Study on Pathophysiology of Gastric Function in Patients with Reflux Esophagitis

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Abstract

Background

Reflux esophagitis (RE) is a type of gastroesophageal reflux disease (GERD) which shows endoscopic injuries. Gastric function has been known as a part of mechanisms of GERD. However, there is still no comprehensive understandings.

Methods

40 patients completed endoscopy and high-resolution manometry (HRM) who meet diagnostic criteria were enrolled in RE group, and 34 healthy volunteers were recruited as control group. Both of them were evaluated gastric motility by a multidimensional system including a nutritional meal test combined with a visual analog scale (VAS) for assessing gastric tolerance and visceral sensitivity, gastrointestinal ultrasound used for evaluating gastric emptying, electrogastrogram (EGG) for gastric myoelectric activity.

Results

There were statistically significant differences between RE group and control group in gastric maximum tolerance, postprandial symptom score, gastric empty rate and postprandial slow wave rate ($P < 0.05$). Heartburn and reflux are the main symptoms in the RE group. There was a positive correlation between heartburn and epigastric discomfort score (VAS) at 0min and 20min postprandial, and between reflux and gastric empties rate (VAS) at 30min postprandial ($P < 0.05$). 30min nausea symptom score (VAS) was negatively correlated with the rest pressure of the lower esophageal sphincter ($P < 0.05$). The 20min fullness score (VAS) was negatively correlated with the distal shrinkage score ($P < 0.05$). Gastroelectric ratio was positively correlated with the percentage of swallowing failure ($P < 0.01$).

Conclusions

The gastric motility of RE patients is characterized by gastric tolerance, visceral sensitivity, gastric empties, and disturbance of gastric muscle electrical activity, some of which may be involved in the occurrence of RE symptoms and esophageal motility disorders.

Introduction

Gastroesophageal Reflux Disease (GERD) is a disease caused by the backflow of stomach contents into the esophagus, causing discomfort symptoms and/or complications. The global incidence is 8–33%^[1], the occurrence rate of GERD has been increasing in the Eastern world^[2], the prevalence of symptom-based GERD was reported at 5.2–8.5% from 2005 to 2010 in Eastern Asia^[3]. Although the incidence rate

in Asian countries is lower than that in western countries, it has increased in recent years and has become one of the common diseases endangering people's health^[4]. According to endoscopy and symptoms, it can be divided into two types: non-erosive reflux disease (NERD) and reflux esophagitis (RE)^[5].

The pathogenesis of GERD is complicated, mainly caused by the imbalance of defense factors and invasion factors. Since Olsen proposed in 1965 that esophageal dysmotility is related to the occurrence of GERD, the study of esophageal motility has gradually received attention^[6]. The time and number of reflux are not only the anti-reflux function of the gastroesophageal junction, it is associated with the ability of the esophageal body to clear the reflux^[7]. For example, Savarino found that The incidence of abnormal esophageal motility in patients with GERD is high^[8, 9]. Esophageal dysmotility may be one of the pathogenesis of GERD, including reduced pressure of the lower esophageal sphincter (LES), abnormal peristalsis of the esophagus, impaired esophageal mucosal barrier, abnormal esophageal and gastric function, hypersensitivity of the esophagus, and squeezing of the diaphragm to the esophagus^[10]. High-resolution manometry (HRM) can intuitively display the peristaltic function of the esophagus, the function of upper esophageal sphincter (UES) and LES when resting and swallowing. Due to its accuracy and operability, it has been widely used recently, but the results are often not sufficient to explain all the symptoms of patients. A number of studies have shown that patients with GERD have abnormal gastric motility, but there is no comprehensive evaluation of the gastric function of patients with GERD. For example, there were gastric electrical disturbances in GERD patients with food reflux, and 50% of participants had delayed gastric empty of solids and fluids or slow gastric empty of liquids^[11–13].

