

Establishment of Multi-Dimensional Detection Series (MDS) For the Assessments of Gastric Motility Alterations in Patients With Functional Dyspepsia

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Abstract

Background: Functional dyspepsia (FD) is sub-categorized into postprandial distress syndrome (FD-PDS) and epigastric pain syndrome (FD-EPS). It is a necessary to determine a series of safe, feasible, non-invasive, and economical assessment methods, which may detect more pathophysiological alterations to guide corresponding treatment.

Aim: To establish a multi-dimensional detection series (MDS) comprehensively evaluating the gastric motility of FD patients and verify the clinical value of MDS.

Methods: FD-PDS patients (meeting Rome IV criteria) were recruited, among which 35 patients were enrolled in FD group. 30 healthy volunteers were recruited into the Control group (C group). After the assessment of psychology and symptom scales, the following tests (measuring gastric motility from different latitude) were conducted in both groups. Then, the differential indexes between the two groups were determined and a multi-dimensional detection series for FD was combined according to the statistical principle. Finally, the MDS was used to test another group for verifying its validity and feasibility.

Results: The differential indexes could be detected ($P < 0.05$), including Maximum gastric tolerance, 10 min, 20min and 30 min Sufficiency score, Postprandial slow wave ratio, Post-meal/pre-meal power ratio, 20 min and 30 min Gastric emptying rate, and Low frequency/High frequency of HRV. A formula was constructed it was proved that MDS could give evidences of normal or abnormal gastric motility.

Conclusions: MDS may help clinicians to discover more pathophysiological alterations of gastric motility in FD patient, and potentially provide a basis for corresponding treatments.

Introduction

Functional dyspepsia (FD) is one of the most common functional gastrointestinal diseases. The main symptoms of FD include epigastric pain or burning, postprandial fullness and/or early satiety, etc [1]. FD patients generally have no obvious organic disease but need to be aware of the possibility of the conversion from functional disease to organic disease. The definition of FD is no longer limited to a single gastrointestinal dysfunction but also emphasizes a disorder of brain-intestinal bidirectional regulation [2]. According to the Rome IV classification, FD is sub-categorized into postprandial distress syndrome (FD-PDS) and epigastric pain syndrome (FD-EPS). The incidence of FD in Asia is approximately 5.3–12.8% and FD consists primarily of the FD-PDS subtype [3, 4]. Although the pathogenesis of FD is currently unknown, the main pathogenic factors are related to symptoms attributed to gastrointestinal motility disorder, visceral hypersensitivity, low vagal tone, mental/psychological abnormalities, disorders in gastric acid secretion, and *Helicobacter pylori* infection [5, 6]. Gastrointestinal motility disorders play a key role in the occurrence and development of FD-PDS subtypes and are mainly manifested in terms of abnormal gastric myoelectric activity, gastric accommodation, and abnormal gastric emptying [7]. Although the diversification of the etiologies and clinical manifestations of functional diseases is recognized, a large number of routine examinations, including endoscopy and lab tests, have not found clear organic lesions. Hence, there is a lack of objective methods for estimating such diseases which currently belong to symptom-based diagnosis, and

corresponding treatment efficacies in these diseases are often poor. Therefore, there have been doubts in the diagnoses and treatments from both doctors and patients. In recent years, more studies evaluated relevant pathophysiological changes in functional diseases and contributed to more objective diagnosis. Most researchers used different parameters of electrogastrograms (EGG) to evaluate gastric myoelectric activity[8]. Moreover, Kindt believed that gastric barostat assessment represents one of the criteria for assessing gastric tolerance [9]. Simren et al. [10] tested the visceral sensitivity of balloon dilatation via an electronic constant-pressure device, confirming the increased sensitivity of FD patients. However, the method of placing a balloon inside the stomach of patient is an invasive and relatively complicated procedure. In addition, it was reported that the functional magnetic resonance imaging and positron emission tomography (fMRI and PET) revealed related pathways in the brain elucidating the neural underpinnings of visceral hypersensitivity [11]. However, the method is not only expensive but also limited on the examined population. According to the satiety evaluation method published by Tack [12], a slow caloric liquid test could be used to assess the regulation of gastric tolerance and the development of early satiety. This test can hardly bring about any pain on patients, and is economic. Furthermore, the liquid load test is simple and more convenient to evaluate the visceral sensitivity, avoiding the symptoms induced severer by the process of test in patients with depression and /or anxiety [13]. It is acknowledged that many researchers used gastric-emptying scintigraphy to assay gastric emptying in FD-PDS patients [14]. Some of them tried oral gastrointestinal contrast-enhanced ultrasound to detect the effects of different external factors on gastric antrum dynamics and gastric emptying [15]. Ultrasonography is non-invasive, non-radiative, and inexpensive, and does not alter the physiology of the gastrointestinal tract. Taken together, the previous studies indicated a variety of measurement methods associated with gastric motility, but it has remained difficult to determine more objective pathophysiological changes in FD patients in a single examination. The subjective symptom scale is still widely used to evaluate FD. Some researchers have used electrocardiograms combined with heart rate variability (HRV) analysis to evaluate the pathophysiology of FD patients after treatment [16], but there is still lack of comprehensive assessment method for various motility abnormalities of stomach in FD. If a multi-dimensional series (MDS) built from different latitude to assess the pathophysiological alterations, especially feasible, non-invasive, economical, and objective, it would provide more positive findings.

The present study compared the available, non-invasive, uncomplicated and economical assessment methods and items from different latitude between FD and control groups, and selected the differential indexes. Then a MDS was established with combination of the tests and differential indexes. Finally, the MDS was used to test another groups of volunteers to verify its rationality. It was expected that the findings from the MDS may help clinicians to discover more characteristics of gastric pathophysiological changes in the FD patient, which may provide more positive evidences for the diagnosis and treatment of FD.

