

Original Article

A study on the esophageal dynamics in patients with gastroesophageal reflux disease and with refractory cough undergoing esophageal high-resolution manometry

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Abstract: Objective: To analyze the esophageal dynamics in patients with gastroesophageal reflux disease (GERD) and with refractory cough while undergoing esophageal high-resolution manometry (HRM). Methods: A total of 32 patients with GERD and with refractory cough and 48 patients with GERD admitted to our hospital from February 2019 to July 2020 were assigned to the combined group and the GERD group, respectively, and 40 healthy volunteers were assigned to the healthy group. All the patients underwent HRM. The lower esophageal sphincter (LES) and the upper esophageal sphincter (UES) parameters, the types of peristalsis of the esophageal body, the esophageal body motility, the i relaxation of LES and UES incidence rates, and the esophageal body motility disorders were compared among the three groups. Results: The combined group and the GERD group had lower esophageal sphincter pressure (LESP) levels and lower 4-s integrated relaxation pressure (4 s IRP) levels, shorter lower esophageal sphincter lengths (LESL), and higher frequencies and longer durations of transient lower esophageal sphincter relaxation (TLESR) compared with the healthy group ($P < 0.05$). The upper esophageal sphincter lengths (UESL) in the GERD group were longer than they were in the healthy group ($P < 0.05$). Compared with the healthy group and the GERD group, the combined group had longer distal latencies (DL), break distances, and peristaltic breaks (PB), longer large and small peristaltic breaks, a greater number of ineffective swallows, lower upper esophageal sphincter pressure (UESP) levels, distal contraction integrals (DCI), contractile front velocities (CFV), and a higher incidence rate of esophageal body motility disorders ($P < 0.05$). Conclusion: Patients with GERD and with refractory cough often also have esophageal body motility disorders, longer PB, elevated UESP levels, and lower DCI. HRM can be used to objectively evaluate the esophageal dynamics and to differentiate among diseases.

Keywords: Gastroesophageal reflux disease, refractory cough, esophageal high-resolution manometry, esophageal dynamics

Introduction

Gastroesophageal reflux disease (GERD) refers to the symptoms or complications caused by the reflux of gastroduodenal contents to the oral cavity, throat, esophagus or lungs. The pathogenesis of GERD involves esophageal and gastric motility disorders [1, 2]. The typical reflux symptoms of GERD are reflux and pyrosis, and the atypical symptoms include dysphagia, pharyngeal foreign body sensations, and epigastric pain. In addition, some patients also have extraesophageal symptoms (e.g., asthma,

cough, and laryngopharyngitis) [3, 4]. Refractory cough is defined as a chronic cough that is hard to diagnose and treat. It leads to delayed healing and can easily induce chronic, persistent injuries [5]. Currently, the pathogenesis of GERD with refractory cough remains to be improved and illuminated, but it is generally thought to be related to esophageal-bronchial reflex, micro-inhalation, neuron dysfunction, mentality and psychology, and immune mediation [6]. A study suggests that most GERD patients also have an esophageal motility disorder, and the main manifestations are achala-

sia of cardia, high-amplitude peristaltic contractions of the esophageal body, and diffuse spasms of the esophagus [7]. However, there is no common consensus regarding whether there are differences between the esophageal motility characteristics and GERD in patients with GERD and refractory cough.

Esophageal manometry is the “gold standard” for evaluating esophageal motor function. Esophageal high-resolution manometry (HRM), with its high spatial resolution, can simultaneously monitor the peristaltic and contractile functions of the esophagus and can reveal the functional anatomical structure of the gastroesophageal junction. A “three-dimensional spatial image” obtained using HRM data clearly shows the esophageal motor function from the pharynx to the stomach [8, 9]. However, most patients with GERD and with refractory cough do not show the typical symptoms, and studies on the esophageal dynamic characteristics of patients with GERD and with refractory cough undergoing HRM have been rarely reported. Therefore, this study compares the esophageal motility characteristics of patients with GERD and with refractory cough, patients with GERD alone, and healthy volunteers undergoing HRM, aiming to analyze the relationship between esophageal motility disorders and disease occurrence and progression. It is reported as follows.