The previous study of our group conducted multi-dimensional evaluation of gastric motility disorders related to functional dyspepsia (FD) and achieved promising results. In this study, the multi-dimensional evaluation method of gastric motility (gastric tolerance, visceral sensitivity gastric emptying and gastric electrical rhythm) was used to patients with RE to find more pathophysiological abnormalities related to RE. HRM was used to evaluate patients' esophageal motility function, and the correlation between gastric function and esophageal function measurement index was analyzed, which may provide more basis for the exploration of mechanism and individualized comprehensive treatment of RE.

Methods

Subjects

Forty RE patients, including 22 females with a median age of 49.5 years, were recruited from outpatients or inpatients of the First Affiliated Hospital of Dalian Medical University from April 2019 to January 2020. They were included in the RE group according to inclusion and exclusion criteria. Thirty-four healthy volunteers without any chronic disease or clinical symptoms were screened as controls, including women aged 18 years and a median age of 50 years. This study was conducted with sufficient consideration for patient rights and privacy, based on the ethical guidelines pertaining to clinical research. The protocol of

this study was approved by the Ethics Committee of Dalian Medical University. The ethical number is PJ-KS-KY-2019-37, and the clinical-trial registration number is ChiCTR1900026457.

RE group

Inclusion criteria: Reflux, heartburn, retrosternal pain and other symptoms were existed. Endoscopic examination revealed signs of reflux esophagitis (LA-C and LA-D according to Los Angeles classification standard^[14]) such as congestion, edema and mucosal injuries.

Exclusion criteria: hiatal hernia patients; presence of other organic diseases; presence of metabolic diseases like diabetes; history of gastrointestinal surgery; history of gastrointestinal and esophageal tumors; pregnant or preparing for pregnancy; allergic to electrodes or nutritious meals; presence of severe anxiety, depression or other mental illnesses.

Control group

Inclusion criteria: Inclusion criteria for individuals in control group were as follows: Endoscopy showed no occupations, hiatal hernia, mucous injuries 6 months before enrollment. Also, they were absence of any chronic diseases or clinical symptoms, such as abdominal pain, bloating, acid reflux, nausea, vomiting, constipation, or diarrhea. No history of alcoholism or heavy smoking.

Exclusion criteria for individuals in control group were the same as those for RE group.

Methods

Scales

Gerd Questionnaire (GERDQ) Frequency of upper digestive tract symptoms in the past seven days should be chosen in the questionnaire, which include six aspects: heartburn, regurgitation, upper abdominal pain, nausea, somnopathy and use of non-prescription drugs^[15, 16]. (Appendix 1)

HADS The Hospital Anxiety and Depression Scale (HADS) is a self-administered questionnaire aimed to detect the state of anxiety and depression in non-psychiatric patients. The HADS is composed of 14 items, seven of which measure anxiety and the other seven measuring depression^[17].

Assessment methods

Nutritional meal testing (monitoring gastric tolerance) The nutrient solution ingredients were Ensure® (Abbott Laboratories, 102 Chicago, IL, USA) replacement products: 0.6 Cal/ml, fat: 19%, protein: 18%, carbohydrate 63%. This study was modified from previously published methods by using 100g milk powder (Nestle company) and 50g Milo (Nestle company) as a nutrient solution, which was added to 1,200 mL of boiling water then cooled to 37°C. Participants drank the nutrient solution at a constant rate of 60 ml/min until their satiety score was 100. Take this volume as the maximum tolerated volume (MTV)^[18, 19].

VAS (estimating visceral sensitivity) The 100mm horizontal visual analog scales were used to record postprandial symptoms of fullness sensation, nausea, and pain^[19]. The scores of these symptoms were recorded at 0, 10, 20, 30 min after meal which reflect the changes in visceral sensitivity of the participants. (Appendix 2)

Gastrointestinal ultrasonography (measuring gastric emptying) The color ultrasound (r Philips HD 15, USA) was used to assess gastric emptying. The gastric emptying rate (GER%) was calculated at 2, 10, 15, 20, and 30 min after a 450ml contrast agent (Dongya Medicinal and Pharmaceutical Substances Company, Huzhou, China). The Bolondi method was used to measure the antral area of stomach. The circumference of stomach was measured during diastolic and systolic phases. $GER\% = \frac{\text{the change in the diastolic area}}{\text{the initial gastric diastolic area}}$ ^[20, 21].