Materials And Methods

Subjects

We screened FD-PDS outpatients who visited the Gastroenterology Division of the First Affiliated Hospital of Dalian Medical University from April 2018 to January 2019. According to the Rome IV criteria, 35 eligible patients were randomly selected into the FD group. In the same period, 30 healthy volunteers were recruited to

serve as the Control group (C group). And other volunteers (FD patients before and after treatment) who agreed to join the validation experiment were enrolled in the Symptomatic group (S group) and Asymptomatic group (AS group). This study was approved by the Ethics Committee of Dalian Medical University. Patients and healthy volunteers were informed of the purpose of the study and signed informed consent before the experiment. The ethical number was PJ-KS-KY-2018-05 (X), and the clinical-trial registration number was ChiCTR1800015983.

FD group

Inclusion criteria: (1) 18–65 years old; (2) met the Rome IV criteria for PDS; and (3) did not take any drugs that could affect gastric motility for four weeks prior to the study. (4) No history of alcoholism and no history of heavy smoking. Exclusion criteria for patients in the FD group were as follows: (1) presence of other digestive diseases (e.g., gastroesophageal reflux disease, irritable bowel syndrome); (2) presence of metabolic diseases (e.g., diabetes, liver disease); (3) history of gastrointestinal surgery; (4) pregnant or preparing for pregnancy; (5) allergic to electrodes or nutritious meals; or (6) presence of severe anxiety, depression or mental illnesses.

Control group

Inclusion criteria for individuals in the C group were as follows: a recent physical examination with 3 months indicated that the volunteers were in good health. 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 and no history of heavy smoking. Exclusion criteria for individuals in the C group were the same as those for the FD group.

Validation group

In the experiment, other groups of FD volunteers as Symptomatic group (S group) were tested by MDS, and then administered treatments. The participants having completed treatments and having symptoms exactly recovery (being asymptomatic for 4 weeks) were selected into Asymptomatic group (AS group). The diagnosis of FD met Rome IV diagnostic criteria and had symptoms of patients to go by. The same patients applied to the validation experiment might increase comparability. Exclusion criteria for individuals in the groups were the same as those for the FD group.

Methods

All participants provided data in the forms of questionnaires, anxiety and depression scales, FD symptom score scales, Visual analogue scale (VAS) filling, nutritional meal tests, gastrointestinal ultrasounds, EGG, and HRV tests. General information included age, gender, height, weight, and calculation of body mass index (BMI). Each items was done by the same research.

Scales

FD symptom score scale The main items evaluated by the FD symptom scale include the frequency of symptoms and the severity of different symptoms [17]. The details could be found in Appendix 1

.Anxiety and Depression Scale Hamilton Anxiety and Depression Scale (HAMA and HAMD), as classic psychological scales were used by one same psychologist in this study to assess the psychological states of participants [18,19]. Hospital anxiety and depression self-rating scale mainly includes problems of nervousness and interest in life which assesses the degree of anxiety and depression of the subjects (Appendix 2). Participants were requested to fill in by themselves. The scales were used to exclude the patients with severe psychological problems.

Assessment methods

Nutritional meal testing (monitoring stomach tolerance) The nutrient solution ingredients are ensure replacement products: 0.6 Cal/ml, fat: 19%, protein: 18%, carbohydrate 63%. This study was modified from previously published methods [16] by using 100 g of Nestle milk and 50 g of high Lego as a nutrient solution, which was added to 1,200 mL of boiling water and cooled to 37°C. The subjects drank the nutrient solution at a rate of 60 mL/min until reaching the maximum tolerance. The volume of the liquid at this time was recorded as the maximum tolerance volume (MTV).

VAS (estimating visceral sensitivity)[20] When the patient reached the MTV, the sense of fullness was determined to be 100 points at 0 min, and bloating, pain, and nausea scores were recorded at 10, 20, and 30 min after the meal to reflect changes in visceral sensitivity of the participants (Appendix 3).

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

Electrogastrogram (assessing gastric slow waves) A 4-channel EDGG device (MEGG-04A China) was used for the assessment of gastric slow waves[22]. The EGG was recorded 30 minutes before and after participants taking the nutritious meal. Following parameters were calculated from the EGG[22] (cite a reference) (1) The dominant frequency (DF): the frequency in the power spectrum at which the power was maximum (the normal range of the DF was 2.4–3.7 cpm); (2) the ratio of post-prandial to fasting in DP. A percentage of normal slow wave frequency of more than 70% was defined as normal and (3) The dominant frequency (DF) reflects the regularity of gastric slow waves and the DP reflects the amplitude of gastric slow waves. The post-meal/pre-meal power ratio (power ratio, PR) was >1.0 in healthy adults.

HRV (detecting autonomic function) One of the common non-invasive methods of autonomic function testing is HRV analysis, which is used to explore the pathophysiology of neuro-mediated syncope[23]. Heart rate variability (HRV) data were derived from the ECG recording using validated software. In the ECG recording, R waves were identified and R-R intervals were calculated, then R-R interval data was interpolated at 100 Hz and was finally down-sampled at 8 Hz for spectral analysis. The index with HRV detector (Cool 96, UFI, MODEL 2283FT/2283FTiFETRODETMAMPLIFIER Morro Bay, CA, USA) were recorded for 30 minutes before and after nutritious meals. The low frequency band in the power spectrum of the HRV signal (LF: 0.07–0.3 Hz) represents mainly sympathetic activity, while the high frequency band (HF: 0.3–4.0 Hz)

represents parasympathetic or vagal activity. The LF/HF ratio is calculated to reflect the sympathovagal balance[56]. Electrogastrogram and HRV were measured in two separate days..

Multi-dimensional detection series (MDS)

The above-mentioned detection methods were applied to test the FD group and C group and the differential indexes between the two groups could be picked out. A formula was constructed by multi-index combination method based on the differential indexes and their variation tendency according to statistical principle. After a comparison of the formula between FD and C groups, it would be clear whether or not a combination of the differential indexes could be applied as MDS. If the comparison was significant statistically, MDS is available. S and AS groups were tested by the MDS. The experiment aimed to establish MDS and to demonstrate that MDS could comprehensively evaluate the gastric motility related functions of FD.