Materials and methods

Clinical data

A total of 32 patients with GERD and with refractory cough and 48 patients with GERD admitted to our hospital from February 2019 to July 2020 were assigned to the combined group and the GERD group, respectively, and 40 healthy volunteers were assigned to the healthy group. This study was approved by the Ethics Committee of Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China. All study participants provided written informed consent before participating in the study. Inclusion criteria: the *Guidelines for Primary Diagnosis and Treatment of Gastroesophageal Reflux Disease* [10] was referred to regarding the diagnostic criteria for GERD, the patients' conditions were confirmed using endoscopy, and no esophageal mucosa damage was observed. The typi-

cal reflux symptoms (e.g., heartburn and sour regurgitation), and the 24-hour esophageal pH monitoring results indicated pathological acid reflux, patients with no intake of drugs affecting gastrointestinal motility within 1 week before enrollment, the *Guidelines for Diagnosis and Treatment of Cough* [11] were referred to regarding the diagnostic criteria for refractory cough, and the onset time was > 8 weeks, and the patients voluntarily signed the informed consent forms. Exclusion criteria: patients also suffering from alimentary tract tumors, esophageal hiatal hernias, and gastroduodenal ulcers, and patients with a history of upper digestive tract surgery, patients with a cough caused by variant asthma, primary respiratory diseases, postnasal drip syndrome, or eosinophilic bronchitis, patients with language or mental disorders, patients also suffering from rheumatic immune system diseases, nervous system diseases, or severe circulatory system diseases, patients treated with H₂ receptor blockers, proton pump inhibitors, calcium channel blockers, or ACEI and gastrointestinal motility drugs one week before their enrollment, and patients who were pregnant or lactating.

Methods

Instruments: A Solar GI 22-channel water-perfused esophageal high-resolution manometry system (MMS, the Netherlands) was selected. There were 22 channels, including 6 channels in the lower esophageal sphincter with an interval of 1 cm, 1 channel in the stomach, and 15 channels in the esophageal body, with an interval of 2 cm.

Examination methods on the day of examination

The patients were denied access to water for 4 h and food for 6 h. The HRM catheter was intubated through the patients' nostrils. After a successful intubation, each patients was placed in a decubitus position, the catheter depth was adjusted according to the height, and the catheter was fixed. 3-5 min later, the 30-s resting pressure was measured (note: swallowing actions were not allowed within 30 s), the patients were instructed to swallow 5 mL of water each time for 10 times every 20-30 s, the swallowing waves (10 times) were collected, the data were stored, the manometric catheter was pulled out, and the pressure measurement ended.

Table 1. A comparison of the general data among the three groups (n/ $\bar{x} \pm S$)

Group	Number of cases	M/F	Age (yo)	BMI (kg/m ²)	Course of GERD (years)	Course of refractory cough (weeks)	History of smoking	History of drinking
Healthy group	40	23/17	53.4±6.2	22.65±1.98	-	-	10	6
GERD group	48	26/22	52.9±5.8	22.06±2.03	1.75±0.32	-	16	9
Combined group	32	19/13	53.2±6.1	23.16±2.37	1.98±0.45	15.26±3.15	9	4
χ^2/F		0.229	0.077	2.678	2.673	-	0.756	0.594
<i>P</i>		0.892	0.926	0.073	0.009	-	0.685	0.743

Observational indices

The parameters of the lower esophageal sphincter: The parameters included lower esophageal sphincter pressure (LESP), lower esophageal sphincter length (LESL), 4-s integrated relaxation pressure (4 s IRP), and the frequency and duration of the transient lower esophageal sphincter relaxation (TLESR), and the Holloway method was referred to regarding the diagnostic criteria for TLESR.