Electrogastrogram (assessing gastric slow waves) A 4-channel Electrogastrogram (EGG) device (MEGG-04A, Medkinetic Incorporated, Ningbo, China) was used for the assessment of gastric slow waves. The EGG was recorded 30 minutes before and after the meal test. The procedures of the test was similar like the former study^[22]. Following indexes were calculated from EGG^[23]: Frequency peak in the power spectrum is dominant frequency (DF) which corresponding frequency is dominant power (DP). DF (normal range of DF is 2.4-3.7cpm) and DP can reflect frequency and amplitude of gastric myoelectric activity. The normal range of gastric electric frequency is 2.4–3.7 times/min. The proportion of normal slow wave is percentage of gastric electric frequency within the normal range. In healthy adults, the proportion of normal slow waves should be > 70%. Power ratio (PR) should be > 1.0 normally, but error ranges could exist.

Esophageal manometry

High-resolution Manometry (HRM) was performed to evaluate esophagus function in patients with RE. GAP-36A (Medkinetic Incorporated, Ningbo, China) was used. 8 hours or more fasting before the investigation was needed. The catheter was passed trans-nasally and positioned from the hypopharynx to the stomach. The catheter was placed through the nose and pharynx to the stomach. Adjust the tubes for 3 to 5 minutes. When the UES and LES pressures are stable, record the resting pressure for at least 30 seconds. The subjects were then asked to swallow 5mL of room-temperature water every 30 seconds. No repeated swallowing after one swallow, more than 10 times in total. Analysis software which was used to analyze is Manoview3.0 according to the Chicago classification v3.0^[24].

Statistical methods

All data in this study were processed by SPSS20.0 statistical analysis software (IBM). Measurement data were expressed as "mean $\pm$ standard deviation" ($\bar{x} \pm s$), one-way ANOVA or repeated measurement ANOVA was used for comparison between groups, and LSD-T test was used for pairwise comparison between groups. Statistical data were expressed in percentage (%), and comparison between groups was performed by χ^2 analysis and Mann-Whitney U test. $P < 0.05$ means the difference is statistically significant.

Results

Demographic characteristics

Basic information of the participants included age, gender, height, weight, and BMI. The results showed that each of these parameters was comparable between control group and RE group (Table 1).

Table 1
Baseline characteristics of control and RE group

	Control(n = 34)	RE(n = 40)	<i>P</i>
Age,years	47.94 ± 8.09	47.88 ± 11.40	0.977
Male,%(n/N)	35.29(12/40)	55(22/40)	0.144
Height,cm	167.79 ± 7.06	169.15 ± 8.59	0.465
Weight,kg	67.47 ± 8.27	65.44 ± 13.48	0.430
BMI	23.99 ± 2.41	22.70 ± 3.41	0.062
GERDQ	6.09 ± 0.87	10.00 ± 2.91	0.000
MTV	942.35 ± 145.94	832.13 ± 235.36	0.017

Scale

GERDQ The scores of GERDQ in RE group were higher than those in control group ($P < 0.01$) (Table 1). It was indicated that heart burn and regurgitation might be the most common symptoms.

HADS The results showed that anxiety and depression scores in HADS increased in RE group compared with control group ($P < 0.01$) (Fig. 1).

Assessment of gastric motility

Nutritional meal testing MTV was decreased in RE group compared to that of the control group ($P < 0.05$) (Fig. 2).

