Analysis of Esophageal Motility and Reflux Characteristics in Patients with Gastroesophageal Reflux Disease With or Without Extraesophageal Symptoms

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ABSTRACT

Background: *The pathogenesis of extraesophageal symptoms of gastroesophageal reflux disease is complex, and esophageal motility and reflux may be involved in it. In this study, we aimed to compare esophageal motility and reflux characteristics in gastroesophageal reflux disease patients with and without extraesophageal symptoms by high-resolution manometry and multichannel intraluminal impedance-pH monitoring.*

Methods: *We retrospectively studied gastroesophageal reflux disease patients between January 2014 and December 2018. All patients had undergone high-resolution manometry and multichannel intraluminal impedance-pH monitoring. The results were compared and analyzed.*

Results: *A total of 59 patients were included in this study. Patients were divided into 3 groups according to their main complaint: only typical symptoms (group A, n = 11), both typical and extraesophageal symptoms (group B, n = 33), and only extraesophageal symptoms (group C, n = 15). Compared with group A, the lower esophageal sphincter basal pressure, integrated residual pressure, and lower esophageal sphincter length were lower, and the proximal reflux percentages of a weak acid and non-acid reflux were higher in group B and group C ($P < .017$). The positive rate of esophageal motility disorders was lower in group A than in other groups ($P < .05$). The proportion of patients with multiple rapid swallows/single swallow—distal contractile integral ratio greater than 1—was higher in group A than in other groups ($P < .05$).*

Conclusions: *Decreased lower esophageal sphincter pressure and lower esophageal sphincter length, increased proximal esophageal reflux of weak acid and non-acid reflux, esophageal motility disorders, and decreased peristaltic reserve are involved in the pathogenesis of extraesophageal symptoms of gastroesophageal reflux disease.*

Keywords: *Esophageal motility disorders, esophageal pH monitoring, extraesophageal symptoms, gastroesophageal reflux, high-resolution manometry*

INTRODUCTION

Gastroesophageal reflux disease (GERD) refers to troublesome symptoms or complications caused by the reflux of gastric contents.[1] The typical symptoms are heartburn and regurgitation. Besides, there are some extraesophageal symptoms, including chronic cough, hoarseness, dysphagia, globus sensation, etc.[2] At present, proton pump inhibitors (PPIs) are the first choice for GERD, but in patients with extraesophageal symptoms, the treatment effect is often poor.[3-5] Therefore, it is necessary to fully understand the pathogenesis of extraesophageal symptoms, which can guide the diagnosis and treatment of GERD.

Abnormal esophageal motility and increased acid reflux are both important pathogenesis of GERD. Compared with patients with typical symptoms, whether GERD patients with extraesophageal symptoms have more severe esophageal motility disorders and acid reflux is still unclear.

High-resolution manometry (HRM) is considered the gold standard for the diagnose of esophageal dyskinesia,[6] and a 24-hour multichannel intraluminal impedance-pH monitoring (MII-pH) is a relatively new auxiliary examination, which is used to evaluate bolus transport and reflux types including acid, weak acid, and weak alkaline.[7] In this study, we use HRM and MII-pH to analyze the esophageal motility and reflux characteristics in GERD patients with and without extraesophageal symptoms, aiming to further clarify the influencing factors of GERD extraesophageal symptoms.

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MATERIALS AND METHODS

Patients

We retrospectively analyzed the data of patients who attended our gastroenterology clinic from January 2014 to December 2018 and were diagnosed with GERD by gastroscopy or MII-pH. Patients with GERD included in the study met the following inclusion criteria: (1) typical symptoms (heartburn and/or regurgitation) or the extra-esophageal symptoms (such as laryngopharyngeal reflux, chest pain, and so on) and (2) undergone esophageal HRM, (3) gastroscopy revealed reflux esophagitis (RE) or pathologic acid reflux was confirmed by MII-pH in those with negative endoscopy. For patients with extraesophageal symptoms, only those with symptom association probability > 95% or symptom index SI> 50% could be included in this study. Patients with the following were excluded from this study: (1) some diseases (such as achalasia and scleroderma) that can affect esophageal motility, (2) other definite diseases that can cause extra-esophageal symptoms, (3) tumors or peptic ulcer verified by endoscopy, and (4) undergone upper abdominal surgery. This study was approved by the Medical Ethics Committee (Approval No. 2016(20K)).