The parameters of the upper esophageal sphincter: The parameters included the upper esophageal sphincter length (UESL) and the upper esophageal sphincter pressure (UESP).

Types of peristalsis of the esophageal body: < 2 cm of defect in the transformation zone indicated euperistalsis, > 5 cm of defect in the transformation zone indicated large peristaltic breaks, 2-5 cm of defect in the transformation zone indicated small peristaltic breaks, aperistalsis indicated an ineffective swallow, and a distal latency (DL) < 4.5 s or CFV > 9 m/s indicated a synchronous contraction.

The esophageal body motility parameters: The 2012 Chicago Classification [12] was referred to regarding the parameters: DL, contraction integral (DCI), contractile front velocity (CFV) and peristaltic break (PB), and break distance.

Statistical information regarding the incidence rates of the relaxation of the lower esophageal sphincter (LES), the upper esophageal sphincter (UES), and the esophageal body motility disorders in each group was collected.

Statistical analysis

SPSS 23.0 was used for the statistical analysis. The measurement data were expressed using $\bar{x} \pm s$. The comparisons between groups were

analyzed using independent sample *t* tests, and the enumeration data were expressed using %, and analyzed using χ^2 tests. *P* < 0.05 indicated a statistically significant difference.

Results

General data

There were no statistically significant differences in terms of gender, age, body mass index (BMI), or smoking and drinking history between the two groups (*P* > 0.05), indicating that the groups were comparable, but the course of disease in the combined group was significantly longer than it was in the GERD group, showing a statistically significant difference (*P* < 0.05) (**Table 1**).

The lower esophageal sphincter parameters

The combined group and the GERD group had lower LESP and 4 s IRP levels and a shorter LESL compared with the healthy group (*P* < 0.05). There was no statistically significant difference in the LESP, LESL, or 4 s IRP levels between the combined group and the GERD group (*P* > 0.05), signaling that LES was closely related to the pathogenesis of GERD and GERD with refractory cough (**Figure 1**).

TLESR

The combined group and the GERD group had higher frequencies and longer durations of TLESR compared with the healthy group (*P* < 0.05). There were no statistically significant differences in the frequency and duration of TLESR between the combined group and the GERD group (*P* > 0.05), suggesting that TLESR was not significantly correlated with the pathogenesis of GERD with refractory cough (**Table 2**).

Gastroesophageal reflux disease

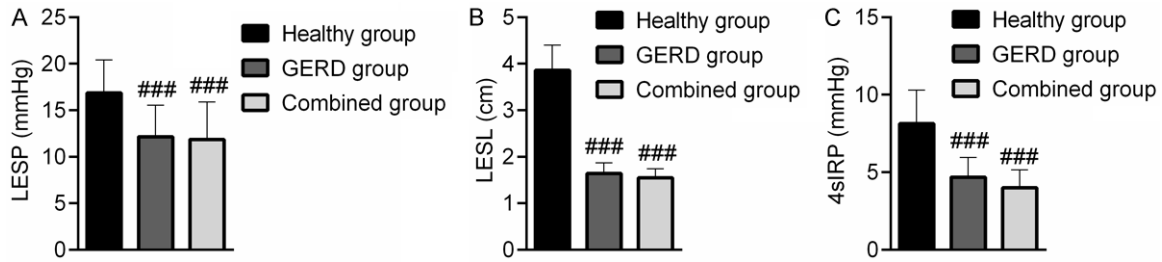


Figure 1. A comparison of the lower esophageal sphincter parameters among the three groups. Note: A: LES (mmHg); B: LESL (cm); C: 4 s IRP (mmHg). There were no significant differences in the LES, LESL, or 4 s IRP levels between the GERD group and the combined group. Compared with the healthy group, *** $P < 0.001$.