VAS There were several significant differences between control group and RE group. For fullness sensation score, RE patients' 10min, 20min, and 30min scores after meal were higher than control group ($P < 0.01$). About nausea symptom score, 0min,10min, 20min, and 30min's were higher than control group ($P < 0.05$). The pain scores of RE group at 0min, 10min, 20min and 30min were higher than those of control group ($P < 0.01$). (Table 2)

Table 2
Comparison of VAS score between control and RE groups

		Control(n = 34)	RE (n = 40)	Pvalue
Fullness	10min	64.85 ± 12.52	74.88 ± 13.94	0.002
	20min	44.85 ± 13.11	61.63 ± 19.79	0.000
	30min	21.91 ± 9.46	48.75 ± 23.34	0.000
Nausea	0min	0(0–0)	0(0-32.5)	0.019
	10min	0(0–0)	0(0–0)	0.006
	20min	0(0–0)	0(0–0)	0.006
	30min	0(0–0)	0(0–0)	0.105
Pain	0min	2.35 ± 13.72	27.25 ± 23.25	0.000
	10min	0(0–0)	0(0-18.75)	0.005
	20min	0(0–0)	0(0–10)	0.001
	30min	0(0–0)	0(0–10)	0.001

Gastrointestinal ultrasonography The gastric empty-rate (GER%) of RE group was significantly decreased at 20 min and 30 min, but not at 10 min and 15 min.(Fig. 3)..

Electrogastrogram The normal slow wave percentages after meal were decreased in RE group than those in control group ($P < 0.05$). The preprandial and postprandial DF and PR had no significant difference between RE group and control group (Fig. 4).

Differential Indexes

From the above results, differential index between the two groups were detected, including MTV, 10min, 20min, and 30min fullness sensation score, 0min, 10min, and 20min nausea score, 0min, 10min, 20min,30min pain score, 20min GER%, and 30min GER% (gastrointestinal ultrasound), postprandial normal slow wave ratio (EGG).

Correlation analysis between the differential indexes and two main symptoms

The above results suggested that heartburn and regurgitation might be the most common symptoms in RE patients. (1) Heartburn were positively correlated with visceral hypersensitivity (0min and 20min fullness sensation score) ($P < 0.05$). (2) Regurgitation was positively related to gastric emptying (30min GER%) ($P < 0.01$). (Table 3)

Table 3
Correlation analysis of visceral sensitivity index and main symptoms in RE group

		r	Heartburn	r	Regurgitation
MTV		-0.027	0.868	-0.050	0.760
Fullness	10min	-0.040	0.806	0.137	0.398
	20min	-0.201	0.213	0.076	0.642
	30min	-0.269	0.094	0.147	0.367
Nausea	0min	0.119	0.464	-0.087	0.593
	10min	-0.044	0.790	-0.217	0.179
	20min	0.111	0.495	-0.117	0.473
Pain	0min	0.748	0.000	-0.075	0.644
	10min	0.293	0.066	0.116	0.477
	20min	0.333	0.036	-0.070	0.667
	30min	0.160	0.325	0.207	0.199
Slow Wave	Preprandial	0.180	0.266	0.088	0.589
GER%	20min	-0.180	0.267	0.272	0.089
	30min	-0.150	0.354	0.512	0.001

Correlation analysis between the differential indexes and anxiety/depression score

Correlation analysis showed that depression score was negatively correlated with gastric empty volume (20min, 30min GER%) ($P < 0.05$). (Table 4)

Table 4
Correlation analysis between visceral sensitivity index and HADS score of RE group

		r	Anxiety	r	Depression
MTV		-0.075	0.644	0.129	0.427
Fullness	10min	-0.069	0.671	-0.002	0.990
	20min	0.012	0.944	0.090	0.579
	30min	0.099	0.542	0.055	0.737
Nausea	0min	0.122	0.454	-0.086	0.596
	10min	-0.037	0.822	-0.066	0.686
	20min	0.000	0.999	-0.120	0.459
Pain	0min	0.011	0.948	-0.012	0.944
	10min	0.071	0.662	0.015	0.926
	20min	0.076	0.640	0.114	0.483
	30min	-0.098	0.548	0.061	0.709
Slow Wave	Preprandial	-0.023	0.888	-0.075	0.646
GER%	20min	-0.202	0.212	-0.317	0.047
	30min	-0.025	0.877	-0.374	0.017