Statistical methods

All data are presented as mean±SE and were analyzed by SPSS 22.0. t-test or 2-way repeated measures ANOVA were used to assess the indexes between FD group and Control group on various measurements. One way ANOVA with repeated measures was performed to compare the LF/HF ratio among different periods in FD group. The Spearman test was used to correlation analysis data. A P value <0.05 was considered to be 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 the C group and FD group. However, the scores of HAMA, HAMD, HAS and HAD in the FD groups were higher than those in the C group (P < 0.05) (Table 1.1).

Table 1.1
General information

	C group (n = 30)	FD group(n = 35)	P	χ^2 χ^{22}	
Age (years)	48.33 ± 7.97	52.55 ± 12.60	0.153	-	
Sex	male (%)	10 (33.33)	10 (28.58)	0.885	0.021
	female (%)	20 (66.67)	25 (71.42)		
Height (cm)	168.1 ± 7.0	166.65 ± 7.72	0.537	-	
Weight (kg)	67.19 ± 7.34	62.65 ± 9.07	0.937	-	
BMI	23.73 ± 1.81	22.85 ± 3.15	0.182		
HAD	3.46 ± 1.67	8.70 ± 3.26	0.000		
HAS	2.96 ± 1.49	6.25 ± 2.98	0.000		
HAMA	9.75 ± 1.28	13.88 ± 3.20	0.007		
HAMD	6.90 ± 0.92	12.95 ± 1.96	0.000		

Fd Symptom Score Scale

All 35 patients with FD were analyzed according to the FD symptom score scale. The following data were obtained: 29 cases having postprandial-fullness, accounting for 82.85% of all FD patients; 21 cases with early satiety, accounting for 60%; 20 cases with symptoms of middle and upper abdominal pain, accounting for 57.14%; 18 cases suffering epigastric burning, accounting for 51.4%; whereas retching and nausea were more rarely accompanied (Appendix 1, Fig. 1A). It was indicated that postprandial fullness and early satiety might be the most common symptoms.

Analysis from symptom severity (Appendix 1, Fig. 1B): The average score of postprandial fullness was 2.48; early satiety 2; upper abdominal pain 2; burning 1.77; radon 1.4; retching 1. It was showed that postprandial fullness and early satiety might also be the most severe symptoms.

Measurement By Different Methods

The pathophysiological changes of the FD patients were observed by each method and the results displayed alterations as follows and in Table 1.2 and Table 1.3.

Table 1.2
Results of the different tests between C group and FD group

Item	Index	C group (n = 30)	FD group (n = 35)	T	P
Gastric tolerance	MTV	984.0 ± 70.15	800.28 ± 138.08	6.590	0.000
Visceral sensitivity	10-min Sufficiency score	64.16 ± 10.59	79.85 ± 9.35	-6.342	0.000
	20-min Sufficiency score	43.16 ± 9.95	65.00 ± 13.50	-7.485	0.000
	30-min Sufficiency score	25.00 ± 9.19	40.28 ± 10.97	-6.027	0.000
Gastric Emptying Rate	10 min (GER%)	15.82 ± 10.43	14.91 ± 8.46	-0.389	0.699
	15 min (GER%)	26.67 ± 11.67	19.26 ± 9.38	-2.836	0.060
	20 min (GER%)	37.71 ± 16.69	24.33 ± 9.43	-3.889	0.000
	30 min (GER%)	48.01 ± 13.37	26.71 ± 11.22	-6.790	0.000
Gastric Electrical Rhythm	Preprandial slow wave ratio	68.82 ± 14.20	66.13 ± 12.90	0.738	0.463
	Postprandial slow wave ratio	74.96 ± 11.37	64.25 ± 14.68	3.246	0.002
	Preprandial DF	2.91 ± 0.41	2.81 ± 0.39	0.901	0.371
	Postprandial DF	3.12 ± 0.33	3.01 ± 0.54	0.971	0.336
	PR	1.14 ± 0.11	1.07 ± 0.14	2.257	0.002
Heart rate variability (HRV) analysis	Low frequency (LF); High frequency (HF); LF/HF	normal	disorder		

Table 1.3
Comparison of HRV parameters

HRV index		Preprandia	Postprandia	T	P
C group	LF	0.471 ± 0.091	0.519 ± 0.082	-4.644	0.013
	HF	0.529 ± 0.090	0.481 ± 0.083	4.644	0.013
	LF/HF	0.943 ± 0.334	1.139 ± 0.349	-4.317	0.027
FD group	LF	0.479 ± 0.078	0.458 ± 0.068	1.125	0.269
	HF	0.520 ± 0.078	0.541 ± 0.069	-1.125	0.269
	LF/HF	0.963 ± 0.294	0.874 ± 0.256	1.214	0.233

Gastric tolerance

The maximum gastric tolerance (MTV) was decreased in the FD group compared to that of the C group ($p < 0.05$).

Visceral sensitivity

Compared with those of the C group, scores of bloating (10 min, 20 min, 30 min) in the nutrient meal test were enhanced in the FD group ($p < 0.05$).

Gastric emptying rate

Compared with those of the C group, gastric emptying rates (20-min GER%, 30-min GER%) were reduced in the FD group ($P < 0.05$), but gastric emptying rates (10-min GER%, 15-min GER%) did not decrease significantly ($P > 0.05$).

Gastric electrical rhythm: The slow wave percentages and PR were decreased in the FD group compared to those in the C group ($P < 0.05$). The preprandial and postprandial dominant frequency (DF) had no significant difference between FD group and C group ($P > 0.05$).

