abdominal surgery other than anticancer treatment, pregnancy and chronic disorders that may affect gastrointestinal and/or autonomic function.

Table 1
Basic characteristics of colon cancer patients (group A).

Parameter	n = 30
sex	M : F = 8 (26.7%) : 22 (73.3%)
mean age (range)	64.8 years (40-85)
TNM staging	I – 6 (20%) II A – 6 (20%) III B- 8 (26.7%) III C- 2 (6.6%) IV – 8 (26.7%)
type of surgical treatment	hemicolectomy – 15 (50%) resection of the colon – 7 (23.3%) abdominoperineal amputation of the rectum – 1 (3.3%) abdominoperineal amputation of the rectum, sigmoidectomy with metastasectomy – 2 (6.7%) abdominoperineal amputation of the rectum and resection of recurrence – 1 (3.3%) anterior resection of the rectum – 1 (3.3%) hemicolectomy and anterior resection of the rectum – 1 (3.3%) anterior resection of the rectum and sigmoidectomy – 1 (3.3%) anterior resection of the rectum and metastasectomy – 1 (3.3%)
surgical treatment	radical – 23 (76.7%) palliative – 7 (23.3%)
chemotherapy	YES – 17 (56.7%) NO – 12 (40%) hyperthermic intraperitoneal chemotherapy (HIPEC) – 1 (3.3%)
CEA level after surgical treatment	normal – 23 (76.7%) abnormal – 7 (23.3%) mean level – 82.86 ± 73.55 ng/ml

All subjects were asked to fast for at least 12 h before the investigation and to withdraw all medications with established effects on autonomic function and gastrointestinal motility for 3 days preceding the study.

None of the study participants showed abnormalities in complete blood count parameters and results of biochemical tests for kidney and liver function. Performance status of all subjects was 0 or 1. The vast majority of them (75%) had radical surgical treatment. Four patients with colon cancer had surgical treatment due to intestinal obstruction. Detailed characteristics of the study subjects are presented in Tables 1, 2 and 3 .

2.1. Assessment of gastric myoelectric activity

The research was performed on patients reporting to the laboratory in the morning, after a 12-h overnight fast. 30-min EGG recordings of gastric myoelectric activity under basal conditions were obtained after an overnight fast and 1 h after a standard meal (Nutridrink, Nutricia, 300 kcal/300 ml). EGG was conducted with a four-channel electrogastrography Polygraf NET (Medtronic, USA) described earlier by Simonian et al. [10], Wang et al. [15] and Krusiec-Świdergoł et al. [27]. After completing a standard preparatory procedure, involving, if necessary, shaving of the skin, and careful skin abrasion with the use of Every paste, and placing a set of six Ag/AgCl electrodes - designed primarily for long-term electrocardiographic monitoring - on the abdominal skin over the stomach (Fig. 1) [1,27]. Four of them were active electrodes: the third active (3) electrode was fixed in the midline, half way between the xiphoid process and the umbilicus (which is a standard position for a single-channel electrogastrography), the fourth (4) electrode was attached 4–6 cm to the right – horizontally in line with electrode 3, whereas the second (2) and the first (1) electrode were placed with a 4–6 cm interval on a line leading up from electrode 3 at a 45° angle towards the left costal margin. The reference electrode (Ref) was placed at the interception of a horizontal line passing through electrode 1 and a vertical line stretching from electrode 3. The

Table 2
Basic characteristics of rectal cancer patients (group B).

Parameter	n = 30
sex	M : F = 14 (46.7%) : 16 (53.3%)
mean age (range)	61.2 years (43-76)
TNM staging	I – 1(3.3%) IIA – 15 (50%) IIB- 1 (3.3%) IIIB – 7 (23.4%) IV- 6 (20%)
kind of surgical treatment	anterior resection of the rectum – 17 (56.7%) abdominoperineal amputation of the rectum - 10 (33.3%) proctocolectomy and partial resection of the ileum -1 (3.3%) TEM (transendoscopic microsurgery) with metastasectomy – 1 (3.3%) anterior resection of the rectum with metastasectomy – 1 (3.3%)
surgical treatment	radical – 25 (83.3%) palliative – 5 (16.7%)
radiotherapy	YES – 21 (70%) NO – 9 (30%)
chemotherapy	YES – 22 (73.3%) NO – 7 (23.3%) transcatheter arterial chemoembolization (TACE) – 1 (3.3%)
CEA level after surgical treatment	normal – 27 (90%) abnormal – 3 (10%) mean: 9.3 ± 33.8 ng/ml

Table 3
Basic characteristics of gastric cancer patients (group C).

Parameter	n = 20
sex	M : F = 15 (75%) : 5 (25%)
mean age (range)	62.9 years (40 -74)
TNM staging	IB – 3 (15%) IIA - 1 (5%) IIB – 3 (15%) IIIB – 2 (10%) IV – 11(55%)
Lauren classification	intestinal type – 4 (20%) diffuse type - 2 (10%) mixed type – 1 (5%) unknown – 13 (65%)
kind of surgical treatment	none – 8 (40%) subtotal gastrectomy – 10 (50%) explorative laparotomy – 1 (5%) gastroenterostomy – 1 (5%)
surgical treatment	radical – 9 (45%) palliative – 3 (15%) none – 8 (40%)
radiotherapy	YES – 7 (35%) NO – 13 (65%)
chemotherapy	YES-16 (80%), NO – 4 (20%) chemotherapy – 11 (55%) chemotherapy + targeted therapy (trastuzumab) – 4 (20%) hyperthermic intraperitoneal chemotherapy (HIPEC) – 1(5%)

grounding electrode (Gnd) was placed on the left costal margin on a horizontal line starting from electrode 3. Finally, a motion sensor was taped to the abdominal skin. The electrodes were connected to a Medtronic POLYGRAM NET EGG 311,224 system (Medtronic Functional Diagnostics A/S). Fig. 2