Association between esophageal motility and gastric motility

UES resting pressure, LES resting pressure, distal contractile integral (DCI), and percentage of invalid swallow were selected to reflect esophageal motility in this study. Correlation analysis showed that 30min nausea symptom score was negatively correlated with LES resting pressure ($P < 0.05$)(Fig. 4a); 20min fullness sensation score was negatively related to DCI ($P < 0.05$)(Fig. 4b); PR on EGG was positively associated with percentage of invalid swallow ($P < 0.01$)(Fig. 4c). (Table 5)

Table 5
Correlation analysis between esophageal motility indexes and gastric motility indexes of RE group.

		LES resting pressure		UES resting pressure		DCI		ISP	
		r	P	r	P	r	P	r	P
MTV		0.186	0.250	0.096	0.554	-0.122	0.455	0.102	0.533
Fullness	10min	-0.256	0.111	0.045	0.783	-0.167	0.304	0.112	0.490
	20min	-0.096	0.555	0.024	0.883	-0.353	0.025	0.183	0.259
	30min	0.021	0.896	0.172	0.290	-0.228	0.158	0.132	0.417
Nausea	0min	-0.202	0.211	0.074	0.651	-0.126	0.440	0.216	0.182
	10min	-0.275	0.086	0.133	0.414	-0.048	0.766	0.046	0.778
	20min	-0.129	0.429	0.062	0.705	-0.019	0.905	0.049	0.762
	30min	-0.324	0.041	0.081	0.618	-0.042	0.795	-0.040	0.806
Pain	0min	-0.018	0.912	-0.045	0.782	0.010	0.949	-0.106	0.514
	10min	-0.041	0.802	-0.027	0.868	-0.070	0.670	-0.079	0.628
	20min	0.102	0.533	0.090	0.580	-0.070	0.669	-0.232	0.150
	30min	0.040	0.806	0.034	0.835	0.115	0.482	-0.164	0.311
Slow wave	postprandial	0.078	0.634	-0.152	0.349	-0.254	0.114	0.168	0.301
DF	postprandial	-0.052	0.748	-0.138	0.396	-0.078	0.634	-0.103	0.527
PR		0.082	0.613	0.067	0.681	-0.055	0.734	0.432	0.005
GER%	10min	-0.011	0.948	-0.113	0.488	-0.059	0.716	0.164	0.313
	15min	0.071	0.664	0.164	0.311	0.210	0.194	-0.125	0.441
	20min	0.067	0.683	0.283	0.077	0.302	0.058	-0.157	0.332
	30min	0.189	0.242	0.225	0.163	0.174	0.284	0.135	0.407

Discussion

In clinical work, when non-erosive reflux disease, like NERD, are found, doctors usually pay attention to a comprehensive assessment of esophagus and stomach function to find out more causes. However, when the patient's endoscopy shows RE, the focus is usually only on the evaluation and treatment of esophageal function only, so plenty of patients' treatment effects are unsatisfied. Therefore, in this study, we selected RE patients to conduct a comprehensive assessment of gastric function. It is expected that

both of esophagus and gastric function of RE patients will be taken seriously in clinical practice. At present, it is believed that the pathogenesis of GERD is mainly concluding reduced LES pressure, abnormal esophageal motility, impaired esophageal mucosal barrier, esophageal-gastric dysfunction, esophageal hypersensitivity, clamping effect of the diaphragm on the esophagus, showing that gastric motility disorders affect the onset of GERD, abnormal gastric motility is currently considered to be one of the pathogenesis. Although it is theoretically recognized, in clinical practice, especially in refractory GERD patients with recurrent symptoms, few people systematically perform gastric function-related examinations. Even though there are existing researches on gastric function of GERD, most of them focus on gastric emptying and myoelectric activity. Researches on the sensitivity and receptivity of internal organs with the stomach as the main body are rare^[24]. According to the Rome IV criteria, the diagnostic criteria of FD are one or more symptoms of postprandial fullness, early satiety, epigastric pain, and epigastric burning sensation, which occurred for more than 3 months in the past 6 months, also examinations such as endoscopy do not indicate obvious organic disease in stomach^[25]. Both RE and FD patients may have upper abdominal burning symptoms, the possible pathogenesis of FD also includes gastrointestinal motility disorders and visceral hypersensitivity^[26, 27]. Therefore, in further research, we will explore the relationship between GERD-RE and FD.