Autonomic function: It was showed in Table 1.3, there were autonomic nervous function disorders in FD groups, manifested as that there was no statistically significant difference on LF, HF and LF/HF preprandially and postprandially, while that of C group was normal, manifested as that postprandial LF/HF were increased than preprandial ($P < 0.05$), postprandial HF were decreased than preprandial ($P < 0.05$), postprandial LF were increased than preprandial ($P < 0.05$).

Differential Indexes

From the above results (Table 1.2), the differential index between the two groups could be detected, including MTV, 10-min Sufficiency score, 20-min Sufficiency score, 30-min Sufficiency score, postprandial slow wave ratio, PR, 20-min (GER%), and 30-min (GER%) and autonomic nerve function disorder.

Correlation analysis between two main symptoms and the differential indexes

It is significant to investigate the relationship between the symptom and the pathophysiological alteration. The above results showed that postprandial fullness and early satiety might be the most common and severe symptoms in FD patients. Then, the correlation analysis between two main symptoms and the differential indexes was necessary. We found that (1) postprandial fullness and early satiety were both positively correlated with visceral hypersensitivity (20-min Sufficiency score) ($P < 0.05$); postprandial fullness was positively correlated with visceral hypersensitivity (30-min Sufficiency score) ($P < 0.05$); (2) there was a negative correlation between postprandial fullness and gastric emptying rate at 20 and 30 min ($P < 0.05$); a negative correlation between early satiety and 20 min GER% was also found ($P < 0.05$); (3) postprandial fullness and early satiety were not associated with gastric tolerance ($P > 0.05$); (4) postprandial fullness and early satiety were not associated with PR ($P > 0.05$) (Table 2).

Table 2
Correlation analysis between main symptoms and the differential indexes

Index	Spearman's rho	P ₁	Spearman's rho	P ₂
MTV	0.080	0.647	0.064	0.716
10 min sufficiency score	0.202	0.244	0.140	0.421
20 min sufficiency score	0.381	0.024	0.420	0.021
30 min sufficiency score	0.374	0.027	0.065	0.712
postprandial slow wave ratio	0.188	0.427	0.305	0.191
PR	-0.306	0.073	-0.160	0.359
20-min GER%	-0.464	0.020	-0.419	0.037
30-min GER%	-0.409	0.042	-0.268	0.196
P ₁ : Postprandial fullness symptom; P ₂ : early satiety symptom				

Establishment of MDS

A: represented MTV; B: Sufficiency score (B1: 10-min Sufficiency score, B2: 20-min Sufficiency score, B3: 30-min Sufficiency score); C: gastric electrical rhythm (C1: postprandial slow wave ratio, C2: PR); D: gastric emptying rate, D1:20-min GER%, and D2:30-min GER%. First, we found that there were no correlation between A, B, C, and D. On the other hand, the higher the value of B1, B2 and B3, the worse the variation tendency. The variation tendency was opposite of A, C and D. In addition, the assessment of autonomic nerve function is difficult to quantify, which belongs to qualitative assessment. In this study, the subjective weighting method in the method of determining the weight of the evaluation index was applied and the same we learn from expert analysis method. Therefore, A-B1-B2-B3 + C1 + C2 + D1 + D2 is used to calculate and compare between the FD group and the C group according to multi-index combination method, and the results suggested that there was a statistical difference (Fig. 2). It was indicated that compose of the differential indexes could be applied as MDS to observe pathophysiological alterations of FD patient. Thus, the MDS was established as Fig. 3.

Validation test of MDS

The scores of HAS, HAD and FD symptoms showed no significant difference between S group and FD group, the same as AS group and C group ($P > 0.05$). It showed that the selection of the validation group was reasonable. (Table 3). All items(the differential indexes) of MDS showed no significant difference between AS group and C group ($P > 0.05$). Also, autonomic nerve function of AS group showed a tendency to normal. The indexes of S group displayed a difference from C group ($P < 0.05$), and no significant difference from the FD group ($P > 0.05$). It was proved that MDS could precisely detect the gastric motility alterations of FD patients. It was indicated that MDS could give evidences of the normal or abnormal gastric motility (Table 4).

Table 3
General information of S group and AS group

	S group (n = 15)	AS group (n = 15)	C group	FD group	P₁	P₂	P₃	P₄
HAD	8,33 ± 2.71	4.73 ± 2.01	3.46 ± 1.67	8.70 ± 3.26	0.000	0.000	0.067	0.817
HAS	6.40 ± 2.89	3.73 ± 1.75	2.96 ± 1.49	6.25 ± 2.98	0.001	0.006	0.255	0.924
FD symptoms scores	9.13 ± 4.27	3.53 ± 2.44	1.60 ± 0.81	8.03 ± 3.92	0.000	0.000	0.051	0.379
P ₁ : S group and C group; P ₂ : S group and AS group; P ₃ : AS group and C group. P ₄ : S group and FD group								

Table 4
Assessment via MDS in FD patient between S group and AS group

Index	C group	FD group	Verification group		P ₁	P ₂	P ₃	P ₄
			S group (n = 15)	AS group (n = 15)				
(A)MTV	984.0 ± 70.15	800.28 ± 138.08	775.33 ± 131.14	970.0 ± 127.89	0.000	0.000	0.697	0.608
(B ₁)10 min Sufficiency score	64.16 ± 10.59	79.85 ± 9.35	79.85 ± 9.35	64.16 ± 10.59	0.000	0.000	0.308	0.678
(B ₂)20 min Sufficiency score	43.16 ± 9.95	65.00 ± 13.50	66.33 ± 12.16	49.33 ± 14.49	0.000	0.001	0.101	0.744
(B ₃)30 min Sufficiency score	25.00 ± 9.19	40.28 ± 10.97	39.33 ± 10.33	27.67 ± 10.67	0.000	0.002	0.389	0.776
(C ₁)Postprandial slow wave ratio	74.96 ± 11.37	64.25 ± 14.68	62.42 ± 15.23	72.62 ± 11.55	0.003	0.023	0.522	0.692
(C ₂) PR	1.14 ± 0.11	1.07 ± 0.14	1.02 ± 0.09	1.13 ± 0.12	0.002	0.003	0.807	0.302
(D ₁)20 min (GER%)	37.98 ± 16.93	24.33 ± 9.43	24.49 ± 11.35	32.49 ± 11.34	0.008	0.035	0.265	0.961
(D ₂)30 min (GER%)	48.01 ± 13.37	26.71 ± 11.22	27.28 ± 11.78	33.24 ± 10.46	0.000	0.068	0.051	0.887
Heart rate variability (HRV) analysis	normal	disorder	disorder	11/15 normal 4/15disorder				
P ₁ : S group and C group; P ₂ : S group and AS group; P ₃ : AS group and C group. P ₄ : S group and FD group								