2.1.1. Multichannel electrogastrogram analysis

The primary signal was sampled at 105 Hz, filtered through a 15 cpm low pass filter, and subsequently down-sampled to 1 Hz and stored in a database on a desktop computer. Next, the high-pass filter with the cutoff frequency set to 1.8 cpm was applied to the signal prior to the EGG-analysis (Polygram NetTM Reference Manual) by a researcher blinded to the experimental conditions linked to a particular data set. At first, a visual inspection of the tracings was performed to identify

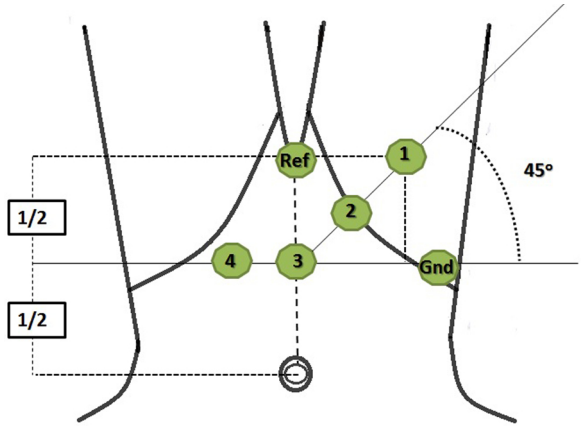

Fig. 1. Placement of electrodes for registering a multichannel electrogastrogram on the abdominal skin: 1–4 - active electrodes, Ref - reference electrode, Gnd - grounding electrode (according to operating manual).

and remove any fragments containing motion artefacts [28]. Three algorithms were then applied to analyze the multichannel electrogastrograms:

1) A running spectrum analysis (RSA) that involved an autoregressive moving average approach executed on consecutive 60-s data sets. The percentage EGG classification ranges were defined as 1.8–2.0 cpm for bradygastria, 2.0–4.0 cpm for normogastria, 4.0–9.0 for tachygastria. A default value of 2.5 dB for the classification threshold was assumed. This stage of analysis yielded the following parameters for each of the four registration channels within a given period: (a) the relative time share of normogastria (3CPM), (b) the share of the power within the normogastria range relative to the total power of the whole considered frequency band;

2) For the overall spectrum analysis a fast Fourier transform using a Hamming window was run on consecutive 256-s data sets with a 128-s overlap. Subsequently, the meal-induced change in DP is compared to the fasted situation.

3) A cross-channel analysis was accomplished using the VAIVA Propalyzer module12 to derive: (a) the percentage of slow wave coupling defined as the relative time within a given period during which the difference in DF between two channels is < 0.2 cpm; averaging the results pertaining to six possible channel pairs yielded the average percentage of slow wave coupling (ACSWC) [2]. EGG recordings were taken to analysis from 1 or 2 channel in patients with gastric cancer after subtotal gastrectomy, in other investigated groups – from 3 channel [27,28].

The definition of normal and abnormal gastric myoelectical activity was based on the validation proposed by Yin et al. [1]. The abnormal response of the EGG to a test meal was defined as a lack of increase in the EGG DP. Changes in the EGG DP were reflected by gastric contractility [1,2]. Gastric myoelectric activity is combined of slow waves associated with electric response activity [15]. The frequency of normal gastric slow waves (normogastria) corresponds to approximately 3 (2–4) cmp; normal gastric slow waves represent > 70% of the EGG percentage time of the normogastria [2,15]. The list of potential deviations from normogastria includes gastric dysrhythmias (bradygastria, tachygastria and arrhythmia), electro-mechanical uncoupling and abnormal slow wave propagation [10,15,29].

2.1.2. Assessment of GI dyspeptic symptoms

All patients completed a self-administered survey (Appendix 1 in supplementary material) on subjective presence and severity of ten dyspeptic symptoms: epigastric pain, abdominal discomfort, heartburn, regurgitation, early fullness, feeling of food retention in the stomach, epigastric bloating, nausea, vomiting, and loss of appetite. The severity of each symptom was scored from 0 to 5 points (0 – absent, 1 –