High-resolution manometry

Preparation before examination: patients were required to discontinue any drug known to affect esophageal motility (e.g., calcium channel blockers and prokinetic agents) for at least 7 days before the examination, and patients were asked to fast for 6-8 hours before the test.

Equipment: the high-resolution solid-state esophageal manometry system (ManoScan System, Given Imaging, Los Angeles, CA, USA) and 36-channel electrode catheter were used for HRM.

Examination process: patients were in a sitting position, and the HRM catheter was inserted through the nose and then fixed in the correct position. Then, they changed to a supine position. Five minutes after acclimatization to the catheter, the collection of the basal pressure was completed. First, the patients were given 10 swallows (5 mL water each) at intervals of 20-30 seconds. After that, they were given 5 swallows (2 mL water each) separated by 2-3 seconds intervals, which were called multiple rapid swallows (MRS). After all the above operations were completed, the HRM examination was finished, and the catheter was pulled out. And, the dedicated software (ManoView ESO v3.0) was used for manometric data analysis.

Multichannel intraluminal impedance-pH monitoring

Preparation before examination: patients were required to discontinue H_2 receptor antagonists and PPI at least 7 days before the examination. Patients would receive this test when they had completed HRM.

Equipment: the AccuTrac pH-Z recorder and pH/Z antimony electrode (Given Imaging, USA) were used for MII-pH.

Examination process: before the operation, the catheter was precalibrated in buffers with pH of 4 and 7. Patients were in a sitting position, and the MII-pH catheter was inserted from the nose and placed 5 cm above the lower esophageal sphincter (LES), which was identified by HRM. During the monitoring period, patients should maintain the usual lifestyle and diet and record the time of meal, time of supine position, and time of any reflux symptoms. After 24 hours, all data were imported into the computer and analyzed by the dedicated software (AccuView 5.2).

Acid exposure time (AET) refers to distal esophageal acid exposure time with pH < 4. AET > 6% is defined as pathologic acid reflux.

Statistical Analysis

Data analysis was performed using SPSS version 23 software. Enumeration data were expressed as count (percentage), and Pearson's chi-square test or Fisher's exact test was used for the comparison of multiple groups. Measurement data with a normal distribution were expressed as mean ± SD, and one-way analysis of

Main Points

- *The pathogenesis of extraesophageal symptoms of gastroesophageal reflux disease (GERD) has not been fully elucidated, but esophageal motility disorders and reflux are involved in it.*
- *Compared with patients with only typical symptoms, the lower esophageal sphincter (LES) basal pressure, integrated residual pressure, LES length were lower, and the proximal reflux percentages of a weak acid and non-acid reflux were higher in patients with extraesophageal symptoms.*
- *Extraesophageal symptoms of GERD are related to esophageal motility disorders and the peristaltic reserve of the esophagus.*
- *These results can serve as a reference for future studies on the pathogenesis and drug treatment for extraesophageal symptoms of GERD.*

variance was used for the comparison of multiple groups. Measurement data with non-normal distribution data were expressed as median (first quartile and third quartile), and Kruskal–Wallis non-parametric test was used for the comparison of multiple groups. A P value < .05 was considered statistically significant. In multiple comparisons, the pairwise comparison test level was adjusted to 0.05/number of comparisons.

RESULTS

A total of 59 GERD patients (26 males and 33 females) were included in our retrospective study. The average age was 57.98 ± 9.36 years. The average body mass index (BMI) was 23.33 ± 3.15 kg/m^2.

Patients were divided into 3 groups according to their main complaint. There were 11 patients in group A (only typical symptoms), 33 patients in group B (both typical and extraesophageal symptoms), and 15 patients in group C (only extraesophageal symptoms). As shown in Table 1, we compared the age, gender, and BMI of patients in the 3 groups and found there was no statistically significant difference in these characteristics (P > .05).

High-Resolution Manometry Parameters

We analyzed the HRM parameters of patients in the 3 groups and found there were significant differences in the LES length, integrated residual pressure (IRP), and LES basal pressure among the 3 groups (P < .05). And, there were no significant differences in the length of the esophagus, upper esophageal sphincter (UES) basal pressure, UES residual pressure, distal contractile integral (DCI), and distal latency among the 3 groups (P > .05). All HRM parameters of the 3 groups are shown in Table 2, and the pairwise comparisons of significantly different data are shown below the tables (P < .017 was considered statistically significant because of multiple comparisons). Compared with group A, the LES length, IRP, and LES basal pressure were lower in group B and group C (P < .017). But, there were no statistically significant differences in these parameters between group B and group C (P > .017).