Discussion

This study confirmed that postprandial fullness and early satiety were the most common and most severe symptoms among various symptoms in patients with FD. In the FD group, compared with the C group, the maximum gastric tolerance volume was reduced, and the scores of bloating were increased at 10, 20 and 30 minutes after the nutritional-meal test, indicating a decrease of gastric tolerance and an increase of sensitivity. The gastric emptying rate decreased at 30 minutes, suggesting a delay of gastric emptying in the FD group. The gastric slow wave ratio and the main power ratio decreased after the meal, indicating the disorders of gastric electrical rhythm and gastric motility in FD patients. HRV analysis showed that patients

had a certain degree of disturbance in autonomic function. Also, it was found that postprandial fullness and early satiety were related to visceral sensitivity and gastric emptying. Finally, the differential indexes were screened to construct MDS. MDS was applied to S group and AS group, and all items of MDS showed no significant difference between AS group and C group. The indexes of S group displayed a difference from C group and no significant difference from the FD group. It was proved that MDS could precisely detect the gastric motility alterations of FD patients. The different individual has different pathophysiological changes. MDS may be more comprehensive to capture the alterations than the single test. During the examination, although the subjective feelings of the patients were included, the researchers also recorded the changes in the gastric volume and the scores of symptoms at the same time. The quantitative differences between the examiners could be found, so MDS could provide a part of objective evidence.

Theoretically, the impaired gastric volume can be caused by sensory devices, vagus nerve reflex pathways, intrinsic inhibitory innervation, or disorders of smooth muscle in the proximal stomach. Also, it was found that impaired tolerability may induce adverse symptoms caused by non-relaxing proximal gastric tension changes [24]. Studies on post-infection functional dyspepsia patients had shown that these patients are prone to tolerance disorders, which can be attributed to impaired cholinergic nerve function [25]. On the other hand, changes in neuromodulation caused by anxiety may also have a negative impact on receptive reflexes [26]. In addition, studies had shown that tolerance disorders may be a cause of early satiety, but there was no significant difference in the relationship between early satiety, postprandial fullness, and gastric tolerance in the present study. Different results may be related to differences in sample sizes, ratios of components in nutrient solutions, drinking speeds, and individual differences. For example, Boeckxstaens[27] tested water and specific nutrient solutions at a rapid uptake rate of 100 mL/min and found that tolerance to fluid intake was only found in 50% of FD patients. It is worth noting that the nutritional meal test is economically, non-invasive and easy to implement, but it is not the gold standard for assessing gastric tolerance. Therefore, MDS is required to comprehensively assess gastric function.

In the present study, the liquid load test generally induced more series gastrointestinal symptoms (such as bloating, nausea, and upper abdominal pain) of FD patients. Cause of the above symptoms might be due to decrease in diastolic function and increase in visceral sensitivity [28]; Vanheel found that visceral hypersensitivity is closely related to FD-PDS [29]. Hamer[30]studied the change of capsaicin-sensitive transient receptors (TRPV1) in health and FD patients to investigate the mechanisms of visceral sensitivity. Tack researched the abnormal sensory signals and found hypersensitive reactions at the level of intestinal mechanoreceptors [31]. Samsom and colleagues demonstrated that FD patients developed a more pronounced visceral sensitivity response when exogenous acid entered the duodenum[32]. Other studies have found that FD patients with high-fat and low-fat soups intake induced more symptoms of dyspepsia, for example, satiety, nausea and bloating)[33], however, glucose infusion does not induce such symptoms [34]. The nutritional meal test combined VAS were safer and more practical than fMRI, PET, and electronic constant-pressure technology. So the scores of bloating could indirectly reflect changes in visceral sensitivity and be used as one of the components of MDS. Thus, it is easy to know whether the gastric function is abnormal or not for every FD patients.

In this study, gastric emptying was detected by assaying changes of systolic and diastolic areas in the gastric antrum under the gastrointestinal ultrasonography. The frequency of gastric sinus contraction was not included in this test because it was difficult for sonographers to capture the frequency of contraction as an assessment index within the limited time. Also in this study, electrogastrogram was applied and may detect gastric electrical activity of muscle and reflect effective contraction of the gastric sinus. At the early stage of taking the contrast agent, although the percentage of emptying of the FD patients did not change significantly, the amplitude of gastric antrum contraction was smaller than that of the C group, suggesting that the antral emptying ability of FD patients was lower in the early stage after meal. The pressure in the antrum might be forced to increase due to the weaker contraction movement, but its weak contraction cannot completely push the chyme into the duodenum within a certain period of time, showing gastric emptying being delayed. Within 30 minutes, after taking the contrast agent, the percentage of gastric emptying appeared increasing in both groups and no clear peak, but the gastric emptying rate showed a difference between the two groups at 20 and 30 min after taking oral contrast agent. This study found that there was a certain correlation between postprandial fullness and the percentage of gastric emptying. Some people found gastric emptying abnormalities by using gastric-emptying scintigraphy to record the time after intaking and retention rate about radiolabeled food in the stomach, but this method might cause postprandial fullness, nausea, and vomiting [35]. Although the gastrointestinal ultrasound cannot observe the fundus and corpus of stomach, it was relatively economical and easy to use in clinic than gastric-emptying scintigraphy. Tarek used ultrasound to study the relationship between gastric emptying and dyspeptic symptoms and calories in the diet [36]. Conversely, the study showed that emptying rate was non-absolutely delayed compared to that of the control group [37]. The different results in the above studies had different reasons: differences in the number of cases, living habits, eating habits, mental states, and different methods of gastric emptying. In addition, gastric antrum motility index (MI) was not included in MDS because the recording of MI required experienced clinicians and taken a long time. MDS would be difficult to popularize it in the future if MI was included. Some researcher concluded that a significant delay of emptying is present in less 40% of patients with FD meeting for Rome II [55], but in this study, we concluded a significant change in different pathophysiological tests measured by MDS evaluation in patients with FD meeting for Rome IV, which indicated a potential increase of positive detection rate.