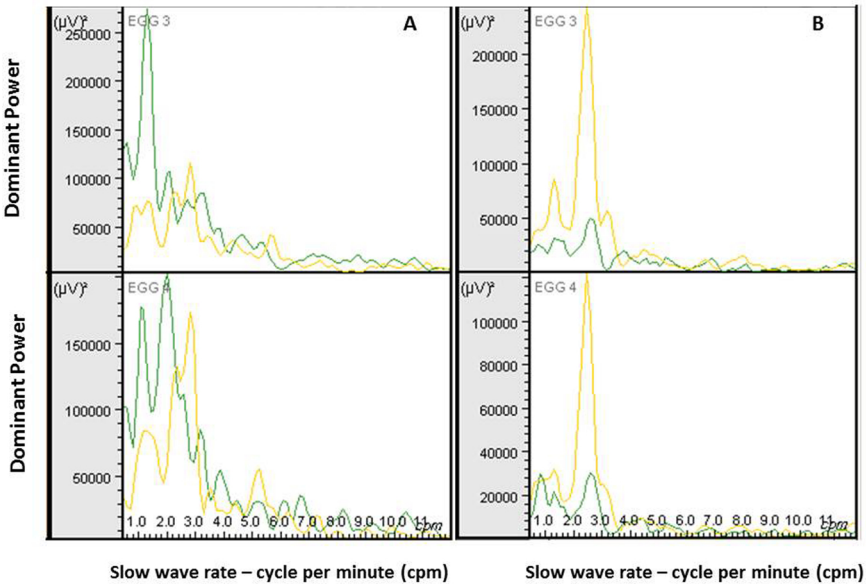

Fig. 2. Recording of the overall spectrum of EGG from 3 channels (EGG 3) and 4 channels (EGG 4): preprandial (green line) and postprandial recording (yellow line). Patients with gastric cancer (A) – abnormal (irregular) rhythm of gastric slow wave, without dominant frequency (DF) peaks, control subject (B) – normal rhythm of gastric slow wave, peaks of dominant frequency (DF) in area 2–4 cycle per minute (cpm), increase of dominant power (DP) after meal.

incidental, 2 – rare, 3 – frequent, 4 – very frequent, 5 – persistent).

2.2. Assessment of autonomic system activity

Autonomic function was determined on the basis of HRV deriving from sinus rhythm. The measurements were taken in the morning (between 8:00 and 10:00 AM), after an overnight (12-h) fast, with the subject in a supine position. Prior to the examination, the participants were provided with detailed information on the testing procedure. Furthermore, we verified if they were in a stable clinical status, refrained from drinking coffee and strenuous physical exercise, and did not take medications with potential modulatory effect on autonomic activity within 72 h prior to the testing [23].

After a 20-min rest and achieving respiratory rate of 14 breaths/min, 30-min ECG recordings simultaneously to the preprandial period of EGG were obtained from 4 conventional leads with Task Force® Monitor 3040i (CNSystems, Austria). The Task Force® Monitor 3040i uses the bipolar principles of EINTHOVEN I and EINTHOVEN II. A 2 channel ECG is included for RR-interval evaluation. These biosignals are recorded in 16bit resolution with a maximum sampling frequency of 1000 Hz. After manual edition of electrocardiograms for potential artifacts, the results were analyzed with Task Force Monitor V2.2 software. Frequency domain analysis of HRV was conducted based on the Aggregating Algorithm Regression (AAR). The following frequency domain HRV analysis parameters were analyzed: power spectral density (PSD) or total power (TP) of the spectrum at 0.0033-0.4 Hz, very low frequency (VLF) component at 0.0033-0.04 Hz – reflecting HRV modulated by chemoreceptors of the renin – angiotensin – aldosterone system (RAA), low frequency (LF) component at 0.04-0.15 Hz – reflecting HRV modulated by the sympathetic system, associated with cyclic changes in the arterial blood pressure and depending on baroreceptors' activity, high frequency (HF) component at 0.15-0.4 Hz – reflecting HRV controlled by the parasympathetic system, associated with breathing, low frequency to high frequency component ratio (LF/HF) - a measure of the relationship between the two components of vegetative modulation, and normalized components, LFnu [LF/(TP-VLF)*100] and HFnu [HF/(TP-VLF)*100] [23].

2.3. Ethical issues

The protocol of the study was approved by the Local Bioethics Committee (opinion no. KBET/98/B/2014). All procedures performed in this study involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All the study participants provided informed written consent.

2.4. Statistical analysis

Statistica for Windows, version 13.0 Pl (StatSoft Inc., Tulsa, OK, USA, Jagiellonian University license) was used for database management and statistical analysis. Normal distribution of quantitative variables was verified with Shapiro-Wilk test, and the statistical characteristics were presented as means and standard deviations (SD). Variables that did not satisfy the criteria of normality were presented as median (Me) and maximum and minimum value (min-max), DP from EGG was subjected to log-normal transformation prior to further analyses. Depending on the distribution type, the significance of intragroup differences was verified with one-way ANOVA followed by Tukey's post-hoc test was performed to examine the differences between groups A, B, C and the control group, when normality was present. The one-way ANOVA on ranks (Kruskal –Wallis test) was performed to evaluate the differences between all the investigated groups in variables without normal distribution. The power of associations between the values of EGG parameters, the severity of dyspeptic symptoms and HRV parameters were estimated on the basis of Spearman's coefficients of rank correlation. The results of all tests were considered significant at $p \leq 0.05$.

3. Results

3.1. EGG parameters

Abnormal EGG is defined as less than 70% of 2–4cpm slow waves percentage time (normogastria) [29]. According to this definition, individuals with GI malignancies presented with abnormal EGG recordings significantly more often than the healthy controls. None of the subjects from the control group showed the evidence of EGG abnormalities in either preprandial or postprandial state. In contrast, abnormal EGG recordings were obtained from 14 (46.6%) patients with colon cancer, 15 (50%) with rectal and 12 (60%) with gastric cancer examined in a preprandial state, and from 14 (46.6%), 11 (36.6%) and 9 (45%) patients examined in a postprandial state, respectively. Also, the prevalence of abnormal EGG recordings in all cancer patients, irrespective of the malignancy location, was significantly higher than in the controls, in both preprandial or postprandial period. During

Table 4
Electrogastrographic parameters of participants from each study group, determined prior to and after a standard meal.