Table 2. A comparison of the TLESR-related parameters among the three groups ($\bar{x} \pm S$)

Group	Number of cases	Relaxation frequency (times)	Relaxation duration (s)
Healthy group	40	0.89±0.42	3.54±0.98
GERD group	48	2.65±0.97***	6.19±1.22***
Combined group	32	2.78±0.86***	6.78±1.43***
<i>F</i>		69.445	83.180
<i>P</i>		< 0.001	< 0.001

Note: Compared with the healthy group, *** $P < 0.001$.

Table 3. A comparison of the upper esophageal sphincter parameters among the three groups ($\bar{x} \pm S$)

Group	Number of cases	UESL (cm)	UESP (mmHg)
Healthy group	40	3.26±0.85	59.62±5.18
GERD group	48	4.62±0.76***	58.17±6.25
Combined group	32	3.55±0.69***	42.36±3.37***,***
<i>F</i>		37.684	115.948
<i>P</i>		< 0.001	< 0.001

Note: Compared with the healthy group, *** $P < 0.001$; Compared with the GERD group, *** $P < 0.001$.

The upper esophageal sphincter parameters

The GERD group had a longer UESL compared with the healthy group ($P < 0.05$). The combined group had a lower UESP compared with the healthy group and the GERD group ($P < 0.05$). This indicated that a lower UESP may induce refractory cough (Table 3).

Types of peristalsis in the esophageal body

The combined group had longer large and small peristaltic breaks and a greater number of ineffective swallows compared with the healthy group and the GERD group ($P < 0.05$). This

revealed that small peristaltic breaks and effective swallows were the most common types of peristalsis of the esophageal body in patients with GERD and with refractory cough (Table 4).

Esophageal body motility

The combined group had longer DL, break distances, and PB, and lower DCI and CFV compared with the healthy group and the GERD group ($P < 0.05$). This suggested that there were esophageal body motility disorders in the patients with GERD and with refractory cough (Figure 2).

The relaxation of LES and UES incidence rates and the esophageal body motility disorders

The combined group had a higher incidence rate of esophageal body motility disorders compared with the healthy group and the GERD group ($P < 0.05$). There were no statistically significant

differences in the incidence rates of the relaxation of LES and UES among the three groups ($P > 0.05$). This demonstrated that the patients with GERD and with refractory cough had a high incidence of esophageal body motility disorders (Table 5).

Discussion

Gastroesophageal reflux occurs in healthy people, and there are no esophageal mucosal injuries as a result of the anti-reflux defense mechanisms (e.g., esophageal mucosal barrier function, esophageal reflux clearance, and anti-reflux barrier function). Lai et al. [13] reported

Table 4. The types of peristalsis of the esophageal body among the three groups (times)

Group	Times	Large peristaltic breaks	Small peristaltic breaks	Ineffective swallows	Synchronous contraction
Healthy group	400	2	9	12	56
GERD group	480	15 ^{##}	35 ^{##}	68 ^{###}	61
Combined group	320	22 ^{###,*}	71 ^{###,***}	102 ^{###,***}	60
χ^2		22.069	86.404	115.825	5.842
P		< 0.001	< 0.001	< 0.001	0.054

Note: Compared with the healthy group, ^{##} $P < 0.01$, ^{###} $P < 0.001$; Compared with the GERD group, ^{*} $P < 0.05$, ^{***} $P < 0.001$.