Table 1. Demographic

	Group A (n = 11)	Group B (n = 33)	Group C (n = 15)	P
Age	60.64 ± 9.45	57.52 ± 9.79	57.07 ± 8.54	.51[a]
Gender				.85[a]
Male	4 (36.4)	15 (45.5)	7 (46.7)	
Female	7 (63.6)	18 (54.5)	8 (53.3)	
BMI	24.19 ± 4.06	23.13 ± 2.55	23.12± 3.72	.63[b]

Group A, only typical symptoms; Group B, both typical and extraesophageal symptoms; Group C, only extraesophageal symptoms.
BMI, body mass index. P values: [a]Kruskal–Wallis test, [b]Fisher's exact test.
Value presented as mean ± standard deviation, or N (column %).

Table 2. High-Resolution Manometry Parameters

	Group A (n = 11)	Group B (n = 33)	Group C (n = 15)	P
Esophageal length (cm)	24.3 (21.2, 26.1)	25.8 (24.0, 26.9)	26.0 (23.0, 27.8)	.30
UES basal pressure (mmHg)	66.5 (42.5, 73.4)	61.9 (44.2, 95.9)	73.5 (35.9, 89.3)	.86
UES residual pressure (mmHg)	5.4 (3.6, 6.2)	6.4 (1.2, 10.2)	4.4 (1.0, 7.6)	.65
LES basal pressure (mmHg)	15.3 (12.3, 20.2)	11.3 (9.0, 12.3)	10.7 (8.3, 13.1)	**.008**
IRP (mmHg)	7.2 (5.7, 9.0)	5.1 (1.6, 6.8)	4.3 (2.4, 5.2)	**.006**
LES length (cm)	3.1 (2.8, 3.8)	2.6 (2.1, 3.0)	2.4 (2.1, 2.9)	**.022**
DCI (mmHg·s·cm)	844.4 (821.1, 1320.1)	866.2 (290.1, 1097.3)	694.3 (322.1, 1238.2)	.37
DL (s)	6.4 (5.6, 8.0)	6.5 (5.8, 7.8)	6.3 (5.3, 6.5)	.41

Group A, only typical symptoms; Group B, both typical and extraesophageal symptoms; Group C, only extraesophageal symptoms. UES, upper esophageal sphincter; LES, lower esophageal sphincter; IRP, integrated residual pressure; DCI, distal contractile integral; DL, distal latency. Statistically significance values are given in bold.
Values presented as median (first quartile and third quartile).
P values:
LES basal pressure: A versus B, P = .007; A versus C, P = .003; B versus C, P = .46.
IRP: A versus B, P = .008; A versus C, P = .002; B versus C, P = .35.
LES length: A versus B, P = .014; A versus C, P = .011; B versus C, P = .61.

Diagnosis of Esophageal Motility Disorders

According to the Chicago Classification v3.0,[8] the diagnosis of esophageal motility of patients in the 3 groups is presented in Table 3. There were significant differences among the 3 groups (P < .05).

Peristaltic Reserve of the Esophagus

Multiple rapid swallow is a complementary test of HRM. It can reflect the peristaltic reserve of the esophagus.[9] Generally speaking, the MRS/single swallow (SS)—DCI ratio greater than 1—is considered normal.[10] We calculated the ratio of MRS/SS-DCI in patients with and

Table 3. The Diagnosis of Esophageal Motility Disorders

	Group A (n = 11)	Group B (n = 33)	Group C (n = 15)	*P*
Esophageal motility disorders				**.029**
Normal esophageal motility	9 (81.8)	11 (33.3)	3 (20.0)	
Fragmented peristalsis	0 (0)	2 (6.1)	2 (13.3)	
Ineffective esophageal motility	2 (18.2)	19 (57.6)	10 (66.7)	
Absent contractility	0 (0)	1 (3.0)	0 (0)	

Group A, only typical symptoms; Group B, both typical and extraesophageal symptoms; Group C, only extraesophageal symptoms. Statistically significance values are given in bold.
Values presented as count (percentage).
P values: Fisher's exact test.

without extraesophageal symptoms. Of the patients with only typical symptoms, 27.3% (3/11) had a DCI ratio less than 1 and 72.7% (8/11) had a DCI ratio greater than 1. Of the patients with both typical and extraesophageal symptoms, 66.7% (22/33) had a DCI ratio less than 1 and 33.3% (11/33) had a DCI ratio greater than 1. Of the patients with only extraesophageal symptoms, 73.3% (11/15) had a DCI ratio less than 1 and 26.7% (4/15) had a DCI ratio greater than 1. The comparisons are shown in Figure 1. There were significant differences in the DCI ratio among the 3 groups ($P = .044$, Fisher's exact test).