EGG	Bradygastria [%]		Normogastria [%]		Tachygastria [%]		Arrhythmias [%]		DF [cpm]		DP [μV^2]		ACSWC [%]	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Group A	**8.2**	**10.7**	**44.2** [15.6-80.0]	**46.4**	**7.6**	**7.1**	**38.5**	**33.3**	**2.75**	**2.8**	**12.8**	**12.1**	**47.1**	**52.0**
Me [min-max]	[0-33.3]	[0-42.9]		[14.3-91.7]	[0-23]	[0-17.4]	[12.0-69.6]	[5.9-47.4]	[2.1-3.2]	[2.1-3.9]	[10.1-12.8]	[8.9-12.2]	[32.1-74.7]	[32.5-90.0]
Group B	**8.9**	**5.0**	**46.5**	**63.0**	**8.0**	**4.5**	**32.6**	**24.0**	**2.7**	**2.8**	**11.7**	**11.8**	**50.8**	**59.0**
Me [min-max]	[0-34.4]	[0-38.6]	[25.0-78.3]	[24.0 -89.7]	[0-26.1]	[0-21.4]	[10.7-66.7]	[3.4-45]	[2.1-3.0]	[2.1-3.4]	[10.6-13.2]	[10.6-13.8]	[27.7-74.6]	[35.3-83.3]
Group C	**8.3**	**4.1**	**47.1**	**50.2**	**8.3**	**5.7**	**36.4**	**29.5**	**2.7**	**2.6**	**12.3**	**11.4**	**47.2**	**45.9**
Me [min-max]	[0-21.7]	[0-30]	[21.7-78.3	[28.6-85.7]	[0-24.0]	[0-39.4]	[13.0-69.9]	[4.8-71.4]	[2.5-2.8]	[2.1-2.9]	[9.8-14.2]	[6.7-14.2]	[33.3-68.0]	[28.7-76.7]
Control	**6.7**	**6.0**	**78.2**	**82.4**	**5.3**	**3.2**	**6.4**	**5.3**	**3.0**	**3.1**	**10.9**	**11.6**	**74.9**	**82.3**
Me [min-max]	[0-9.0]	[0-13.2]	[68.6-100]	[74.1-100]	[0-12.1]	[0-9.8]	[0-18.6]	[0-24.2]	[2.5-3.4]	[2.6-3.6]	[8.9-12.1]	[9.27-13.2]	[65.4-100]	[78.2-100]
p ANOVA														
p A&Control	**0.001**	**0.0000**	**0.0000**	**0.0000**	**0.009**	NS	**0.0000**	**0.0000**	**0.007**	**0.006**	**0.035**	NS	**0.0000**	**0.0000**
p B&Control	**0.0001**	**0.004**	**0.0000**	**0.0000**	**0.002**	NS	**0.0000**	**0.0000**	**0.001**	**0.0009**	NS	NS	**0.0000**	**0.0000**
p C&Control	NS (0.051)	NS (0.062)	**0.0000**	**0.0000**	NS (0.056)	NS	**0.0000**	**0.0000**	NS (0.09)	**0.0002**	NS	NS	**0.0000**	**0.0000**

Legend: Me – median value; min – minimum; max – maximum; p < 0.05 - significant differences between patients groups A&B&C&Control (ANOVA analysis). The significant differences between groups A&B, A&C and B &C were not found. Pre – preprandial state, Post – postprandial state. Percentage EGG classification range 1.8–2 cpm – bradygastria, 2–4 cpm – normogastria, 4–9 cpm – tachygastria, DF – dominant frequency, DP – dominant power, ACSWC – average percentage of slow-wave coupling; NS – nonsignificant.

examination in a preprandial state, patients from group A, B and C presented with significantly lower percentages of normogastria time (A:44.23 vs. B:46.5 vs. C:47.10 vs. Control:78.2%) and average percentage slow wave coupling (ACSWC) (A:47.1 vs. B:50.8 vs. C:47.2 vs. Control:74.9%), and with higher values of DP (A:12.8 vs. B:11.7 vs. C:12.3 vs. Control:10.9) than the controls. Contrary to the controls, no significant improvement in the percentage of normogastria time, DP, DF and ACSWC was observed in patients with GI malignancies during examination in a postprandial state, especially in group C. In group A the percentage of arrhythmias time decreased from 38.5% to 33.3% (p = 0.01). The patients in group B presented the increase of normogastria (from 46.5% to 63%, p = 0.0009) and the highest decrease of arrhythmias (from 32.6% to 24.0%, p = 0.005). The results are summarized in Table 4 and shown in Fig. 3.

3.2. EGG response to food

Abnormal EGG response to the test meal was defined as a lack of increase in DP [1,2]. A power ratio of DP < 1 correlates with a decreased distal gastric motor response to meal. Whereas all healthy controls showed normal response to the test meal, abnormal DP responses were documented in 18 (60%) patients from group A, 16 (53.3%) from group B and 14 (70%) from group C. Abnormal EGG responses to the test meal occurred significantly more often in gastric cancer patients than in individuals with colorectal malignancies (p < 0.05). Changes in EGG parameters documented after administering the standard meal are summarized in Table 4 and Fig. 2 and 3. When compared to GI cancer patients overall, EGG recordings from healthy controls included a larger proportion of regular 3-cpm slow waves. Overall, EGG abnormalities were found in 41 (51.3%) study subjects (coexistence of the disorder in response to a meal and percentage of normogastria time > 70%).

3.3. Dyspeptic symptom score

Most individuals with GI malignancies in our study did not show an evidence of dyspeptic symptoms. The most frequently reported ailment was bloating, present in 52.5% of all cancer patients. In turn, vomiting was of extremely rare evidence (8.75%). The results are presented in Table 5.