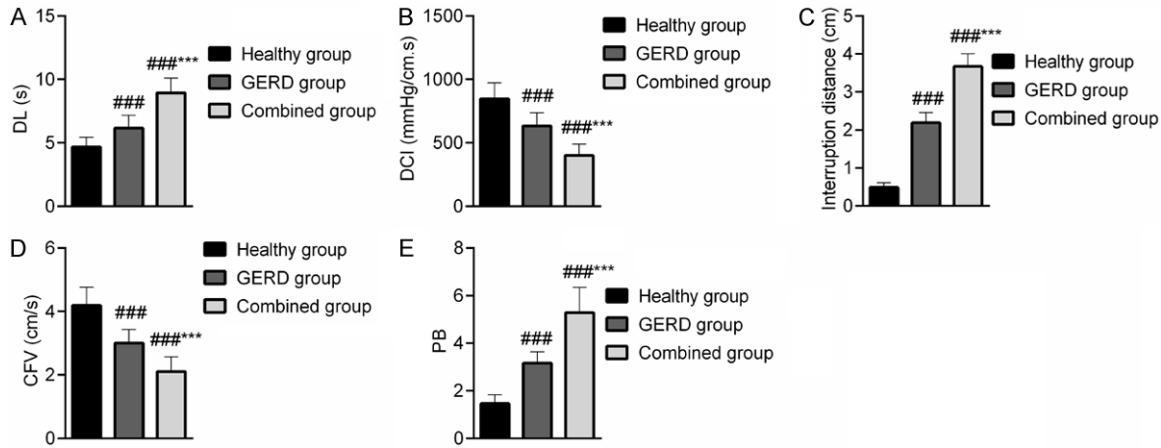


Figure 2. A comparison of the esophageal body motility parameters among the three groups. Note: A: DL (s); B: DCI (mmHg/cm.s); C: Break distance (cm); D: CFV (cm/s); E: PB. Compared with the healthy group, ^{###} $P < 0.001$; Compared with the GERD group, ^{***} $P < 0.001$.

Table 5. A comparison of the LES and UES relaxation incidence rates and the esophageal body motility disorders among the three groups n (%)

Group	Number of cases	Relaxation of LES	Relaxation of UES	Esophageal body motility disorders
Healthy group	40	26 (65.00)	24 (60.00)	3 (7.50)
GERD group	48	27 (56.25)	29 (60.42)	23 (47.92) ^{###}
Combined group	32	22 (68.75)	20 (62.50)	27 (84.38) ^{###,***}
χ^2		1.673	0.053	43.061
P		0.433	0.974	< 0.001

Note: Compared with the healthy group, ^{###} $P < 0.001$; Compared with the GERD group, ^{**} $P < 0.01$.

that patients with GERD also often suffered from respiratory symptoms of varying degrees, and gastroesophageal reflux made up 4.6% of the causes of chronic cough. Phua et al. [14] found that compared with healthy volunteers, patients with GERD and with refractory cough had a reduced mechanical sensitivity of their laryngeal adductor reflexes and esophageal motility disorders. Therefore, the identification of esophageal motility characteristics in patients with GERD and with refractory cough remains key to the early diagnosis, treatment, and improvement of the patients' prognoses. In

order to achieve the aforementioned objectives, healthy volunteers, patients with GERD, and patients with GERD and a refractory cough were selected as the study subjects, and the LES, the UES, and the indicators related to esophageal body motility in the three groups were observed and compared, so as to differentiate the diseases using the HRM-related parameters.

HRM can dynamically analyze the pressure of each segment of the esophagus through the real time continuous recording technique and

multiple pressure sensors. Compared with traditional manometric mapping, HRM can simultaneously monitor the peristaltic contractions and tensions of the esophagus and can clearly show the esophageal motility data and images. HRM can output color graphs of the pressure zone, more intuitively reflecting the esophageal pressure and the average pressure of each channel. Additionally, HRM can record even a slight pressure in the esophagus, thus providing a basis for the diagnosis of esophageal motility disorders [15, 16]. The resting LES pressure and the pressure differences in the stomach play a pivotal role in preventing esophageal reflux. LES dysfunction (e.g., reduced resting pressures and shorter lengths, TLESR, and ineffective esophageal motility) can elevate risk of recurrence [17, 18]. UES can prevent the reflux contents from entering the respiratory tract and oral cavity, and a high pressure can lead to dysphagia and pharyngeal foreign body sensations [19]. In this study, the combined group and the GERD group had lower LESP and 4 s IRP levels and a shorter LESL compared with the healthy group, indicating that LES plays an important role in the pathogenesis of GERD and GERD with a refractory cough. There were no significant differences in the LESP, LESL, or 4 s IRP levels or the frequencies and durations of TLESR between the combined group and the GERD group. Therefore, it is necessary to further expand the sample size to obtain more clinically significant study conclusions. The combined group had a higher UESP compared with the healthy group and the GERD group, which may be due to the fact that a lower UESP can induce aspiration and pharyngolaryngeal reflux, stimulate the airway, and thus cause cough.