Reflux Characteristics

The results of MII-pH of patients in GERD patients with and without extraesophageal symptoms are shown in table 4, and the pairwise comparisons of significantly different data are shown below the tables ($P < .017$ was considered statistically significant because of multiple comparisons). Compared with group A, the proximal reflux percentages of a weak acid and non-acid were higher in group B and group C ($P < .017$). But, there were no statistically significant differences between group B and group C ($P > .017$).

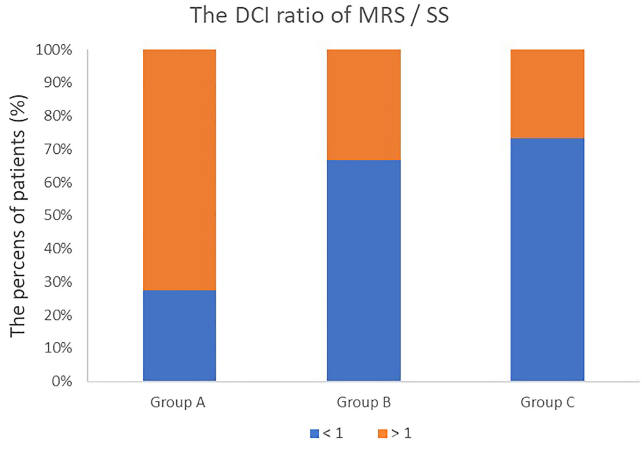

Figure 1. The DCI ratio of multiple rapid swallows (MRS)/single swallow (SS) in different groups.

DISCUSSION

In clinic practice, extraesophageal symptoms are common in patients with GERD. Min et al[11] conducted a questionnaire survey on 1712 GERD patients in 64 hospitals in South Korea and found that the prevalence of extraesophageal symptoms was as high as 90.3%. Since the pathogenesis of extraesophageal symptoms of GERD is complex, there is still a lack of standard or effective treatment. In the present study, we attempted to find some characteristics of esophageal motility and acid reflux in GERD patients with extraesophageal symptoms, which may provide some ideas for disease treatment.

With the clinical application of HRM, the diagnosis of esophageal motility and the measurement of LES pressure and length become simpler than before. Knight et al[12] performed esophageal manometry on 100 patients with laryngopharyngeal reflux (LPR) symptoms and found that almost half of them had ineffective esophageal motility (IEM) and that about 10% of them had hypertensive LES. Diener et al[13] studied the diagnosis of esophageal motility of 1006 GERD patients and found that respiratory symptoms were more severe in patients with IEM and that the IEM patients had a shorter and weaker LES compared with the normal patients. However, Kim et al[14] demonstrated that there was no association between IEM and LPR. In our study, the patients with only typical symptoms had a longer LES length and higher LES pressure than patients who had extraesophageal symptoms. Besides, the positive rate of esophageal motility disorders was lower in patients with only typical symptoms. The differences in the conclusions of these studies may be due to the different patients with extraesophageal symptoms included. This study included those with various symptoms such as LPR, chronic cough, and so on, and the study by Knight et al[12] and Kim et al[14] focused on those with LPR.

MRS is a complementary test of HRM. It can reflect the peristaltic reserve of the esophagus.[9] Jain et al[15] did a retrospective analysis with 68 GERD patients (38 normal