Bloating was the main symptom reported by patients from group A, the severity of dyspeptic symptoms (bloating and abdominal discomfort) in this group was the highest. Subjects from group B most often reported bloating, heartburn and epigastric pain. Epigastric pain as well as feeling of food retention in the stomach and bloating were predominant symptoms in more than half of the patients from group C. The results are summarized in Table 5 and Table 6.

3.4. HRV parameters

3.4.1. Colon cancer patients (Group A)

The values of resting HRV parameters - LF and HF - turned out to be significantly lower in colon cancer patients than in the controls (LF: 85.98 vs. 836.0 [ms^2], p = 0.0000; HF: 94.99 vs. 965.5 [ms^2], p = 0.0000). Moreover, cancer patients presented with nonsignificant higher values of LF/HF ratio (1.46 vs. 1.0, p < 0.05) in comparison to the controls (Table 7). These findings correspond to the disruption of parasympathetic-sympathetic balance in colon cancer patients.

3.4.2. Rectal cancer patients (Group B)

The resting HRV parameters - LF and HF - were also significantly lower in the rectal cancer patients than in the controls (LF:195.35 vs. 836.0 [ms^2], p = 0.0000; HF: 115.23 vs. 965.5 [ms^2], p = 0.0002). The LF/HF ratio was higher in the cancer patients (1.72 vs. 1.0, p < 0.05). These indicators point to the imbalance of autonomic nervous system activity in rectal cancer, primarily in the form of sympathetic

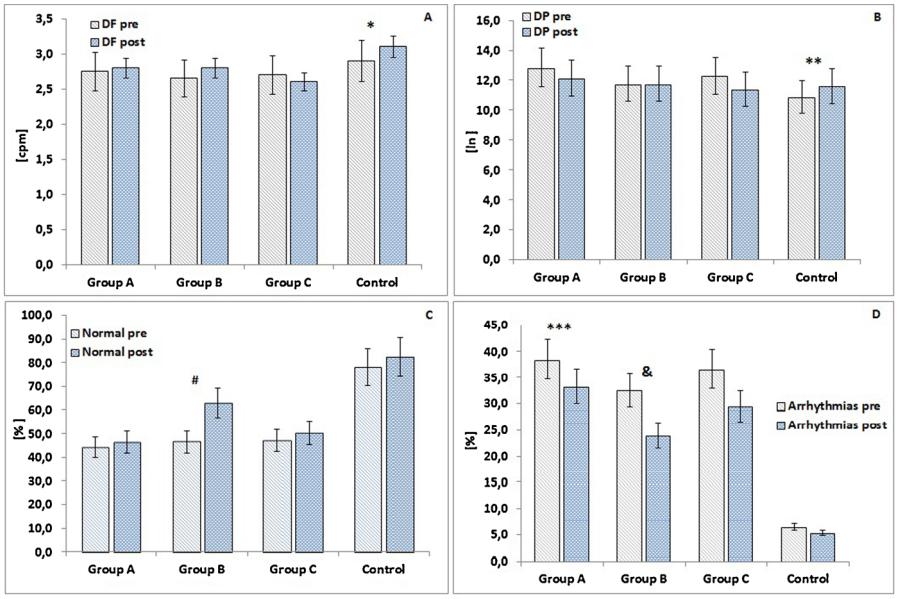

Fig. 3. The influence of food intake on selected EGG parameters - the differences between each of the investigated groups.

overactivity. The results are presented in Table 7.

3.4.3. Gastric cancer patients (Group C)

In the gastric cancer group resting HRV indices - LF and HF - were also significantly lower than in the control group (LF 100.29 vs. 836.0 [ms^2], p = 0.0000; HF: 94.99 vs. 965.5 [ms^2], p = 0.0000). The LF/HF ratio was higher in the cancer group (LF/HF: 2.15 vs. 1.0, $p < 0.05$). These parameters of HRV analysis indicate abnormal modulation of autonomic nervous system in the gastric cancer patients. The results are collected in Table 7.

3.5. Correlations

Positive correlations between the feeling of fullness in the epigastric region and the percentage of preprandial bradygastria were found in patients from group C and A (r = 0.61; p = 0.035 vs. r = 0.71; p = 0.027, respectively). Moreover, the feeling of food retention in the stomach correlated positively with dysrhythmia in a preprandial state (r = 0.61; p = 0.037) and showed an inverse correlation with DP (r = -0.76; p = 0.038) in subjects from group C.

4. Discussion

Motility, sensation, absorption, secretion, digestion and barrier function are the pivotal roles of gastrointestinal tract. A variety of motor patterns can be observed in the small and large intestine, both innervated by the autonomic nervous system. Intrinsic peristaltic movements facilitate the anterograde propulsion of luminal contents [30,31].

Enteric nervous system (ENS) is under the autonomic nervous system control. Neurons of the enteric ganglia communicate via chemical synapses, forming an independent nervous system, similar to the brain and spinal cord. Moreover, the brain-in-the-gut includes interneurons and motor neurons, which due to chemical neurotransmission act as a neural network, similar to that present in the central nervous system [30,31].

Enteric mast cells are a type of immune/inflammatory cells providing paracrine signaling for the ENS. The brain-to-mast cell connection explains the relationship between stress and irritable bowel syndrome-like symptoms in the gut [31]. Furthermore, this mechanism may contribute to carcinogenesis and processes taking place in neoplastic tissue.