In this prospective study, through the evaluation of gastric tolerance, visceral sensitivity, gastric emptying and gastric myoelectric activity, it was proved that RE patients had differential indexes related to gastric motility. The results indicated that the maximum tolerance volume of RE group was reduced, which suggested that the gastric tolerance of RE patients was reduced. After the nutritional diet test, satiety score at 10, 20 and 30 minutes, nausea score at 0, 10 and 20 minutes, and upper abdominal pain score at 0, 10, 20 and 30 minutes in RE group were all increased, indicating visceral hypersensitivity. Through gastrointestinal ultrasound examination, results demonstrated that gastric emptying rate at 20 and 30min decreased, suggesting that RE patients had gastric empty delay. Postprandial normal gastric slow wave ratios decreased in electrogastrogram, indicating that there were gastric arrhythmia in RE group. After analyzing the correlation between the main symptoms of RE, heartburn and regurgitation, and differential indexes, it was found that these symptoms were related to visceral sensitivity and gastric emptying. In this study, anxiety and depression scores were increased in THE HADS of RE patients, suggesting that depressive status may also have some influence on gastric motility. GERDQ is one of the common diagnostic methods of GERD currently, and GERDQ > 8 points is considered positive. GERDQ scale score is proportional to the severity of RE under endoscopy^[28]. Regurgitation and heartburn are the two main symptoms of GERD patients. This study found a significant increase in GREDQ scores in the RE group, which is consistent with the existing view. With the in-depth discussion on the pathogenesis of gastrointestinal diseases, the concept of brain-gut axis was proposed, that is, brain signals and gastrointestinal signals interact with each other^[29]. The autonomic nervous system is an important part of the nervous axis, and anxiety and depression can affect autonomic nervous function, that is, emotions may aggravate gastrointestinal symptoms^[30]. This study showed that RE patients had higher anxiety and depression scores on HADS than healthy controls, which was consistent with existing studies^[31, 32].

In general, the proximal stomach ADAPTS to relaxation after meal, and the stomach contents increase, while the pressure in the stomach does not increase significantly, so the stomach accepts food^[33]. Impaired receptivity of the proximal stomach is an important mechanism leading to reduced intake of liquid test meal. Similar nutrient solution test was used to evaluate gastric receptivity in this study. The RE group was more receptive than the control group. Visceral hypersensitivity is an abnormality of perception-reflex, which increased sensitivity of internal organs to acid and/or mechanical stimuli. Also, it leads to discomfort, pain and other intuitive changes. Nervous system pathophysiological changes can affect visceral sensation including peripheral sensitization, central nervous system plasticity changes and facilitation of endogenous pain suppression systemin. Autonomic nervous system, mental and psychological factors are also involved and be thought to play an important role^[34, 35]. Lyon Consensus propose that GERD patients need to be alert to esophageal hypersensitivity. Existing studies have shown that patients with GERD-NERD have esophageal hypersensitivity, but few studies focus on visceral sensitivity with stomach^[36, 37]. VAS scale is a commonly used form for judging symptoms, like pain and nausea. After a nutritional meal test, this scale is usually used to access postprandial symptoms. In this study, compared with the healthy control group, visceral sensitivity of RE patients were significant increased. Therefore, it can be induced that the visceral sensitivity of RE patients is higher than that of healthy person.