Table 4. The Reflux Characteristics in Different Groups

	Group A (n = 25)	Group B (n = 65)	Group C (n =36)	*P*
AET (%)	8.8 (6.6, 10.4)	9.0 (7.0, 13.4)	9.9 (6.9, 21.5)	.54
DeMeester score	33.6 (23.4, 42.0)	35.5 (27.1, 42.9)	38.1 (27.3, 73.6)	.50
Number of acid reflux (n)	11 (9, 19)	12 (5, 16)	15 (9, 23)	.25
Number of weak acid reflux (n)	5 (4, 10)	9 (6, 15)	10 (4, 10)	.08
Number of non-acid reflux (n)	2 (1, 6)	3 (2, 5)	5 (3, 7)	.09
The proximal reflux percentages of acid reflux (%)	63.2 (52.6, 88.9)	66.7 (47.6, 89.7)	77.8 (60.0, 91.3)	.61
The proximal reflux percentages of weak acid reflux (%)	39.1 (20.0, 58.3)	57.1 (43.7, 75.0)	66.7 (50.0, 80.8)	**.018**
The proximal reflux percentages of non-acid reflux (%)	16.7 (10.0, 33.3)	33.3 (20.9, 62.0)	33.3 (20.0, 50.0)	**.019**

Group A: only typical symptoms; Group B: both typical and extraesophageal symptoms; Group C: only extraesophageal symptoms.
Values presented as median (first quartile, third quartile).
AET, acid exposure time
P value: Kruskal–Wallis test.
The proximal reflux percentages of weak acid reflux: A versus B, *P* = .012; A versus C, *P* = .008; B versus C, *P* = .57.
The proximal reflux percentages of non-acid reflux: A versus B, *P* = .010; A versus C, *P* = .011; B versus C, *P* = .713.

motility and 30 minor motility disorders) and found that the latter had a higher frequency of poor peristaltic reserve and showed significant discordance in the inhibition phase of MRS. However, there is still a lack of studies on the relationship between the peristaltic reserve and extraesophageal symptoms of GERD. In this study, we found GERD patients who had extraesophageal symptoms had poorer peristaltic reserve compared with patients with only typical symptoms. Shaker et al[16] conducted a study of 63 patients who underwent antireflux surgery and found that lack of augmentation of smooth muscle contraction following MRS is associated with late postoperative dysphagia following antireflux surgery. So, patients with extraesophageal symptoms may not be suitable to undergo antireflux surgery. Anyway, more studies are needed to confirm the relationship among extraesophageal symptoms, peristaltic reserve, and antireflux surgery.

Acid reflux is important pathogenesis of GERD, but weak acid and non-acid reflux also play an indispensable role in it. Fornari et al[17] analyzed the impedance-pH results of 11 healthy subjects and 76 GERD patients and found that nocturnal weakly acidic reflux was as common as acid reflux in patients with GERD. Cronin et al[18] demonstrated that weak acid reflux could increase the expression of NF-kB, which contributed to esophageal epithelial barrier dysfunction, and cause the occurrence of GERD symptoms. Patterson et al[19] found that non-acid reflux episodes reaching the pharynx were important factors associated with cough. Johnston et al[20] reported that pepsin in non-acidic refluxate can damage hypopharyngeal epithelial cells. In this study, we found that proximal reflux percentages of weak acid and non-acid reflux were higher in patients who had extraesophageal symptoms, which was consistent with previous studies. Compared with acid reflux, weak acid and non-acid reflux are more likely to damage the pharynx and cause the extraesophageal symptoms of GERD.

There were some limitations in this study. It was a retrospective study, and the results should be confirmed in a future prospective study. Besides, the number of patients is not large enough, so we cannot further group patients with extraesophageal symptoms based on their different symptoms. In the future, we will include more patients and healthy volunteers for further research, which can help us to better understand the pathophysiology of GERD with or without extraesophageal symptoms.

In summary, we retrospectively analyzed the data of HRM and MII-pH of GERD patients with and without extraesophageal symptoms. We found that decreased LES pressure and LES length, increased weak acid and non-acid reflux in the proximal esophagus, esophageal motility disorders, and decreased peristaltic reserve are involved in the pathogenesis of extraesophageal symptoms of GERD. And, we hope these results can serve as a reference for future studies on the pathogenesis and drug treatment for extraesophageal symptoms of GERD.

Ethics Committee Approval: The study was approved by the medical ethics committee of Medical Ethics Committee of Zhejiang Hospital (No: 2016[20K]).

Informed Consent: All patients included in this study had signed an informed consent form.

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Author Contributions: Consept – P.Z.; Design – Y.C., G.J.; Supervision – P.Z.; Resources – P.Z.; Materials – P.Z.; Data Collection and/or Processing – G.J., Y.C.; Analysis and/or Interpretation – G.J., Y.C.; Literature Search – G.J., F.Z.; Writing Manuscript – G.J., Y.C.; Critical Review – P.Z.

Declaration of Interests: The authors declare that they have no competing interest.

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