Some studies suggested that disorders of gastric electrical activity after meals in PDS patients may influence different symptoms [38], and the mechanism was considered that electrical rhythm disorders could cause abnormal gastric muscle contraction and abnormal gastric emptying. However, Jebbink did not find any obvious abnormalities of gastric electrical activity in FD patients [39]. Some people believed there was a positive correlation between abnormal EGG and gastric emptying delay [40, 41], whereas others thought gastric emptying abnormalities, visceral sensitivity, and dyspepsia symptoms were related to each other. Lee [42] found that mice in anxious states had increased sensitivities due to gastrointestinal dilatation and abnormal gastric emptying, resulting in functional dyspepsia. Chen [43] found that gastric antrum peristalsis was strengthened and gastric emptying accelerated if stimulating the Zusanli acupoint of FD rats and that the result might be related to the SCF/c-kit signaling pathway. In this study, there was a positive correlation between postprandial fullness, early satiety and gastric emptying ability. Apart from this, gastric emptying disorder was found in female FD patients in a previous study and there was a significant correlation with postprandial fullness and vomiting [44]. However, some studies have failed to confirm that the degree of

gastric emptying is associated with dyspeptic symptoms. It is believed that impaired tolerance and increased sensitivity to gastric dilatation are associated with partial symptoms of FD (e.g., premature saturation, weight loss) [45]. In conclusion, there were some connections between different gastric pathophysiology mechanisms, so it was necessary to establish MDS to research more.

The autonomic nervous system (ANS) regulates gastrointestinal motility by the sympathetic and vagal nerves. A large number of studies have shown that ANS dysfunction affects gastrointestinal motility, which has important effects on mood, pain, early satiety, and other symptoms, and is closely related to FD symptoms [46]. This study found that there were autonomic dysfunctions in the FD group; Similar to this study, Hausken [47] found that the autonomic nerve tension of FD patients is significantly higher than that of healthy people under calm and stressed conditions. Some researchers believed the decrease of LF in HRV is indirectly affected because of changing the relationship between the central nervous system and the enteric plexus. Additionally, some studies have found that there is no difference in these parameters before and after meal [48]. The reasons about different results were that the FD patients were not grouped according to gastric-emptying function in the present study. The study researched that the frequency of gastric antrum contraction was reduced, HF was also reduced and suggested that the reduction of vagal power was related to delayed gastric emptying [49]. However, the cause of delayed gastric emptying remains unclear. Holtmann[50] suggested that the increased visceral sensitivity in FD patients may be associated with vagal dysfunction. The decline of vagus nerve function can also cause abnormal tolerance of the gastric fundus and produce symptoms of early satiety. Detecting autonomic nerves function was a qualitative study. However, MDS for evaluating gastric function showed intuitively which pathophysiology change was abnormal and which one was normal under either qualitative or quantitative research.

Psychological factors (anxiety and depression) in FD patients may aggravate gastrointestinal symptoms [51, 52]. Mild anxiety and/or depression are very common in FD patients, and it is not easy for us to except them in the study. Some of them may need to take anti-anxiety and/or anti-depression agents for relieving the symptoms.

At present, the diagnostic criteria of FD are mainly based on the subjective symptoms. It was indicated from current study that compose of the differential indexes of the above tests (between FD and control groups) could be applied as MDS to observe pathophysiological alterations of FD patients. Another group of FD patients (S group) were selected. They had exactly recovered after treatment and had no any discomfortable for at least 4 weeks(AS group). It was suggested that the MDS was reasonable and believable via the comparison of the items' alterations between S group and AS group. We had not emphasized the treatment method in this article because the purpose of the verification experiment was to verify that MDS could well detect the recovery of gastric motility of the FD patient rather than to verify the efficacy of a treatment plan. MDS may potentially give evidences of gastric motility abnormalities in FD patients. Although Mirim researched that motiliton1 acted on multiple targets involved in the pathophysiology of FD [53], we did not find similar report about the MDS and its significant value in the assessment of FD pathophysiological alterations.

We hoped MDS applying to practical medical care for FD patients. On the surface, it seemed to be complicated, but in fact, the operation process is very simple and some procedures can be used

simultaneously or successively, such as the detection of visceral sensitivity and gastric receptivity and gastric electrical rhythm. The process: 30 min electrogastrogram test—nutritional meal test to detect gastric tolerance —postprandial electrogastrogram test for 30 minutes and postprandial 10 min, 20 min, 30 min VAS score. In addition, the screening and determination of the optimum sub-indicators in future large-scale research will make MDS more streamlined.

Additionally, the sample size of this study was small, so multi-center research will be needed in future studies to increase the sample size of follow-up studies. Although the various methods in our MDS are non-invasive, the design and the accuracy of these assessment methods still require further optimisation. In this study, *Helicobacter pylori* (Hp) infection was not used as an exclusion criterion and HP infection detection was not considered as the composition of MDS because it is one of the more common infections and the highest incidence of Hp infection in developing countries was reported to reach 80%[54]. Subsequent research can be conducted if there will be a sufficient number of samples.