Previous studies have confirmed that the gastric volume measured by ultrasound may be related to that measured by radionuclide imaging^[38]. Antrum contraction frequency is also an indicator of gastric emptying rhythm. Color Doppler ultrasonography was used to examine gastric emptying after oral contrast agent. Compared with nuclide phenomena, oral contrast agent GASTROINTESTINAL ultrasound is easier to operate, safer, and more reproducible^[39]. In this study, Bolondi method was used to measure the gastric antrum area and calculate the gastric emptying capacity reflected by GER. The results showed that the RE group had no significant change compared with the control group at the beginning (10min, 15min), but the RE group GER decreased significantly at 20min and 30min.

It is generally believed that the pacing potential of gastric contraction is slow wave, which is also the basis of gastric myoelectric activity^[40]. The electrical activity of gastric electromyography reflected by EGG is same as those in body^[41]. It was confirmed that patients with GERD have abnormal gastric myoelectric activity^[44]. EGG was used in this research to evaluate electrical activity of gastric muscle, the average values of the four channels were selected for comparison. The data demonstrated that postprandial normal slow wave ratio of RE group is significantly lower. It was speculated that the gastric myoelectric activity of GERD patients is mainly abnormal rhythm, the pacing potential of myoelectric activity had no obvious change. Although the results of this article indicated that there is no significant change between the average pre-meal slow-wave ratio of the four channels and the pre-meal main power after the meal, for single channel, those of the fourth channel in RE group was significantly lower than control group. The decrease in PR indicates that postprandial gastric motility was weakened, so it was speculated that the gastric motility disorder may be more obvious near the pyloric area.

In this study, only MTV was found to be associated with nausea symptoms at 0min and 10min postprandial, suggesting that all of the above tests are necessary. Esophageal motor dysfunction can cause symptoms in patients with GERD^[42, 43]. GERD patients with delayed postprandial gastric empty had a significantly higher incidence of reflux than patients with normal gastric empty. citation In this study, the correlation between two major symptoms of heartburn reflux and abnormal gastric parameters was analyzed, and visceral sensitivity was found to be correlated with heartburn reflux, suggesting that visceral sensitivity may play an important role in the pathogenesis of GERD-RE. Regurgitation was also associated with a 30min GER, consistent with existing studies. However, the correlation between anxiety/depression score and abnormal gastric motility parameters showed that depression score was negatively correlated with 30min GER. It is speculated that depression may affect gastrointestinal motility through the brain-gut axis. Therefore, if the patient has reflux as the main manifestation and the treatment effect is not good, abnormal gastric emptying should be considered, and more attention should be paid to the patient's emotional state.

This study and previous studies found that GERD patients also had gastric motility abnormalities. We hypothesized that there was a close relationship between esophageal and gastric motility. Transient reduction of LES pressure is an important pathogenesis of GERD. The data in this paper also proved that 75% of RE patients had reduced LES pressure, which is consistent with existing studies^[44]. The study also found a weak negative correlation between LES resting pressure and the visceral sensitivity parameter (30min nausea symptom score). UES is composed of cricopharyngeal muscle, glossopharyngeal muscle, upper esophageal muscular tissue, all of which are skeletal muscle components. Throat muscles and pressure changes are affected and regulated by multiple internal and external factors, UES pressure changes caused by neuro-muscular regulation. Changes in indicators such as pressure and opening time under different swallowing methods^[45]. In this study, the correlation analysis between various parameters of gastric motility and UES was carried out, but there was no correlations, so it was speculated that abnormal gastric motility in GERD does not lead to changes in UES pressure.