In the present study, we analyzed an association between gastric myoelectric activity disturbances, dyspeptic symptoms and autonomic system disturbances in patients with gastrointestinal malignancies. Principal findings of our study can be summarized as follows:

1) Up to 50% of the study subjects presented with abnormal electrogastrographic findings. When examined in a fasted state, colon, rectal and gastric cancer patients showed lower percentages of normogastria time, lower percentages of ACSWC and higher values of DP than the controls.

2) Contrary to the controls, no improvement in the percentage of normogastria time, DP, DF and ACSWC was observed in patients with GI malignancies during examination in a fed state. Abnormal response to the test meal was observed in 60% (48 subjects) of cancer patients.

3) Severity of dyspeptic symptoms correlated with EGG parameters. A positive correlation was found between the feeling of fullness in the upper abdomen and increased preprandial bradygastria in the colon and gastric cancer patients. Moreover, the feeling of food retention in the stomach correlated positively with dysrhythmia in a fasted state and showed an inverse correlation with DP in the gastric cancer patients.

4) Patients with colorectal and gastric cancers showed lower values of HRV parameters (LF, HF) at rest than the healthy controls. These findings corresponded to the disruption of parasympathetic-sympathetic balance in the GI cancer patients, primarily in the form of sympathetic overactivity. The most severe changes were observed in the patients with gastric cancer.

So far, GI dysmotility problems have been only sporadically studied in the oncological patients. Several previous experimental and clinical studies analyzed a relationship between the EGG parameters and gastric emptying [9,11,12,32]. Delayed gastric emptying turned out to be linked to EGG changes, namely to a decrease in the percentage of normal gastric slow waves and to a smaller postprandial increase in DP. In previous studies, gastric myoelectric activity was generally evaluated after gastrectomy performed due to gastric cancer [19,20,33,34]. Murakami et al. [33] observed that patients after vagus nerve-preserving distal gastrectomy presented with better preserved gastric myoelectric activity than individuals subjected to standard distal gastrectomy without vagal sparing. Moreover, they found significant inverse correlations between the percentage of slow wave coupling and GSRS scores (reflux, abdominal pain, indigestion scores and total score) in patients who have been operated on without vagus nerve

Table 5
Questionnaire to determine the severity of dyspeptic symptoms (the intensification of symptoms) in each investigated patient's groups. (n = 80).

Symptom	Group A Colon Cancer (n = 30)	Group B Rectal Cancer (n = 30)	Group C Gastric Cancer (n = 20)
epigastric pain	absent - 22 (73.3%) incidental – 2 (6.7%) rare – 2 (6.7%) frequent – 3 (10%) very frequent – 1 (3.3%)	absent - 24 (80%) incidental – 3 (10%) rare – 2 (6.7%) frequent – 1 (3.3%)	absent – 8 (40%) incidental -2 (10%) rare – 4 (20%) frequent – 3 (15%) very frequent – 1 (5%) persistent – 2 (10%)
abdominal discomfort	absent – 14 (46.7%) incidental – 2 (6.7%) rare – 9 (30%) frequent – 3 (10%) very frequent – 1 (3.3%) persistent – 1 (3.3%)	absent – 24 (80%) incidental – 1 (3.3%) rare – 3 (10%) frequent – 1 (3.3%) persistent – 1 (3.3%)	absent – 10 (50%) incidental – 1 (5%) rare- 5 (25%) frequent – 3 (15%) very frequent– 1 (5%)
heartburn	absent- 16 (53.3%) incidental – 3 (10%) rare – 9 (30%) frequent – 2 (6.7%)	absent- 21 (70%) incidental – 5 (16.7%) rare – 4 (13.3%)	absent – 16 (80%) incidental – 1(5%) rare – 1 (5%) persistent – 2 (10%)
regurgitation	absent – 26 (86.7%) incidental – 2 (6.7%) rare – 1 (3.3%) frequent -1 (3.3%)	absent – 29 (96.7%) incidental – 1 (3.3%)	absent -14 (70%) incidental – 4 (20%) frequent – 1 (5%) persistent - 1 (5%)
early fullness	absent- 22 (73.3%) incidental -2 (6.7%) seldom – 4 (13.3%) frequent – 1 (3.3%) very frequent – 1 (3.3%)	absent - 28 (93.3%) rare – 2 (6.7%)	absent – 14 (70%) incidental – 1 (5%) rare- 3 (15%) frequent – 1 (5%) persistent -1 (5%)
feeling of food retention in the stomach	absent – 17 (56.7%) incidental – 5 (16.7%) rare – 4 (13.3%) frequent – 3 (10%) very frequent – 1 (3.3%)	absent – 25 (83.3%) incidental – 2 (6.7%) rare – 3 (10%)	absent – 9 (45%) incidental – 4 (20%) rare – 4 (20%) frequent – 1 (5%) very frequent– 1 (5%) persistent – 1 (5%)
epigastric bloating	absent – 11 (36.7%) incidental – 5 (16.7%) rare – 9 (30%) frequent – 2 (6.7%) very frequent – 1 (3.3%) persistent – 2 (6.7%)	absent– 18 (60%) incidental – 4 (13.3%) rare – 6 (20%) frequent – 1 (3.3%) very frequent – 1 (3.3%)	absent-9 (45%) incidental -3 (15%) rare -6 (30%) frequent – 1 (5%) persistent – 1 (5%)
nausea	absent – 21 (70%) incidental – 4 (13.3%) rare – 4 (13.3%) frequent – 1 (3.3%)	absent – 28 (93.3%) incidental – 1 (3.3%) rare – 1 (3.3%)	absent – 16 (80%) incidental – 2 (10%) rare – 2 (10%)
vomiting	absent- 27 (90%) incidental – 1 (3.3%) frequent – 2 (6.7%)	absent- 30 (100%)	absent -16 (80%) incidental – 1 (5%) rare – 2 (10%) persistent – 1 (5%)
loss of appetite	absent – 23 (76.7%) incidental – 4 (13.3%) rare – 2 (6.7%) frequent -1 (3.3%)	absent – 26 (86.7%) incidental – 2 (6.7%) rare – 1 (3.3%) frequent – 1 (3.3%)	absent – 13 (65%) incidental – 1 (5%) rare –2 (10%) very frequent – 2 (10%) persistent – 2 (10%)