Further research about MDS in the present study will take some time, but comprehensive assessment methods of gastric function might provide a basis for individualized treatment of refractory PDS. In the future, MDS may further guide the development and application of alternative treatment plans and provide a novel detection method for the evaluation of the therapeutic effect. MDS can be further optimized and promoted to help FD patients and provide a reference and research basis for the emergence of more accurate diagnostic methods and individualized treatment plans for FD.

Abbreviations

FD:Functional dyspepsia

PDS: Postprandial distress syndrome

EPS: Epigastric pain syndrome

VAS: Visual analogue scale

HRV: Heart rate variability

HP: *Helicobacter pylori*

GER%: Gastric emptying rate

LF: Low frequency

HF: High frequency

Declarations

Statements

Availability of data and materials

The dates used and analyzed during the current study available from the corresponding author on reasonable request.

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Ethics approval and consent to participate

The Ethics Committee of First Affiliated Hospital of Dalian Medical University Ethical approved the report of scientific research project. All methods were performed in accordance with the relevant guidelines and regulations. It confirmed that project program and informed consent were reviewed. All the human subjects in the study had signed the informed consent. (Approval number PJ-KS-KY-2018-05 (X)).

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Contributions

JY and YY designed the research study, prepared the manuscript, and analyzed data. MXL, XYW, LXW, DY, and ZFX contributed to acquisition and interpretation of data. JY and XYS, analyzed and calculated the data. MXL and XYW provided Gastrointestinal ultrasonography data. ZJD ,JDC and XKH contributed to the study design, revising it critically for important intellectual content, and gave final approval of the version to be submitted. All authors read and approved the final manuscript.

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Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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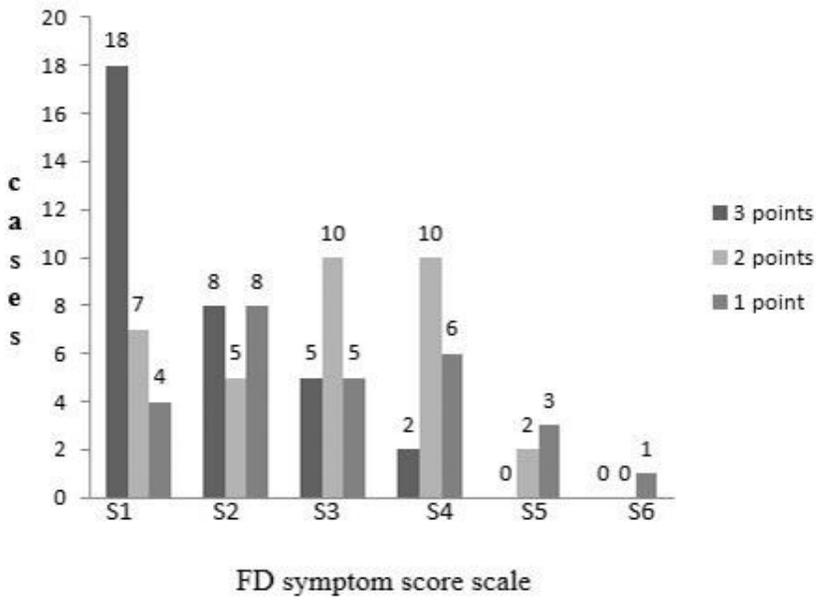
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Figures

A



B

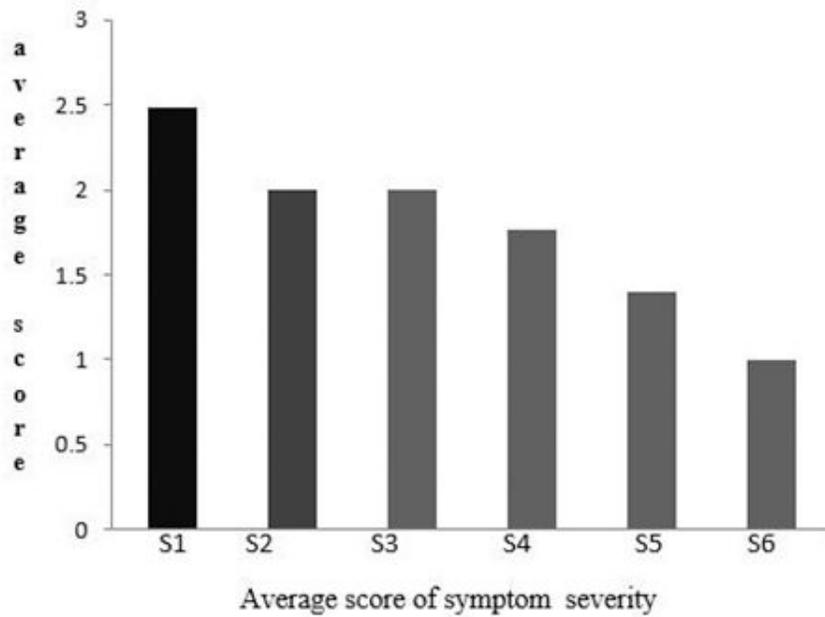


Figure 1

Scores of FD symptoms and symptom severity S1: postprandial fullness; S2: early satiety; S3: middle and upper abdominal pain; S4: burning sensation; S5: sputum; S6: retching