Esophageal function is subjected to multiple factors, including the LES, the esophageal muscle fibers, the microenvironment, and the nerves. When the factors are abnormal, there is an elevated risk of esophageal motility disorders (e.g., esophageal aperistalsis, achalasia of cardia, large and small peristaltic breaks) [20, 21]. In this study, the 32 patients in the combined group had 320 liquid swallows, and the 48 patients in the GERD group had 480 liquid swallows, and the 30 healthy volunteers in the healthy group had 300 liquid swallows. The combined group had longer large and small peristaltic breaks and a greater number of inef-

fective swallows compared with the healthy group and the GERD group, showing that patients with GERD and with refractory cough had a low liquid swallow success rate, and small peristaltic breaks and ineffective swallows were frequently observed. An increase in the number of ineffective swallows can easily lead to food staying in the esophagus and pharyngeal portion of patients, and a decline in the contractility of the distal esophagus can result in a reduced esophageal reflux clearance effect. Under indirect stimulation, the stagnated reflux contents can affect the vagus nerves related to the cough reflex and thus induce coughing. In addition, the contents can delay esophageal emptying, resulting in a prolonged exposure duration to the non-acid substances or the acid substances in the reflux contents, an increased stimulation of the local mucosa, and changes to the esophageal muscle fibers, microenvironment, and neurological functions, further aggravating the esophageal dysfunction [22, 23].

DCI can be used as an indicator for the intensity of the contraction wave of the esophageal body and the contraction strength of the esophageal smooth muscle. A reduced intensity of the esophageal body's contraction wave causes a decreased esophageal reflux clearance ability, and long-term acid reflux can induce abnormal changes in the esophageal muscle fibers. Clinical findings show that a decreased contraction strength is a common cause of dyskinesia in patients with GERD [24]. CFV is a parameter for evaluating rapid conduction. Generally, its slope is < 10 cm/s. A decreased CFV can lead to a prolonged exposure duration of acid in the esophagus, a decreased peristaltic speed in the esophagus, and a reduced esophageal reflux clearance ability. A refractory cough may be accompanied by varying degrees of anoxia. Dombkowski et al. [25] found that anoxia can reduce the gastrointestinal peristaltic rate and the contraction frequency of the esophageal sphincter. According to the 2012 Chicago Classification, the DL of normal swallowing should be ≥ 4.5 s, a very short DL indicates a very fast transmission of the contraction waves, and a $DL < 4.5$ s indicates premature swallowing. In this study, the combined group had a longer DL, break distance, and PB, and a lower DCI and CFV compared with the healthy group and the GERD

group ($P < 0.05$). This demonstrated that the pathogenesis of GERD with refractory cough is closely correlated with esophageal body motility disorders.

However, this study also has certain limitation. As it is a preliminary study, the included sample size was small, leading to a certain bias in the results. Also, the fact that this was not a multicenter study may cause some doubts about the credibility of the results. In our next study, we will carry out a multicenter study with a large sample size to further confirm the soundness of this study.

In summary, patients with GERD and with refractory cough also often suffer from esophageal body motility disorders, a longer PB, an elevated UESP, and a dropped DCI. HRM can be used to objectively evaluate the esophageal dynamics and to differentiate among diseases.

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Disclosure of conflict of interest

None.

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