Table 6
Severity of gastrointestinal symptoms determined with the dyspeptic symptoms questionnaire in gastrointestinal cancer's patients. (Appendix 1 in supplementary material).

Gastrointestinal symptoms	Group A Me (min-max)	Group B Me (min-max)	Group C Me (min-max)	p A&B	p A&C	p B&C
Epigastric pain	0.63 [0-4]	0.33 [0-3]	1.65[0-5]	NS	NS	**0.02**
Abdominal discomfort	1.26 [0-5]	0.50 [0-5]	1.20 [0-4]	NS (0.08)	NS	**0.024**
Heartburn	0.90 [0-3]	0.43 [0-2]	0.65 [0-5]	NS	NS	NS
Regurgitation	0.23 [0-3]	0.03 [0-1]	0.60 [0-5]	NS	**0.02**	**0.02**
Early fullness	0.56 [0-4]	0.13 [0-2]	0.75 [0-5]	**NS (0.07)**	NS	**NS (0.07)**
Feeling of food retention in the stomach	0.86 [0-4]	0.26 [0-2]	1.20 [0-5]	NS	NS	**0.04**
Epigastric bloating	1.50 [0-5]	0.76 [0-4]	1.15 [0-5]	**NS (0.09)**	NS	NS
Nausea	0.46 [0-3]	0.10 [0-2]	0.30 [0-2]	**NS (0.07)**	NS	NS
Vomiting	0.23 [0-3]	0.00 [0-0]	0.50 [0-5]	**NS**	NS	NS (0.05)
Loss of appetite	0.36 [0-3]	0.23 [0-3]	1.15 [0-5]	NS	NS	NS

Legend: Me – median value; Min – minimum; max – maximum; $p < 0.05$ – statistical significant differences between groups A&B&C (ANOVA analysis). NS – nonsignificant.

Table 7
Comparison of frequency domain HRV parameters in patients groups with cancer and healthy controls.

Parameter	Group A	Group B	Group C	Controls	p A&B	p A&Control	p B&Control	p C&Control
LFnu-RRI [%] Mean ± SD	51.3 ± 20.21	54.24 ± 15.9	55.30 ± 19.05	52.44 ± 15.42	NS	NS	NS	NS
HFnu-RRI [%] Mean ± SD	48.69 ± 20.21	45.75 ± 15.9	44.69 ± 19.05	47.56 ± 15.42	NS	NS	NS	NS
LF-RRI [ms^2] Me [min-max]	85.98 [11.13-4991.6]	195.35 [20.10-2495]	100.29 [14.18-819.28]	836.0 [108-5544]	0.036	0.0000	0.0000	0.0000
HF-RRI [ms^2] Me [min-max]	94.99 [9.15-12755.6]	115.23 [9.67-6262.00]	94.99 [12.24-1045.20]	965.5 [30.61-6927]	NS	0.0000	0.0002	0.0000
LF/HF-RRI Me [min-max]	1.46 [0.04-8]	1.72 [0.31-5]	2.15 [0.21-6.41]	1.0 [0.4-3.2]	NS	NS	NS	NS

Legend: Me – median value; min – minimum; max – maximum; $p < 0.05$ - significant differences between groups A&B&C&Control; The significant differences between groups A&C and B&C were not found, NS – nonsignificant statistical.

preservation [33]. In another study [19], total gastrectomy was associated with complete loss of a 3-cpm power peak or a significant decrease in its amplitude. In contrast, no significant total gastrectomy-related changes were observed in the case of an 11-cmp power peak characteristics. Moreover, patients after subtotal gastrectomy and gastric tube formation presented with lower postprandial values of post-operative to preoperative power ratio at 3-cpm [19]. Our findings are partially consistent with these results, since the patients after distal gastrectomy also showed gastric myoelectric activity disturbances. However, in the study by Hayashi et al. [20], motility of the residual stomach was the same as for the non-resected stomach whenever more than half of the gastric volume was preserved (i.e. if the length of the greater curvature of the residual stomach was > 20 cm). In contrast, our patients presented with EGG disturbances, namely with a decrease in the percentages of normogastria time and ACSWC, as well as with an increase in DP, when examined in a preprandial state.

Chang et al. [21] demonstrated that contrary to the controls, gastric cancer patients do not show a postprandial increase in the DF, present with marked power response after meal and obvious power ratio. Advanced gastric cancer turned out to be the only factor contributing to the evident postprandial increase in the DP. Our findings are consistent with those presented by Chang et al., since up to 60% of our patients showed an abnormal response to the test meal [21]. The most likely pathomechanism leading to these abnormalities is mechanical damage of Cajal's cells or a decrease in the number thereof, associated with either gastrectomy or the presence of gastric cancer itself. The decrease in the number of Cajal's cell might induce changes in the gastric myoelectric activity of our patients. Importantly, the EGG abnormalities were found not only in the gastric cancer patients, but also in the individuals with colorectal malignancies. In our opinion, abnormalities observed in the latter group might reflect an influence of the brain-gut axis on the regulation of GI motility or result from direct injury of the ENS.