Esophageal body peristalsis dysfunction is one of the pathogenesis of GERD, which may be mainly manifested in the decreased distal esophagus peristalsis. Esophageal motility disorder is a prerequisite for acid reflux and acid exposure, which could also reduce the effectiveness of the esophagus in removing food and acid from esophagus. According to DCI value, absent sequences and weak sequences are called failed sequences. Therefore, the correlation between the multi-dimensional evaluation parameters of gastric motility and esophageal motility parameters of RE patients was analyzed. Results showed that visceral sensitivity parameter (20min fullness score) is negatively correlated with DCI, indicated that maybe there is a correlation between visceral hypersensitivity and abnormal esophageal motility. And there was a slight positive correlation between 20min GER and DCI ($r = 0.034$, $P = 0.058$). Although there was no statistical significance, it could roughly point to the relationship between esophageal motility and gastric emptying. PR is postprandial main power/pre-prandial main power, so correlation between the post-prandial, pre-prandial main power and the percentage of failed sequence is further analyzed respectively, suggesting that main power after meal was more related to the percentage

of ineffective swallowing. In the role of the brain-gut axis, gastrointestinal peristalsis signals are transmitted back to the central nerve system. After integration, they are transmitted to the enteric nervous system or gastrointestinal effector cells through the autonomic nervous system and neuroendocrine system so that various organs could be modulated^[46]. When myoelectric activity of gastric peristalsis increases, the esophageal peristalsis function changes correspondingly through the regulation of the vagus nerve.

In this research, we found some abnormal indexes of gastric and esophageal function in RE patients by series evaluation. In the future study, 24h-PH-impedence examination would be involved, then more indexes like acid exposure time and post-reflux swallow-induced peristaltic wave would be used to analyze.

Conclusion

1. The pathophysiological functions related to gastric motility in patients with RE showed several disorders, including decreased gastric tolerance, visceral hypersensitivity, delayed gastric emptying and gastric electrical arrhythmia, indicating that gastric motility is involved in the pathogenesis of RE.
2. Delayed gastric emptying and visceral hypersensitivity in gastric motility indicators may participate in the occurrence of RE symptoms.
3. Gastric motility disorders may be related to changes in esophageal motility, so a combined gastroesophageal regimen may be used in clinical treatments.

In summary, multi-dimensional changes related to gastric motility are involved in the pathogenesis of RE; when the effect of GERD treatment is not good, it is necessary to take into account the improvement of gastric function.

Declarations

Ethics approval and consent to participate:

This study was conducted with sufficient consideration for patient rights and privacy, based on the ethical guidelines pertaining to clinical research. The protocol of this study was approved by the Ethics Committee of Dalian Medical University. The ethical number is PJ-KS-KY-2019-37. All methods were carried out in accordance with relevant guidelines and regulations. For this study informed consent was obtained from all participants/patients.

Availability of data and materials:

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Authors' contributions:

Yi Yang and Xueying Yin and Xiaoyan Wang wrote the main manuscript text. Xiaoyu Sun and Lixia Wang and Jun Yu prepared the part of table 1-2 and figures 1-2. Xiaoyan Wang and Xiukun Hou were responsible for the data statistics and collation of gastrointestinal color ultrasound, they prepared the part of table 3 and figures 3. Dong Yang and Xiukun Hou prepared the part of figures 4. Zhifeng Zhang prepared the part of table 4. Zhijun Duan and Jing Zhang and Xiukun Hou were the main reviewers. All authors reviewed the manuscript.

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Figures

Figure 1

The scores of anxiety and depression in RE patients were significantly higher than those in control group and RE group ($P < 0.01$).

Figure 2

Compared with the control group, THE MTV in the RE group was significantly lower ($P < 0.05$).

Figure 3

The GER% of RE group was significantly decreased at 20min and 30min after meal ($P < 0.01$), but not significantly decreased at 15min after meal ($P > 0.05$).

Postprandial SLOW wave rate in group E was significantly decreased ($P < 0.01$), but there was no significant difference between postprandial slow wave rate and power ratio ($P > 0.05$).

Figure 4

Correlation analysis between esophageal motility indexes and gastric motility indexes of RE group. **a** 30min nausea symptom score was negatively correlated with LES resting pressure ($P < 0.05$); **b** 20min

fullness sensation score was negatively related to DCI ($P<0.05$); **c** PR on EGG was positively associated with percentage of invalid swallow ($P<0.01$).

Supplementary Files

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