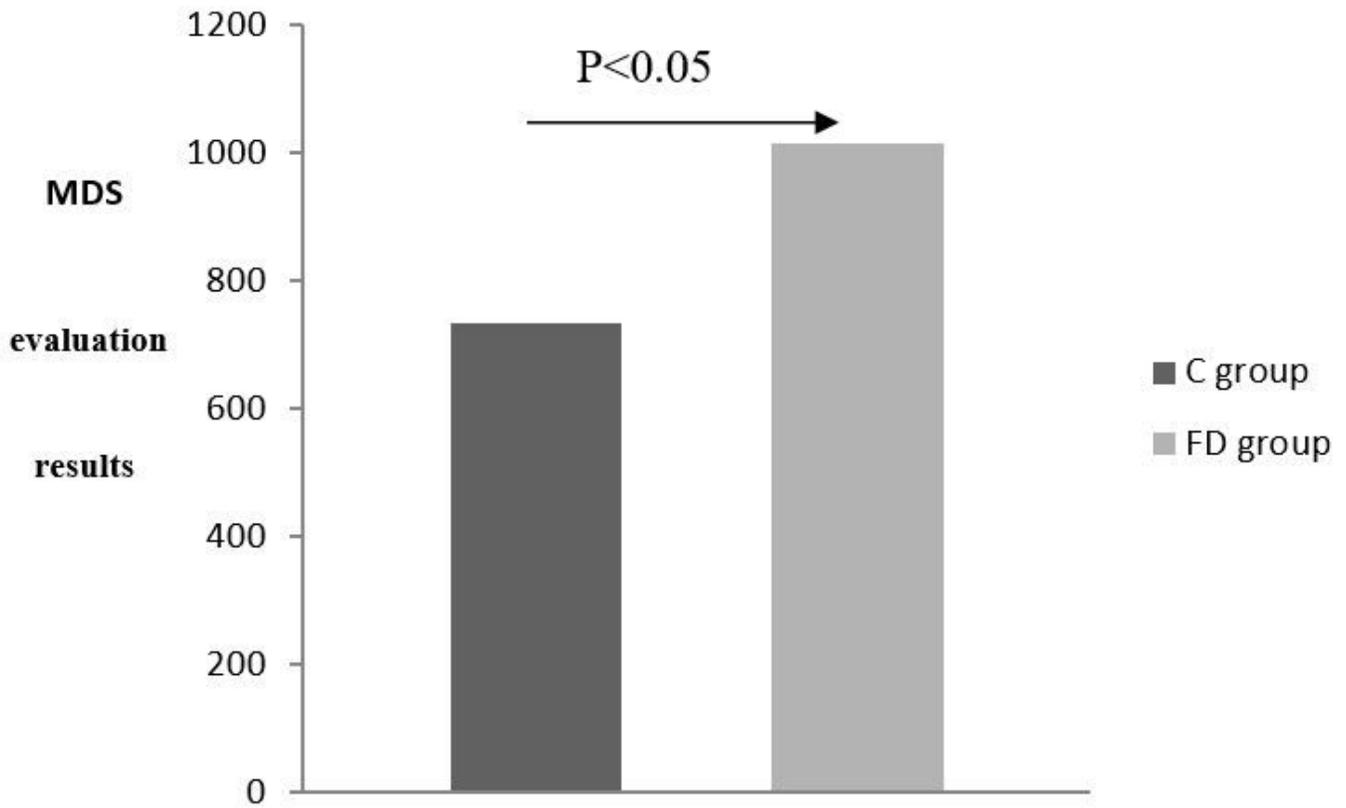


Figure 2

Evaluation results via MDS between C group and FD group

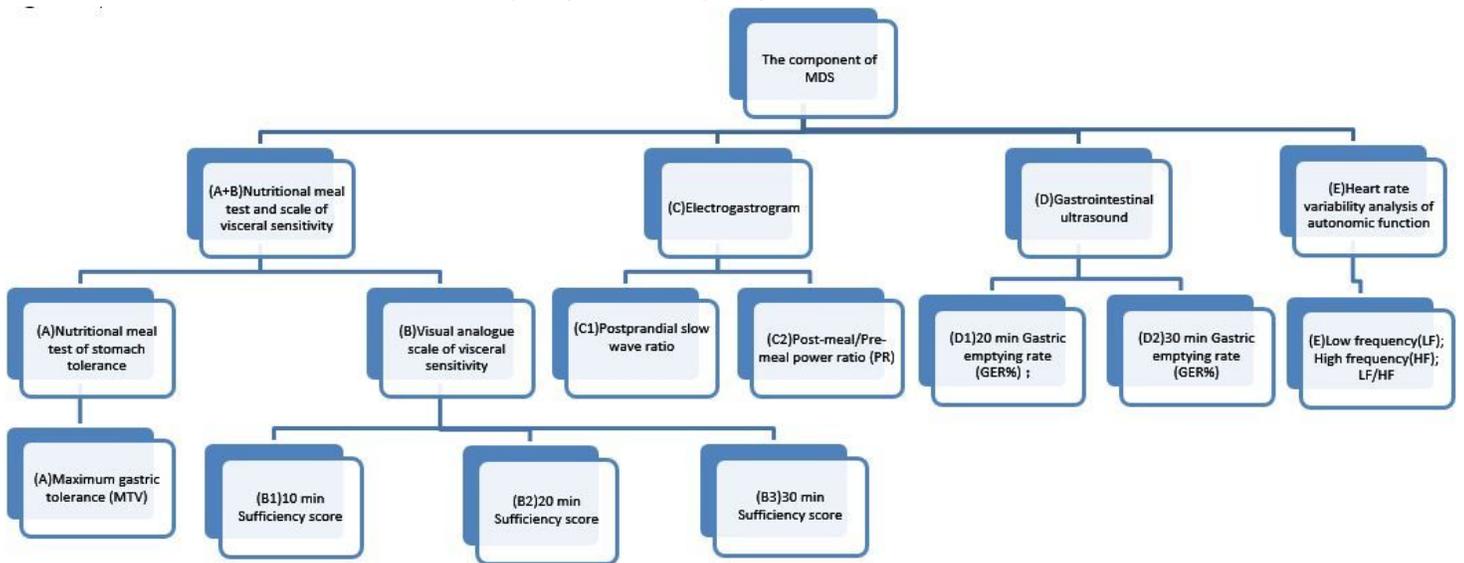


Figure 3

The component of MDS

Supplementary Files

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