Central nervous system (CNS) communicates with the intestines directly via the brain-gut axis. CNS recognizes GI inflammation associated with the presence of colorectal tumor as an activation of vagal afferent signaling. Inflammatory signals originating from the large bowel may significantly alter peripheral neuronal signaling, which results in both peripheral and central sensitization. This phenomenon is reflected by an enhanced afferent neuronal activation [35,36]. Both, cancer itself and anticancer surgery, may result in acute or chronic inflammation of the colon or rectum.

Chemotherapy may induce upper GI symptoms suggestive of motility disorders. A study of patients subjected to Roux-en-Y reconstruction after previous Billroth gastrectomy and chemotherapy showed that such dyspeptic symptoms are associated with abnormal electrogastrographic recordings [37,38]. In another study, conducted by Chasen and Bharqava [22], patients with advanced cancer, either with normal or abnormal ECG findings, presented with loss of appetite or were listless for food intake, nausea, vomiting and early satiety. The most commonly observed dysmotility-like symptoms included in the Dyspepsia Symptom Severity Index were frequent burping and belching, bloating, feeling full after meals, inability to finish a normal-sized meal, abdominal distention and postprandial nausea. In turn, the list of the most frequent reflux- and ulcer-like symptoms included regurgitation of bitter fluid and abdominal pain before meals [22]. In contrast, we did not find the evidence of dyspeptic symptoms in the majority of our GI cancer patients. The most frequent ailment was bloating in the epigastric region, reported by 52.75% of all cancer patients. Epigastric pain, feeling of food retention in the stomach, and overfilling of the epigastric region were primarily reported by individuals with gastric malignancies. In turn, bloating was the main dyspeptic symptom in colorectal cancer patients. Perhaps, these discrepancies between our findings and the results published by Chasen and Bharqava [22] should be attributed to better performance status of our patients. In addition, our patients were not examined during ongoing chemotherapy, but only in a stable period.

Lawlor et al. [18] used EGG to evaluate gastric function in esophageal cancer patients after neoadjuvant chemoradiotherapy and following surgery. Chemoradiotherapy contributed to a significant increase in the abnormal gastric myoelectric activity, involving changes in tachygastria and a decrease in motility as measured by power ratio. In turn, a significant increase in bradygastria, which persisted at 6 months but not at 12 months post-surgery, was documented [18]. Our series included 75% of patients subjected to chemotherapy, and probably it was the systemic treatment which also contributed to the profound myoelectric abnormalities observed in this group. However, the performance status of all of them was good (0 or 1). Our patients were not treated with chemotherapy during the investigation. Hence, the results of our study are not direct effect of chemotherapy but indirect. The systemic treatment might contribute to the sympathetic overactivity and cardiovascular hemodynamic consequences thereof observed in our series. Both, cancer itself and anticancer surgery, may result in acute or chronic inflammation of the colon or rectum. The impairment of autonomic control or direct damage to autonomic fibers may be additional pathophysiological mechanisms involved in carcinogenesis [25,26,39]. However, our knowledge regarding the influence of chemotherapy on GI function is still limited.

In our present study, colorectal and gastric cancer patients presented with lower values of HRV indices: LF and HF parameters, and higher LF/HF ratio at rest than the controls. These findings point to disturbances of sympathetic-parasympathetic balance of the autonomic nervous system. The results of previous studies imply that cancer patients show less fluctuations in vagal activity (as demonstrated by lower values of HRV indices), which can be attributed either to an increase in sympathetic activity or to a decrease in parasympathetic drive [23,40,41].

The principal limitation of this study stems from the fact that the

EGG recordings were not obtained at the same time as the measurements of gastric emptying. Moreover, GI motility was evaluated indirectly, on the basis of contractility index values determined during EGG. Finally, the pathomechanism of abnormal gastric myoelectric activity in colorectal cancer patients still remains unclear and needs further investigation.

Both our findings and the results of previous studies imply that carcinogenesis may contribute to disturbances in gastric myoelectric activity due to inflammatory damage of the ENS. Dysfunction of the autonomic nervous system in cancer patients, especially disturbances of the sympathy-vagal balance, can cause effect in cardiovascular system regulation, due to hemodynamic disturbances. Lesser responsiveness to sympathetic and parasympathetic modulation points to autonomic dysfunction as a potential common pathophysiological mechanism of gastric dysmotility in cancer patients.

5. Conclusions

Colorectal and gastric cancers affect gastric myoelectric activity, decreasing normogastria and slow wave coupling. Moreover, GI cancer patients do not show adequate gastric motility response to food. Cancer - induced autonomic disturbances may contribute to impaired gastric electric motility.

Conflict of interest

The authors declare no conflict of interest.

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The author contribution

Study Design: Aneta Zygulska, Agata Furgała, Krzysztof Krzemieniecki, Piotr Thor
Data Collection: Aneta Zygulska, Beata Włodarczyk
Statistical Analysis: Agata Furgała
Data Interpretation: Agata Furgała, Aneta Zygulska
Manuscript Preparation: Aneta Zygulska, Agata Furgała
Literature Search:Aneta Zygulska, Agata Furgała
Funds Collection: Krzysztof Krzemieniecki

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.advms.2018.08.004.

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